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## Chemotherapy induced immune-modulation via the TXNIP/GDF15 pathway in colorectal cancer

Deng, Jinhai

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Chemotherapy induced immune-modulation via the TXNIP/GDF15 pathway in colorectal cancer

Jinhai Deng

A Thesis submitted for the degree of Doctor of Philosophy

Division of Cancer and Pharmaceutical Sciences
Faculty of Life Sciences and Medicine, King's College London
Guy's Campus, London, SE1 1UL

This work is dedicated to my supervisor, friends and family who have helped guide me throughout my studies. I could not have done this without their endless help and support.

## Declaration of originality

I hereby confirm that I am the sole author of the enclosed thesis titled "Chemotherapy induced immune-modulation via the TXNIP/GDF15 pathway in colorectal cancer" and that I have compiled it with my own words. I confirm that I have documented all methods, processes and data and have not manipulated any of the data obtained and findings in this project.

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#### Abstract

Colorectal cancer is the fourth most lethal cancer worldwide. Conventional cytotoxic chemotherapy is the standard of care treatment for patients with advanced disease. The evasion of immune cell recognition is a hallmark of cancer, promoting tumour progression. Restoring immune homeostasis in cancer contributes to long-lasting therapeutic success. It is increasingly recognised that chemotherapies, which do not directly target the immune system, can activate immune responses to help promote favourable clinical outcomes. However, the pathways linking chemotherapy with immune modulation of the tumour microenvironment (TME) are poorly understood. Here, in colorectal cancer we identify that Thioredoxin Interacting Protein (TXNIP), a tumour suppressor gene, is induced by chemotherapy by RNA sequencing analysis. Moreover, we find that increased TXNIP, modulated by MondoA, contributes to improved prognosis by regulating the expression and secretion of Growth/ differentiation factor 15 (GDF15). Further experiments show that secreted GDF15 both promotes the differentiation of regulatory T cells (Tregs) and inhibits Natural killer (NK) cells degranulation by binding to CD48, a member of the CD2 subfamily participating in cell activation and differentiation. Accordingly, more analyses on cell lines derived from secondary sites, chemotherapy-resistant models and patient-derived tumour organoids (PDTOs) demonstrate that inactivation of TXNIP/GDF15 axis, and high GDF15 expression, is associated with advanced disease. Collectively, these findings illuminate potentially common pathway whereby chemotherapy-induced cellular stress drives immune remodelling.


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## List of Abbreviations

2D Two-dimensional
3D Three-dimensional
5-FU $\quad$-fluorouracil
AICAR 5-Aminoimidazole-4-carboxamide ribonucleotide
AJCC American Joint Committee on Cancer
AKT Ak strain transforming
ALI Air-liquid interface
ALK-5 Activin receptor-like kinase 5
ALL Acute Lymphoblastic Leukaemia cells
AML Acute myeloid leukemia
AMPK AMP-activated protein kinase
ANG2 Angiopoietin-2
APCs Antigen presenting cells
Arg $1 \quad$ Arginase 1
ARRB1 Arrestin Beta 1
ARRDC Arrestin-Domain Containing Protein
ASK1 The apoptosis signal-regulating kinase 1
ATF4 Activating Transcription Factor 4
ATF6 Activation Transcription Factor 6
ATG4B Autophagy Related 4B Cysteine Peptidase
ATP Adenosine triphosphate
AUC Area Under the ROC Curve
AURKA Aurora-A kinase
BAX Bcl-2-associated X protein
BCL-6 B-cell lymphoma 6
$\mathrm{BiP} \quad$ Binding immunoglobulin protein
BMPs Bone morphogenetic proteins
CAFs Cancer associated fibroblasts
CAR-T Chimeric antigen receptor T cells
CD2 Cluster of Differentiation 2
CD3 Cluster of Differentiation 3
CD11B Cluster of differentiation molecule 11B

CD28 Cluster of Differentiation 28
CD48 Cluster of Differentiation 48
CD56 Cluster of Differentiation 56
CD107a Cluster of Differentiation 107a
CD122 Cluster of Differentiation 122
CD163 Cluster of Differentiation 163
CD244 Cluster of Differentiation 244
CDDP Cisplatin
CDK2 Cyclin dependent kinase 2
CHOP C/EBP-homologous protein
ChIP Chromatin immunoprecipitation
ChREBP Carbohydrate response element binding protein
CISD2 CDGSH Iron Sulfur Domain 2
CLL Chronic lymphocytic leukemia
CMSs consensus molecular subtypes
c-Myc Cellular myelocytomatosis oncogene
COAD Colon Adenocarcinoma
COX-2 Cyclooxygenase-2
CPT1a Carnitine palmitoyltransferase 1A
CRC Colorectal cancer
CRISPR Clustered regularly interspaced short palindromic repeats
CRT Calreticulin
CSR Class-switch recombination
CTLA4 Cytotoxic T-lymphocyte-associated antigen 4
CXCL9 Chemokine (C-X-C motif) ligand 9
CXCL10 C-X-C motif chemokine 10
CXCL16 C-X-C Motif Chemokine Ligand 16
CXCR4 C-X-C chemokine receptor type 4
DACH Diaminocyclohexane
DAMP Damage-associated molecular patterns
DCs Dendritic cells
DFS Disease-free survival
DPC DNA-protein cross-links

| DSCR3 | Down syndrome critical region protein 3 |
| :---: | :---: |
| ECAR | Extracellular acidification rate |
| ECM | Extracellular Matrix |
| EGFR | Epidermal growth factor receptor |
| EGR-1 | Early Growth Response 1 |
| eIF2a | Eukaryotic Translation Initiation Factor 2A |
| EIF2AK3 | Eukaryotic translation initiation factor 2 alpha kinase 3 |
| EMT | Epithelial-mesenchymal transition |
| ER | Endoplasmic reticulum |
| ERAD | ER-associated protein degradation |
| ERK | Extracellular signal-regulated kinase |
| ERN1 | Endoplasmic reticulum to nucleus signaling 1 |
| EZH2 | Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit |
| FACS | Fluorescence-activated single cell sorting |
| FBW7 | F-box and WD repeat domain containing 7 |
| FDA | The Food and Drug Administration |
| FFPE | Formalin-Fixed Paraffin-Embedded |
| Fizz1 | Found in inflammatory zone protein |
| FoxM1 | Forkhead box protein M1 |
| FOXP3 | Forkhead box P3 |
| FoxO1 | Forkhead box protein O1 |
| GAPDH | Glyceraldehyde-3-phosphate dehydrogenase |
| GCs | Germinal centres |
| GDF15 | Growth/Differentiation Factor-15 |
| GDC | The Genomic Data Commons |
| GFRAL | GDNF-family receptor a-like |
| GLUT | Glucose transporters |
| GO | Gene Ontology |
| GPCR | G-protein-coupled receptor |
| GSEA | Gene set enrichment analysis |
| GSK-3 $\beta$ | Glycogen synthase kinase-3 $\beta$ |
| HCC | Hepatocellular carcinoma |
| HER2 | Human epidermal growth factor receptor 2 |


| HIF-1 $\alpha$ | Hypoxia-inducible factor 1-alpha |
| :---: | :---: |
| HLA | Human leukocyte antigen |
| HMGB1 | High mobility group box 1 |
| HSCs | Hepatic stellate cells |
| HSP70 | Heat shock protein 70 |
| HSPA5 | Heat shock protein family A member 5 |
| HUVEC | Human Umbilical Vein Endothelial Cells |
| IAPP | Islet amyloid polypeptide |
| ICB | Immune checkpoint blockade |
| ICD | Immunogenic cell death |
| IFN- $\gamma$ | Interferon-gamma |
| IGF1 | Insulin-like growth factor 1 |
| IL-1 $\beta$ | Interleukin-1 beta |
| IL-4 | Interleukin 4 |
| IL-6 | Interleukin 6 |
| IL-10 | Interleukin 10 |
| IL-12 | Interleukin 12 |
| IL-17A | Interleukin 17 |
| IL-18 | Interleukin 18 |
| ILC2 | Group 2 innate lymphoid |
| IRE1 | Inositol-Requiring Enzyme 1 |
| ISR | Integrated stress response |
| ISC | Inter-strand DNA cross-links |
| IC50 | Half-maximal inhibitory concentration |
| iCMS | Intrinsic-consensus molecular subtypes |
| IRI | Ischemia-reperfusion injury |
| iTreg | Inducible Treg |
| JAB1 | Jun activating binding protein |
| KRAS | Kirsten rat sarcoma virus |
| LCN2 | Lipocalin-2 |
| LncRNA | Long noncoding RNA |
| LPS | lipopolysaccharide |
| LS | Laron syndrome |


| Max | MYC Associated Factor X |
| :---: | :---: |
| MCSF | Macrophage colony-stimulating factor |
| MDSCs | Myeloid-derived suppressor cells |
| MERTK | Mer Tyrosine Kinase |
| MHC | Major histocompatibility complex |
| miRNA | microRNA |
| mLI | Mitochondrial labile iron |
| MLX | Max-like protein X |
| MMP-26 | Matrix Metallopeptidase 26 |
| MondoA | MLX interacting protein |
| MRC1 | Mannose Receptor C-Type 1 |
| MSI | Microsatellite instability |
| MSS | Microsatellite Stable |
| MT1-MMP | Membrane type 1-matrix metalloproteinase |
| mTOR | Mammalian target of rapamycin |
| MUC5AC | Mucin-5AC |
| NAC | N-acetyl-L-cysteine |
| NAD/NADH | Nicotinamide adenine dinucleotide/ nicotinamide adenine dinucleotide (NAD) + hydrogen (H) |
| NAF-1 | Sodium fluoride-1 |
| NAPDH | Nicotinamide adenine dinucleotide phosphate |
| NCAM1 | Neural cell adhesion molecule 1 |
| NF-Kb | Nuclear factor kappa B |
| NK | Natural Killer |
| NRF2 | Nuclear factor erythroid 2-related factor 2 |
| NLRP3 | NLR family pyrin domain containing 3 |
| Notch4 | Neurogenic locus notch homolog 4 |
| Nos2 | Nitric oxide synthase 2 |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| nTreg | Natural Treg |
| ORF | Open reading frames |
| OS | Overall survival |
| OXA | Oxaliplatin |


| OXAR | Oxaliplatin resistant |
| :--- | :--- |
| OXPHOS | Oxidative phosphorylation |
| p27kip1 | Cyclin-dependent kinase inhibitor 1B |
| PACE4 | Paired Basic Amino Acid-cleaving Enzyme 4 |
| PBMCs | Human peripheral blood mononuclear cells |
| PD1 | Programmed cell death 1 |
| PDI | Protein disulphide isomerase |
| PD-L1 | Programmed death-ligand 1 |
| PERK | PRKR-like endoplasmic reticulum kinase |
| PDC | Patient-derived cells |
| PDGF | Platelet-derived growth factor |
| PDTOS | Patient-derived tumour organoids |
| PDS | Patient-derived spheroids |
| PDTX | Patient-derived tumour xenograft |
| PI3K | Phosphoinositide 3-kinase |
| PMN-MDSC | Polymorphonuclear myeloid-derived suppressor cell |
| POMC | Pro-opiomelanocortin |
| PPAR $\gamma$ | Peroxisome proliferator-activated receptor- $\gamma$ |
| Prxs | Periaxin gene |
| Pt | Platinum |
| PTEN | Phosphatase and tensin homolog deleted on chromosome 10 |
| qPCR | Quantitative Polymerase Chain Reaction |
| QRICH1 | Glutamine-rich protein 1 |
| RAGE | The receptor for advanced glycation end products |
| RANKL | Receptor activator of nuclear factor-kB ligand |
| RAS | Rat sarcoma |
| RCC | Renal cell carcinoma |
| REDD1 | Regulated in development and DNA damage responses 1 |
| REDOX | Reduction-oxidation |
| RET | Rearranged during transfection |
| rhGDF15 | Recombinant human GDF15 protein |
| Regulated IRE1-dependent decay |  |
| RNuencing |  |


| ROR $\gamma \mathrm{t}$ | Retineic-acid-receptor-related orphan nuclear receptor gamma |
| :---: | :---: |
| ROS | Reactive Oxygen Species |
| PRSS2 | Protease, serine, 2 (trypsin 2) |
| SAM | Synergistic Activation Mediator |
| SEMA3F | Semaphorin-3F |
| SERPINA1 | Serpin Family A Member 1 |
| SHM | Somatic hypermutation |
| SMAD | Suppressor of Mothers against Decapentaplegic |
| STAB1 | Stabilin-1 |
| STAT4 | Signal Transducer And Activator Of Transcription 4 |
| STUB1 | STIP1 homology and U-Box containing protein 1 |
| SLAM | Simultaneous localization and mapping |
| STAT3 | Signal transducer and activator of transcription 3 |
| STING | Stimulator of interferon genes |
| SunTag | Tagging system SUperNova |
| T2D | Type 2 diabetes |
| TAM | Tumour-associated macrophages |
| TCA | Tricarboxylic acid |
| TCGA | The cancer genome atlas project |
| TGF- $\beta$ | Transforming growth factor-beta |
| TGF- $\beta$ RI | Transforming growth factor-beta receptor type I |
| TH1 | T helper type 1 |
| TH2 | T helper type 2 |
| TH17 | T-helper 17 |
| TLR4 | Toll-like receptor 4 |
| TME | Tumour microenvironment |
| TIME | Tumour immune microenvironment |
| TNBC | Triple negative breast cancer |
| TNF $\alpha$ | Tumour Necrosis Factor alpha |
| TNFRSF | Tumour necrosis factor receptor superfamily |
| TOPO1 | Type I topoisomerase |
| TP53 | Tumour Protein P53 |
| Tregs | Regulatory T cells |


| TRX | Thioredoxin |
| :--- | :--- |
| TrxR | Thioredoxin reductase |
| TSG | Tumour suppressor gene |
| TXNIP | Thioredoxin-interacting protein |
| UCA1 | Urothelial cancer associated 1 |
| UHRF1 | Ubiquitin Like with PHD And Ring Finger Domains 1 |
| UPR | Unfolded protein response |
| VEGF | Vascular endothelial growth factor |
| VEGFA | Vascular Endothelial Growth Factor A |
| VGF | Nerve growth factor |
| VPS26 | Vacuolar protein sorting-associated protein 26A |
| WNT | Wingless-related integration site |
| XBP1 | X-box-binding protein 1 |
| ZEB1 | Zinc Finger E-Box Binding Homeobox 1 |

## List of Publications

The following is the list of work published during the course of this doctorate.

## Original Research

2022: Jinhai Deng, et al. Chemotherapy-induced tumour microenvironment remodelling via the MondoA/TXNIP/GDF15 axis. In submission to cancer discovery.

2022: Shaorong Zhao, et al. Exosomal transfer of miR-181b-5p confers senescencemediated doxorubicin resistance via modulating BCLAF1 in breast cancer. Br J Cancer. 2022; Online ahead of print.

2022: Ge X, et al. Integrative pharmacogenomics revealed three subtypes with different immune landscapes and specific therapeutic responses in lung adenocarcinoma. Comput Struct Biotechnol J. 2022; 20:3449-3460.

2022: Weng, S. et al. SCG2: A Prognostic Marker That Pinpoints Chemotherapy and Immunotherapy in Colorectal Cancer. Front. Immunol. 13, (2022).

2022: Jose Vicencio Bustamante, et al. Osimertinib and anti-HER3 combination therapy engages immune dependent Tumour toxicity via STING activation in tran. Mar 2022, In: Cell Death \& Disease. 13, 3, 274.

2020: Paul R. Barber, et al. HER2-HER3 heterodimer quantification by FRET-FLIM and patient subclass analysis of the COIN colorectal trial. Sep 2020, In: Journal of the National Cancer Institute. 112, 9, p. 944-954.

## Reviews

2020: Zhengwen An, et al. Pleiotropic Role and Bidirectional Immunomodulation of Innate Lymphoid Cells in Cancer. 4 Feb 2020, In: Frontiers in Immunology. 10, 3111.

Chapter I. Introduction

### 1.1 Prologue

Colorectal cancer (CRC) is one of the most common malignancies worldwide, with a high prevalence and mortality ${ }^{1}$. Colorectal cancers begin as benign adenomatous polyps and might develop into advanced adenomas with high-grade dysplasia. During this process, the progressive accumulation of genetic mutations and epigenetic alterations drives malignant transformation of cells and tumour development ${ }^{2,3}$. In the clinic, the American Joint Committee on Cancer (AJCC) classification is commonly used to stage patient tumours for assessing the risk and evaluating treatment plans. The efficacy of this classification system is limited due to the high heterogeneity of CRCs. Clinical treatment of primary colorectal cancer includes surgical resection (open or laparoscopic surgery) and chemo-radiotherapy, while in the metastatic setting, palliative chemotherapy, targeted therapies such as cetuximab, an anti-epidermal growth factor receptor monoclonal antibody, and immune checkpoint inhibitors are employed ${ }^{4,5}$. Even though clinical treatments have been shown to prolong overall survival (OS) and reduce the risk of recurrence ${ }^{6}$, the selection of patients for suitable treatment regimens is currently suboptimal, giving rise to either over- or under-treatment ${ }^{7}$. For example, adjuvant chemotherapy is beneficial to only a minor population of stage III CRC patients, while the majority of patients are exposed to unnecessary toxicity ${ }^{8}$. Over the last two decades, it has been established that the ability of tumour cells to evade immune cell surveillance is a key hallmark of cancer. Importantly, the success of immunotherapies has highlighted the importance of the cross-talk between cancer cells and the immune system within the tumour microenvironment ${ }^{9,10}$. Moreover, it is becoming clear that even non-immunological therapeutic strategies, such as chemotherapies, require the activation of the immune system to improve treatment outcome ${ }^{11}$. In this study, we aim to identify the mechanisms by which chemotherapies
modulate the tumour-immune cells crosstalk. By understanding how chemotherapies modulate the tumour immune microenvironment (TIME), this will allow us to predict the response of patients to chemotherapies and guide clinical decisions.

### 1.2 Colorectal cancer

### 1.2.1 Colorectal cancer subtypes

CRC is the fourth most deadly cancer worldwide, with almost 0.93 million cases of deaths annually. CRC typically develop as a result of mutations in the tumour suppressor gene $A P C$, followed by $R A S$ activation mutation or loss of function mutations in TP53 ${ }^{12}$. CRC is characterised by strong heterogeneity, with variable molecular pathogenesis, natural history and response to treatments ${ }^{13,14}$. Colorectal cancer cells display distinctive biological behaviours compared to other types of cancers, such as rapid tumour growth, early treatment relapse, and metastasis ${ }^{15}$. Currently, the AJCC stage system evaluation has been used for the assessment of the clinical treatment and prognosis of colorectal cancer patients. However, the efficacy of this system is limited due to the heterogenicity of CRCs, even among same-staged patients.

Gene expression-based subtyping is well-accepted for cancer stratification ${ }^{16}$. To facilitate the translation of molecular subtypes into clinic, a consensus molecular subtypes (CMSs) was proposed by an international consortium in 2015 to predict various clinic outcomes independent of cancer stage. The CMS classification system defines four distinct subtypes, including CMS1, CMS2, CMS3 and CMS4. These subtypes represent microsatellite instability immune, canonical, metabolic and mesenchymal phenotypes, respectively ${ }^{14}$. CMS classification is based on bulk transcriptomics and hugely influenced by the tumour microenvironment ${ }^{14}$. For example, the CMS4 subtype presents strong mesenchymal signature in tumours and is associated
with poor prognoses ${ }^{17,18}$. In addition, the use of single-cell RNA sequencing has provided an understanding of the diversity of epithelial cells in colorectal cancer and has allowed the further refinement of CMS classification. The refined consensus molecular classification consists two epithelial groups intrinsic-consensus molecular subtypes (iCMSs), such as iCMS2 and iCMS3 ${ }^{19}$.

However, other studies reported that subtyping of rectal cancer patients according to the CMS criteria may not be able to predict disease-free survival (DFS) ${ }^{20}$. In the study conducted by Adele M. Nicolas et al, they highlighted an imperative need for more reliable and accurate predictive biomarkers for personalized prediction of prognosis and selection of suitable drug treatment regimens ${ }^{20}$.

### 1.2.2 The application of 3D tumour models in CRC study

For decades, two dimensional (2D) cell culture has been used as in vitro model in most research, becoming a critical tool to understand the mechanisms of drug actions in cancer studies ${ }^{21}$. The 2D model has pushed the development of research due to its simplicity, low-cost maintenance and acceptable performance in functional tests. However, many disadvantages limit this model as an ideal tool to mimic physiological conditions: 1) Firstly, 2D models fail to represent the natural structures and behaviours of cells growing in in vivo resections. Culturing cells in 2D alters the interactions of cells with each other and their surrounding environment. These changes affect cellular proliferation, differentiation, nutrient sensing and viability ${ }^{22}$. 2) Secondly, cells lose the capacity to keep diverse phenotypes in 2D cultures, resulting in the elimination of tumour cell complexity and alterations in cell signalling ${ }^{23,24}$.3) Thirdly, cells grown in monolayers have infinite access to components found in the medium like oxygen, nutrients and drugs. The distribution of nutrients and/or drugs in three dimensional (3D) cultures causes variability in responsiveness to stimuli when compared to 2D models ${ }^{22}$.
4) Fourthly, 2D cell lines are not readily established for every individual patients, which makes it a difficult tool for clinical decision-making ${ }^{25}$. 5) Lastly, due to the isolated nature of 2D cell cultures, many biological conclusions taken from them lack the complexity observed in larger organs. For instance, multiple cell types interact within the organ and with circulating factors and cells such as the lymphatic, immune, endocrine and neurological systems.

Intra-tumoral heterogeneity can be observed across cancer types, contributing to therapeutic failure and drug resistance ${ }^{26}$. To improve the mechanistic studies of cancer biology and preclinical evaluation of drug treatment, three dimensional (3D) cultures, including multicellular spheroids and patients-derived tumour organoids (PDTOs), have been developed. 2D and 3D culture systems show differences in several aspects (Table 1-1). Several studies highlight changes in protein expression and drug response in patient-derived spheroids (PDS) compared with corresponding patient-derived cells $(\mathrm{PDC})^{27}$. Spheroids have been reported to have similar features to solid tumours in comparison to 2 D culture models. These features include structural and growth-rate similarities ${ }^{28}$. There are several methods for spheroid preparation, including the hanging-drop method ${ }^{29}$, cultures on non-adherent plates ${ }^{30}$ and cultures on a scaffold ${ }^{31}$.

Table 1-1 Comparison of 2D and 3D cell culture methods. (Adapted from Marta Kapatczyńska et. al ${ }^{21}$ and amsbio organoid culture handbook ${ }^{32}$ )

| Type of culture | 2D | 3D |
| :---: | :---: | :---: |
| Time of culture formation | Within minutes to a few hours | From a few hours to a few days |
| Culture quality | High performance, reproducibility, long-term culture, easy to interpret, simplicity of culture | Worse performance and reproducibility, difficult to interpret, cultures more difficult to carry out |
| In vivo imitation | Do not mimic the natural structure of the tissue or tumour mass | In vivo tissues and organs are in 3D form |
| Cells interactions | Deprived of cell-cell and cellextracellular environment interactions, no in vivo-like microenvironment and no "niches" | Proper interactions of cell-cell and cell-extracellular environment, environmental "niches" are created |
| Migration \& Invasion | Cell motility is reduced, cell direction is Changed, very limited cell-ECM interaction | Very complex motility models taking into consideration not only stiffness but also the rheology and geometry of ECM |
| Angiogenesis | Only observational | Can be functional |
| Genetic profile | Modified | Preserved. Better representation of growth factors, pro-angiogenic and adhesion molecules genes |
| Multicellular studies | Better when studying immune response | Good in co-culture, but might be complicated with more than two cell types |
| Characteristics of cells | Changed morphology and way of divisions; low proliferation rate; loss of diverse phenotype and polarity | Preserved morphology and way of divisions; More pronounced proliferation rate; diverse phenotype and polarity |
| Access to essential compounds | Unlimited access to oxygen, nutrients, metabolites and signalling molecules (in contrast to in vivo) | Variable access to oxygen, nutrients, metabolites and signalling molecules (same as in vivo) |

Patient-derived tumour organoids (PDTOs) are cultures of tumour cells derived from individual tumour samples. Over the last decade, 3D organoid culture models have been established and achieved a high success rate ${ }^{33}$ (Figure 1-1). PDTOs can expand indefinitely and recapitulate morphological and genetic features of the original tumour ${ }^{34}$, which has been suggested to be used to predict clinical responses of individual patients ${ }^{35}$. Both adult and embryonic stem cells can be used to develop 3D models, which reflect the tissue of origin with their ability to self-organize. The first colorectal cancer organoids was established in 2011, and identified to be capable of being cultured for long-term due to their enrichment in the stem cell population ${ }^{33}$. Importantly, colorectal organoids can be established from both surgical tumour resections and needle biopsies ${ }^{25,36}$, with success rates of $60 \%-90 \%$ and $\sim 70 \%$, respectively. High successful rate for biopsies is critical for the specific setting when biopsies is the only available source of fresh tumour tissue, like metastases ${ }^{25}$.


Figure 1-1 Timeline of PDTOS development. (Adapted from Margit Bleijs ${ }^{37}$ )
2009, first organoids culture establishment ${ }^{38}$; 2011, colorectal cancer organoids ${ }^{33}$; 2014, prostate cancer organoids ${ }^{39} ; 2015$, pancreatic cancer organoids ${ }^{40} ; 2017$, liver cancer organoids ${ }^{41}$; 2018, breast cancer organoids ${ }^{42}$, gastric cancer organoids ${ }^{43}$, lung cancer organoids, bladder cancer organoids ${ }^{44}$, oesophageal cancer organoids ${ }^{45} ; 2019$, ovarian cancer organoids ${ }^{46}$, kidney cancer organoids ${ }^{47}$.

Similar to patient-derived tumour xenograft (PDTX), PDTOs are also able to accurately recapitulate tumour heterogeneity, providing great potential to study sub-clonal dynamics within individual tumours during tumour progression and therapy resistance ${ }^{37}$. Moreover, organoids can be used in the generation of complex co-culture system to understand the interaction of tumour cells with other cell types including immune cells or fibroblasts ${ }^{48}$. There are currently two widely used methods described to study the interactions of PDTOs with immune cells: namely the holistic approach and the reductionist approach. The holistic method uses endogenous immune cells preserved from the initial tumour biopsy to culture with cancer organoids. The latter method uses Human peripheral blood mononuclear cells (PBMCs) or isolated immune
cells subsets isolated from blood samples to co-culture with cancer organoids ${ }^{48,49}$. Given these advantages, PDTOs have received widespread attention due to their potentials to recapitulate the TME in vitro. However, there are several limitations to consider when PDTO models are used for cancer study, including a lack of cellular components leading to imperfect establishment of the TME, lacking of standardized protocols globally, high cost for long-term culture, the inability to extend to whole organs studies and outcomes heterogeneity owing to diversity between individuals and protocols ${ }^{50}$.

### 1.2.3 Chemotherapies used in the treatment of CRC

Over the past decades, new targeted agents and immunotherapies have revolutionized the treatment regimen in clinic. However, these therapies have only showed success in a selected number of patient groups. Thus, chemotherapy is still predominantly used as the standard of care in most cancer types ${ }^{51}$. Conventional chemotherapeutics are generally subdivided into several categories, comprising: 1) alkylating and platinumbased agents which cause inter- or intra-strand DNA crosslinks and destabilise DNA during replication (e.g., oxaliplatin); 2) topoisomerase inhibitors which impede the correct DNA unwinding during replication and transcription (e.g., irinotecan); 3) antimetabolites which inhibit DNA and RNA synthesis (e.g., 5-fluorouracil [5-FU]); 4) microtubular poisons which interfere with the polymerisation or depolymerisation of tubulin to inhibit the mitotic spindle (e.g., paclitaxel); and 5) cytotoxic antibiotics which exert antitumour effects by DNA intercalation and over-production of reactive oxygen species (e.g., bleomycin) ${ }^{52}$.

In colorectal cancer, 5-FU, oxaliplatin and irinotecan are predominantly used as firstline (FOLFOX) and second-line (FOLFIRI) treatments ${ }^{53}$. Oxaliplatin (OXA) is a thirdgeneration platinum analogue of cisplatin (CDDP), and shows an improved anti-tumour
safety profile ${ }^{54,55}$. It has been used in clinic as it forms both inter-/intra- strand crosslink in DNA, leading to the inhibition of DNA synthesis and DNA replication. As a conventional DNA-damaging drug, oxaliplatin is proved to be more efficient at inducing tumour regression in immunocompetent than immunocompromised mice compared to cisplatin ${ }^{56,57}$. This data suggests that the immune system is necessary to modulate the responses of OXA. In support of this, OXA has been reported to induce immunogenic cell death (ICD) of CRC cells by triggering necroptosis or apoptosis via the release of danger-associated molecular patterns (DAMPs), which requires innate and adaptive immune components ${ }^{58,59} .5-\mathrm{FU}$ is the fluorinated analog of uracil as a type of anti-metabolic chemotherapies. The mechanism of action is to block synthesis of thymidylate which is required for DNA replication ${ }^{60,61}$. $5-\mathrm{FU}$ has been applied in diverse types of cancers and shown the greatest impact in $\mathrm{CRC}^{62}$. Similar to oxaliplatin, 5-FU has also been observed to modulate anti-tumour immune responses other than direct cytotoxic effects to tumour cells ${ }^{62,63}$. Anti-tumour immune response mediated by 5-FU is achieved by both deactivation of immunosuppressive cell populations and stimulation of immunogenic cell death ${ }^{63}$. For instance, $5-\mathrm{FU}$ is observed to deplete Myeloid-derived suppressor cells (MDSCs) and Regulatory T cells (Tregs) ${ }^{64,65}$. Moreover, the fact of 5-FU inducing immunogenic cell death is supported by the evidence that $5-\mathrm{FU}$ is capable of inducing the release of HMGB1 and HSP70, which belong to DAMPS, and further facilitate the activation of dendritic cells (DCs) ${ }^{66,67}$. Both OXA and 5-FU therapies have been reported to modulate ROS production and activation of associated signalling pathways ${ }^{68,69}$. Irinotecan is an analog of camptothecin to interact with topoisomerase I (Topo I), further causing S-phasespecific cytotoxicity ${ }^{70}$. Topoisomerases function to generate temporary single- or double-strand breaks in the DNA, preventing excessive twisting and supercoiling of

DNA induced during processes including DNA transcription, replication and other cellular processes ${ }^{70-72}$. Topo I introduces single-strand breaks and irinotecan-mediated Topo I-DNA complex stabilization DNA breaks ${ }^{73}$. Similarly, irinotecan has also been reported to show immunogenic effects by regulating the function of regulatory T cells and the expression of MHC-I and PD-L1 ${ }^{74}$.

As the responses of CRC patients to chemotherapies are heterogenous, the conventional AJCC classification fails to identify patients who are most likely to be responsive to specific treatment regimens ${ }^{75}$. Moreover, in contrast to targeted therapies, patient response to chemotherapy is challenging to stratify based on genomic data alone. This is in part due to an incomplete understanding of diverse mechanisms of action in cells ${ }^{76}$. Therefore, the identification of reliable biomarkers is needed for in-depth selection of subpopulation of patients who would benefit from chemotherapy.

### 1.2.4 Chemotherapy-induced immunogenic cell death

Immunological cell death (ICD) is an essential modulator of the immune system when exposed to cytotoxic stress, helping to maintain long-term anti-cancer effects ${ }^{77}$. ICD is associated with the secretion of DAMPs, proteins which can efficiently alert the immune system ${ }^{78}$. For instance, high mobility group box 1 (HMGB1), a non-histone nuclear protein, is a well characterised DAMP that regulates gene expression through interactions with transcription factors ${ }^{79}$. Secreted HMGB1 alarmin protein interacts with its cognate receptor TLR4 on dendritic cells (DCs), licensing host DCs to process and present tumour antigens and further cross-priming T lymphocytes in vivo ${ }^{57,67}$. Depletion of TLR4 or inhibition of HMGB1 release causes DCs to be defective in antigen-presentation ${ }^{57}$. Notably, chemotherapy-induced ICD contributes to the initial step of " Cancer-Immunity Cycle", which comprises a series of stepwise events for effective immune activation and cancer cell killing ${ }^{80}$. In summary, the Cancer-

Immunity cycle contains 7 steps (Figure 1-2): 1) Step 1, the release of neoantigens and proinflammatory cytokines and factors. (Chemotherapy-induced ICD begins with this process.) 2) Step 2, the presentation of captured antigen peptide by antigen presenting cells (APCs, mainly DCs). This is followed by cross-presentation of tumour cellderived neoantigens on DCs by MHC-I complex to drive an 'endogenous anti-viral antitumour' CTL response ${ }^{81-83}$. 3) Step 3, the priming and activation of cytotoxicity effector T cells, which is activated by recognising MHC-peptide complex. 4) Step 4, trafficking of T cells into tumour. 5) Step 5, infiltration of T cells into the tumour bed. 6) Step 6. recognition of targeted cancer cells. 7) Killing of cancer cells by effector $T$ cells ${ }^{80}$. Notably, this cycle doesn't include the cell killing mediated by innate immune cells (like macrophages and NK cells ${ }^{84}$ ), which is also proved to be critical in anticancer immune activation ${ }^{85,86}$.


Figure 1-2 The Cancer-Immunity Cycle (Adapted from Daneil S. Chen ${ }^{80}$ ).
Neoantigen and proinflammatory cytokines are initially released in response to cytotoxic stress induced by chemotherapy. This step is the most important process for chemotherapy to initiates ICD. Subsequently, antigen presenting cells (APCs, mainly dendritic cells) capture and crosspresent antigen peptide via MHC class I. Cytotoxic effector T cells are then primed and activated by recognising peptide bound MHC-peptide complex on the antigen presenting cells. Activated effector T cells traffic to and infiltrate into the tumour bed where they selectively kill cancer cells. Abbreviation: CTL: Cytotoxic T lymphocytes.

### 1.3 Thioredoxin-interacting protein

In this thesis, the significantly upregulated expression of thioredoxin-interacting protein (TXNIP) was observed in colorectal cancer cells after chemotherapy treatment. Combined with other experiments, we identified TXNIP is a biological target mediating the effects of chemotherapy.

Thioredoxin-interacting protein (TXNIP), an alpha-arrestin protein, is commonly known as a master regulator of cellular oxidation by regulating the activity of Thioredoxin (TRX) via direct binding ${ }^{87}$. Hydrogen peroxide $\left(\mathrm{H}_{2} \mathrm{O}_{2}\right)$ used to be regarded as the inevitable but unwanted by-product of aerobic cellular respiration. Several studies implicate an important role of "Reduction-Oxidation (redox) responses" in regulating essential physiological cellular functions, supported by evidence that low cellular ROS levels are pivotal for cellular signalling like tyrosine phosphorylationdependent pathways, responsible for cell proliferation, differentiation and migration ${ }^{88-}$ ${ }^{90}$. Within mitochondria, normal oxidative phosphorylation requires ROS during normal flux of the electron transport chain. However, chronic excessive production of ROS by mitochondria leads to oxidative stress, contributing to pathological diseases, including neurodegenerative disorder ${ }^{91}$, diabetes $^{92}$, cancer $^{93}$ and autoimmune disease ${ }^{94,95}$, suggesting that the balance of redox regulation is critical for homeostasis. Thioredoxins, together with glutathione, constitutes the two major thiol antioxidants ${ }^{96}$. The thioredoxin system is comprised of thioredoxin, thioredoxin reductase and nicotinamide adenine dinucleotide phosphate (NAPDH), playing an important role in defence against oxidative stress through the regulation of protein dithiol/disulfide balance ${ }^{97}$. Specifically, electron flux is catalysed from NAPDH to thioredoxin by thioredoxin reductase. Reduced thioredoxin are essential in reducing its target proteins through disulfide-dithiol exchange processes, leading to the maintenance of
intracellular redox state ${ }^{96,98}$. The direct biding between TXNIP and thioredoxin leads to the inhibition of the reducing activity of thioredoxin through disulfide exchange, enhancing oxidative stress ${ }^{99}$. Physiologically, TXNIP expression is induced by various stresses, including DNA damage stress, ER stress and oxidative stress ${ }^{87,100}$. TXNIP shows additional functions in regulating glucose and lipid metabolism, leading to therapeutic inhibitor development in the treatment of metabolic diseases such as diabetes mellitus ${ }^{101}$. The last two decades have also seen an accumulation of evidence implicating the pleiotropic roles of TXNIP in cancer. TXNIP is identified as a tumour suppressor gene (TSG), and is observed to be silenced by genetic or epigenetic events in a variety of primary human tumour tissues and human cancer cell lines ${ }^{102}$. Its function as a tumour suppressor is also supported by the observation that Txnip-deficient mice show a higher incidence ( $40 \%$ higher) of spontaneously developing hepatocellular carcinoma, which can appear as early as 8 months ${ }^{103}$. Moreover, single-cell RNA sequencing of T-cell lymphoma reveals that the downregulation of TXNIP expression is observed in malignant clones and correlates with disease progression ${ }^{104}$. Indeed, cumulative evidence suggests that low expression of TXNIP in cancers correlates with poor prognosis. Collectively, these studies suggest that TXNIP shows tumoursuppressive effects in cancer.

In contrast to this, other reports show that high TXNIP levels can also correlate with poor clinical prognosis in some cancers. For example, lung cancer patients with high levels of TXNIP exhibit decreased progression free survival compared to patients with low TXNIP levels ( 18.0 vs. 23.0 months $)^{105}$. In hepatocellular carcinoma and conventional renal cell carcinoma, overexpression of TXNIP has also been observed to increase angiogenesis and metastasis ${ }^{106,107}$. These observations suggest that the roles of TXNIP in cancers show specificity.

In addition to tumour specific functions, TXNIP may also exert opposite functions at different stages during cancer progression. When analysing TXNIP in early $v s$. latestage cases separately, its expression shows different associations with different clinical outcomes, namely, improved survival in early-stage disease but poor survival in latestage disease ${ }^{108}$, indicating that the roles of TXNIP may have different implications depending on different stages of cancer. The underlying mechanisms of these controversial findings need to be integrated in a comprehensive way, and the role of TXNIP acting as a TSG vs. an oncogene needs to be further elucidated in order to address the questions currently unanswered.

### 1.3.1 Regulatory network of TXNIP

### 1.3.1.1 Common regulatory pathways

It is well established that TXNIP expression is tightly regulated by diverse signals, like glucose-sensing transcriptional complexes, especially the ChREBP/MondoA: MLX complex ${ }^{109}$. MondoA (also known as MLXIP) belongs to the Mondo family of transcription factors, transcriptional biosensors of intracellular glucose concentration ${ }^{110}$. MondoA has been reported to regulate TXNIP expression and promote a decrease in glucose uptake and glycolysis ${ }^{111-113}$. Moreover, intracellular ROS is involved in regulating the MondoA-TXNIP signalling. Specifically, increases in ROS levels stimulate the formation of MondoA-mTOR complexes at the expense of transcriptionally active MondoA-MLX complexes, resulting in decreased transcriptional activation of TXNIP ${ }^{114}$

Other than these complexes, more factors are also involved in regulating TXNIP. These factors constitute a comprehensive regulatory network that can be broadly divided into four classes: 1) transcription factors (MondoA ${ }^{111}$, ChREBP ${ }^{115}$, PTEN $^{116}$, MLX ${ }^{109}$, FoxO1 ${ }^{117}$, Max ${ }^{118}$, STAT3 $^{119}$ ), 2) MicroRNAs and circular RNAs (miR-21 ${ }^{120}$, miR-
$148 \mathrm{a}^{121}$, miR-135b-5p ${ }^{122}$, miR-152-5p ${ }^{123}$, miR-204 ${ }^{124}$, miR-211, miR-224 ${ }^{125}$, miR$373^{126}, m i R-411-5 p^{127}, m i R-177^{128}, m i R-128-3 p^{129}, m i R-27 a-3 p^{130}, m i R-424-5 p^{131}$, CircECE1 ${ }^{132}$, circDCUN1D4 $\left.4^{133}\right), 3$ ) epigenetic regulators (EZH2 ${ }^{134}$, UHRF1 $^{135}$ ) and 4) regulators of mRNA and protein stability (LncRNA Gm15441 ${ }^{136}$, LncRNA SNHG15 ${ }^{137}$ ). To be noted, these regulatory signalling pathways are bi-directional. For instance, expression of various microRNAs (for example, miRNA-204 and miR-124a) are reported to be regulated by TXNIP and further affect insulin production ${ }^{124}$ as well as islet amyloid polypeptide (IAPP) signalling ${ }^{138}$. Insulin, in turn, can also regulate TXNIP expression by modulating glucose levels ${ }^{139}$.

### 1.3.1.2 Oncogenes and TSGs

TXNIP can be induced by oncogenes ${ }^{140}$. For instance, in breast cancer, c- Myc has been exhibited to antagonise TXNIP expression in MondoA-dependent pathway ${ }^{141}$. c-Myc competes with MondoA to bind TNXIP promoter, leading to decreased TXNIP expression ${ }^{111}$. When compared with iAP mice (mice harbouring conditional null alleles of Apc and Trp53), iKAP mice (engineered with a doxycycline - inducible oncogenic Kras allele and conditional null alleles of $A p c$ and Trp53) exhibit reduced TXNIP expression, suggesting that oncogenic KRAS is capable of TXNIP regulation ${ }^{142}$. The oncogenic GTPase Ras has also been shown to inhibit TXNIP expression by suppressing the translation of TXNIP mRNA ${ }^{143}$. Additionally, HER2 overexpression is observed to induce the upregulation of TXNRD1 and downregulation of TXNIP, suggesting HER2 can cause the shift of the redox balance in a prognostically unfavourable way in breast cancer ${ }^{144}$. Consistently, another study shows that oncogenic activation of HER2 is associated with decreased TXNIP expression. Treatment of HER2 inhibitor significantly induces TXNIP expression, which mediates G1 cell cycle arrest and cell proliferation inhibition ${ }^{145}$, and a concomitant increase in reactive oxygen
species (ROS) production in breast cancer ${ }^{145}$. Reciprocally, TXNIP has also been demonstrated to modulate the signalling of tumour suppressors. For example, in ARPE19 cells, TXNIP depletion promotes autophagy through increased stabilization of $\mathrm{p} 53^{146}$. Similarly, HCC tumours in TXNIP-deficient mice also have increased p53 expression ${ }^{103}$. In oxidative tissues (like skeletal and cardiac muscle), genetic silence of TXNIP leads to the accumulation of oxidized PTEN (an inactive form of PTEN) and elevated AKT signalling ${ }^{147}$. Collectively, on one hand, TXNIP expression can be modulated by oncogenic proteins; on the other hand, TXNIP mediates tumour suppressive activity by regulating the expression and activation of tumour suppressors.

### 1.3.1.3 ER stress signalling

TXNIP signalling is also implicated in endoplasmic reticulum (ER) stress, participating in the different branches of the unfolded protein response (UPR). ER stress signalling is regulated by three major functional sensors (Figure 1-3): activating transcription factor 6 (ATF6), inositol-requiring enzyme $1 \alpha$ (IRE1 $\alpha$ ) and protein kinase R-like ER kinase (PERK). Under homeostatic conditions, the luminal ER master chaperone protein BiP is bound to these sensors, maintaining them in an inactive state. Under ER stress conditions, misfolded proteins accumulate in the ER lumen, BiP binds to these misfolded proteins with high affinity, resulting in its displacement from the ER stress sensor proteins, which leads to the activation of sensor proteins and ultimately transcriptional reprogramming to maintain ER homeostasis. The whole process is known as unfolded protein response (UPR). UPR is an evolutionarily conserved cellular stress response, triggered to cope with damage.


Figure 1-3 Unfolded protein response and its three major sensors.
BiP dissociates from UPR sensors (IRE1 $\alpha$, PERK and ATF6) priming them to be activated, which results in the initiation of the UPR ${ }^{148}$.

Recent studies emphasise the requirement of ER stress for TXNIP induction, in particular through signalling pathways by IRE1a and PERK ${ }^{149,150}$. The first UPR branch, PERK, is activated by dimerization and autophosphorylation, further phosphorylating eIF2a at S51 (Figure 1-3). Phosphorylated eIF2a is proposed to initiate the integrated stress response (ISR), shutting down general translation initiation but favouring newly transcribed mRNAs for UPR adaptive functions ${ }^{151}$. Another UPR branch, IRE-1a undergoes autophosphorylation, conformational change and higher order assembly upon BIP dissociation ${ }^{152}$. IRE1 $\alpha$ excises a small 26-nucleotide intron from the mRNA encoding the transcription factor X-box-binding protein 1 (XBP1), resulting in the expression of an active spliced form XBP1s. XBP1s is involved in the folding, translocation and secretion of ER proteins, ER/Golgi biogenesis and ER-associated protein degradation (ERAD). In addition, IRE-1a activation can lead to another process
known as regulated IRE1-dependent decay (RIDD), with the degradation of a small set of mRNAs or precursor microRNAs (miRNAs) ${ }^{153}$, a process that contributes to stabilise ER homeostasis.

TXNIP signalling is implicated in endoplasmic reticulum (ER) stress, participating in the different branches of the unfolded protein response (UPR). The regulation of TXNIP expression following ER stress is dependent on cell type and cellular condition. Both PERK and IRE- 1 are required for TXNIP induction in ER-stress-induced $\beta$-cell death ${ }^{150}$. PERK on its own can also regulate TXNIP. After subarachnoid haemorrhage, TXNIP induced by PERK promotes apoptosis of neurons, and suppression of either PERK or TXNIP attenuates cerebral edema and early brain injury ${ }^{154}$. IRE1 $\alpha$ and its downstream effector XBP1 are also shown to be responsible for TXNIP-induced mitochondrial dysfunction upon RB51 (brucella abortus vaccine strain) infection, without involvement of PERK signalling ${ }^{155}$. Conversely, XBP1-independet control of TXNIP activity by IRE1 $\alpha$ has also been reported in estrogen receptor positive breast cancer ${ }^{149}$. Similarly, IRE1 $\alpha$-microRNA signalling axis has been described to control TXNIP expression and activation of the NLRP3 ${ }^{128}$. Notably, TXNIP can also regulate ER stress by modulating other ER components, including protein disulfide isomerases (PDI) or apoptosis signal-regulating kinase 1 (ASK1) ${ }^{156,157}$.

### 1.3.1.4 Cytokines and Growth factors

Cytokines play a crucial part in immunity and the TME by mediating cell-to-cell communication. The signalling driven by inflammatory, regenerative, and antiinflammatory cytokines modulate the recruitment, development and behaviour of different cell types from the innate and adaptive immune repertoires. For example, in mice, TH17, TH1 or TH2 development is mastered by TGF- $\beta 1$, IFN- $\gamma$ and IL-4, respectively ${ }^{158}$. TXNIP activity is also regulated by cytokines to achieve different
functions in cells. In naïve T cells, TNF $\alpha$ treatment triggers TXNIP downregulation, leading to increased glucose uptake and the activation and differentiation of T cells ${ }^{159}$. Insulin-like growth factor 1, a growth factor which promotes cancer development, negatively regulates TXNIP expression in order to enhance antiapoptotic effects ${ }^{160}$. In addition, IL- $1 \beta$ and TGF $\beta 1$ suppress TXNIP activation in fibroblasts and mesenchymal progenitors, respectively ${ }^{161,162}$. However, TGF- $\beta 1$ can also induce TXNIP expression to achieve transcriptional repression in HL-60 cells ${ }^{163}$. Conversely, TXNIP has also been shown to regulate cytokines production. TXNIP is highly involved in the activation of NLRP3 inflammasome, promoting IL-1 $\beta$ and IL-18 production ${ }^{150}$. In gastric cancer, TXNIP limits the induction of expression of TNF $\alpha$ and COX-2, which is demonstrated to decrease Helicobacter pylori-induced tumourigenesis ${ }^{164}$. Thus, TXNIP expression can be a consequence of combined effects of several cytokines within TME.

### 1.3.1.5 Other regulatory conditions

Additional endogenous and environmental factors have been reported to induce TXNIP expression. Under hypoxia conditions ${ }^{165,166}$, HIF-1 $\alpha$ induction has been shown to increase TXNIP expression. Reversely, TXNIP also causes the degradation and export of HIF-1 $\alpha$, suggestive of a regulatory loop between TXNIP and HIF-1 $\alpha^{167}$. The CISD2 (CDGSH iron sulfur domain 2) protein is reported to regulate TXNIP expression through a process that involves the perturbation of mitochondrial labile iron (mLI), mitochondrial ROS (mROS) and triggered ferroptosis in breast cancer cells ${ }^{168}$. Retinoic acid-mediated TXNIP suppression is found to de-activate hepatic stellate cells and thereby help prevent liver fibrosis and carcinogenesis ${ }^{169}$. In conclusion, TXNIP expression and function is regulated by diverse factors associated with different tissues and conditions, and a complex network of positive and negative regulatory loops.

### 1.3.2 Biological role of TXNIP

So far, TXNIP has been identified to be involved in multiple cellular responses, including oxidative stress, tumour suppression, angiogenesis, drug-induced effects and glycolysis (Figure 1-4).


Figure 1-4. TXNIP is closely involved in various biological processes.
(A) TXNIP and ROS; (B) TXNIP and tumour suppression; (C)TXNIP and drug effects; (D) TXNIP and glycolysis; (E) TXNIP and angiogenesis ${ }^{170}$. For example, TXNIP ${ }^{+}$macrophages tend to be M2-like phenotype and associated with angiogenic endothelial cells, suggesting TXNIP+ macrophages may facilitate angiogenesis ${ }^{170}$.

### 1.3.2.1 TXNIP and Oxidative stress

TXNIP was originally identified as a key regulator of cellular redox and has then been reported to be closely related with ROS levels under different conditions, leading to various cell outcomes ${ }^{97}$. The effect is mainly mediated by its antagonistic effects on Trx by an intermolecular disulphide interaction ${ }^{171}$. Consequently, the TXNIP-Trx binding increases ROS production and oxidative stress ${ }^{134}$. A study, which assessed
blood samples from chronic lymphocytic leukemia (CLL) patients, demonstrated that TXNIP levels robustly correlated with ROS production ${ }^{172}$. Moreover, silence of TXNIP has been demonstrated to decrease ROS levels due to removal of suppressive effects on Trx in macrophages ${ }^{173}$, but overexpressed TXNIP causes high oxidative stress, leading to DNA damage and cell death ${ }^{174}$ and autophagy-related apoptosis ${ }^{175}$. However, in hematopoietic cells, TXNIP acts as an antioxidant protein to prevent oxidative stress and promote cell survival ${ }^{176}$. The mechanism is that TXNIP can directly bind and stabilise p 53 , which has been proved to show antioxidant functions ${ }^{177}$. Conversely, ROS is also shown to regulate TXNIP expression. For instance, oxidative stress can protect Laron syndrome (LS) from cancer induction by increasing TXNIP expression ${ }^{160}$. Additionally, inhibition of ROS generation alleviates Dextran Sodium Sulfate-induced colitis through inhibiting TXNIP-dependent NLRP3 inflammasome ${ }^{178}$. In summary, TXNIP and ROS have a complex relationship and are involved in several feedback loops in order to exert different functions in cells.

### 1.3.2.2 TXNIP and tumour progression

Increased TXNIP expression leads to decreased Trx function which, in turn, leads to decreased Prx function and s-ribonucleotide-reductase function ${ }^{98}$. TXNIP can both induce cell death and inhibit proliferation, thus being regarded to play tumoursuppressing roles in various signalling pathways. TXNIP overexpression leads to G1/S phase arrest by modulating cell cycle regulatory proteins (p27kip1, JAB1, CDK2 and cyclinE) ${ }^{179}$. In contrast, loss of TXNIP facilitates rapid cell division and DNA replication activation, leading to oncogenesis and cell proliferation in breast and lung cancer ${ }^{180,181}$. After shuttling into the mitochondria, TXNIP binds to thioredoxin and abolishes its inhibitory effect on ASK1-mediated apoptosis ${ }^{157}$. In addition, TXNIP is also involved in autophagy and senescence ${ }^{182,183}$. Mechanistically, TXNIP interacts
with REDD1 to form a complex. Since both REDD1 and TXNIP are pro-oxidant protein ${ }^{184,185}$, the formation of this complex has been shown to promote mitochondrial rearrangement and ROS production, further suppressing ATG4B catalytic activity and inducing autophagy ${ }^{184}$. Moreover, TXNIP can promote the differentiation of leukemiainitiating cells and colorectal cancer cells in glycolysis-independent and glycolysisdependent manners, respectively ${ }^{186,187}$. As a result, TXNIP-dependent cell differentiation suppresses oncogenesis ${ }^{186,187}$. Additionally, in HCC, a reduction in TXNIP in cancer cells induced by M2 macrophage-derived exosomes (containing exosomal miR-27a-3p) has been observed to be critical for maintaining cancer 'stemness' and promoting tumour progression ${ }^{130}$.

TXNIP has also been observed to reduce the migratory capacity of tumour cells. Downregulation of TXNIP keeps the $\operatorname{Trx} / \operatorname{Trx}$ reductase (Trx/TrxR) system continually active for epithelial-mesenchymal transition, which increases the metastatic potential of cancer cells ${ }^{188}$. In pancreatic cancer, elevated TXNIP expression leads to repression of malignant transcripts and impairment of metastatic tumorigenesis through the epigenetic reprogramming of chromatin ${ }^{189}$. Similarly, TXNIP mediates the internalisation and degradation of EGFR, decreasing migratory capacity of breast cancer cells ${ }^{190}$. Interestingly, exosomes derived from breast cancer cells, which contains exosomal miR-146a, leads to the decrease of TXNIP expression and subsequent activation of the WNT/ $\beta$-catenin pathway, resulting in the transformation of normal fibroblasts to cancer associated fibroblasts (CAFs) ${ }^{191}$. Reciprocally, activated CAFs promote the invasion and metastasis of cancer cells ${ }^{191}$. However, another study in HCC observes that TXNIP expression is positively associated with the migratory and invasive ability of hepatocellular cancer cells ${ }^{192}$, indicating the double-edged sword roles pf TXNIP in migration of tumour cells.

Nonetheless, TXNIP may also drive tumorigenesis through its association with metabolic disorders. From epidemiological and clinical evidence, cancer patients with diabetes are associated with higher rate of morbidity and mortality in several cancer types ${ }^{193}$. The mechanisms of diabetic stress-associated tumour progression and metastasis include inhibition of anti-tumour immune responses ${ }^{194,195}$, metabolic transcriptional modulation of cancer cells ${ }^{196}$, decellularization of extracellular matrix scaffolds ${ }^{197}$, and even vascular dysfunction ${ }^{198}$. The master roles of TXNIP in fasting, insulin sensitivity and $\beta$-cell apoptosis are well known, and these functions have been linked to an increased risk of diabetes ${ }^{199-200}$. These data collectively suggest TXNIP acts as a driver of metabolic diseases, indirectly contributing to the development of cancers ${ }^{201}$.

### 1.3.2.3 TXNIP and Chemotherapeutic effects

Interestingly, cancer cells, displaying high baseline levels of ROS, are vulnerable to further damage caused by ROS accumulation. A number of studies have shown that increased TXNIP expression can enhance the cytotoxicity of chemotherapeutic agents by modulating the levels of ROS $^{202}$. This anti-tumour strategy is exploited by several agents, including dBET-3, vorinostat, pterostilbene and resveratrol ${ }^{203,204}$. Additionally, platinum-based drugs can also inhibit the activity of TrxR; a process that has been demonstrated to be critical to promote the anti-tumour effects ${ }^{205,206}$.

TXNIP can also enhance treatment efficacy independent of ROS. In oesophageal cancer, cisplatin treatment leads to TXNIP upregulation, mediating its cytotoxicity by an unreported mechanism ${ }^{207}$. In oral cancer, overexpression of TXNIP potentiates the effectiveness of radiotherapy via DNA damage repair pathways ${ }^{208}$. In contrast to cells sensitive to cisplatin, cisplatin-resistant cells exhibit downregulation of TXNIP mRNA mediated by UCA1, suggesting a role of UCA1/ TXNIP axis in contributing to cisplatin
resistance in lung adenocarcinoma ${ }^{209}$. In line with this, exogeneous overexpression of TXNIP in glioma cell lines decreases the IC50 of cisplatin ${ }^{210}$. Combining a TXNIP agonist, D-allose, with chemotherapy or radiotherapy results in enhanced anti-tumour effects in head and neck and lung cancers ${ }^{211,212}$. These studies collectively suggest that increased TXNIP expression mediates or enhances the cytotoxicity of chemo- and radio- therapies.

### 1.3.2.4 TXNIP and tumour angiogenesis

Angiogenesis, another hallmark of cancer, enables tumours to meet nutrient and oxygen needs to sustain proliferative and metabolic requirements. Recent studies reveal the involvement of TXNIP in cancer angiogenesis in both ROS-dependent and independent manners. In conventional renal cell carcinoma (cRCC), immunohistochemical staining in a cohort of 691 patients revealed patients with high TXNIP expression have a marked reduced tumour free survival and a higher occurrence of metastasis. Interestingly, this study showed a significantly positive correlation between TXNIP expression and inefficient vascularisation favouring tumour cell survival ${ }^{107}$. Mechanistically, TXNIP overexpression leads to upregulation of angiogenesis-related proteins (VEGFA, PDGF and ANG2), along with an angiogenic phenotype ${ }^{129}$. In osteosarcoma, different functional subtypes of myeloid cells have been identified by single-cell RNA sequencing analysis. Among them, TXNIP ${ }^{+}$macrophages tend to be M2-like (antiinflammatory phenotype) and express M2 signature markers, including MERTK, MRC1, STAB1 and CD163. Furthermore, ligand-receptor interaction analysis identifies an association between TXNIP ${ }^{+}$macrophages and angiogenic endothelial cells, suggesting TXNIP+ macrophages may facilitate angiogenesis ${ }^{170}$. In contrast, exogenous TXNIP expression in CRC lines (LoVo and HT29) represses angiogenesis ${ }^{122}$. Similarly, inhibition of a cyclin-dependent kinase (p21)
transcriptionally represses TXNIP expression, which consequently promotes endothelial cell invasion, migration and vascular sprouting in breast, lung and prostate cancer cell lines ${ }^{213}$. Thus, these data suggest the important role of TXNIP in angiogenesis.

### 1.3.2.5 TXNIP and glycolysis

Metabolic reprogramming is another hallmark of cancer development and metastasis. Elevated glycolysis is closely associated with the initiation of cancer, producing glucose-dependent ATP and glycolytic intermediates for macromolecular biosynthesis. c- Myc, a well-known modulator of metabolism, mediates metabolic and phenotypic changes in cancer ${ }^{214}$. TXNIP is reported to regulate lipid and glucose metabolism ${ }^{101,215}$ and mediate c-MYC-driven metabolic impacts ${ }^{77,132,180,181}$. For instance, a study in triple negative breast cancer (TNBC) identified that TXNIP suppression by c-Myc can reprogram the metabolic phenotype of cancer cells ${ }^{111}$. Additionally, in ER+ breast cancer, tumour cells can be categorised into different metabolic subtypes dependent on TXNIP expression ${ }^{149}$. For example, MCF7 cells exhibit a mitochondrial oxidative phosphorylation (OXPHOS) phenotype with higher expression of TXNIP. In contrast, low expression of TXNIP in T47D cells display an aerobic glycolysis phenotype ${ }^{149}$. Interestingly, estrogen is shown to repress TXNIP expression and drive the Warburg effect (aerobic glycolysis phenotype) ${ }^{149}$. TXNIP-dependent glucose metabolism is associated with prognosis. In pancreatic cancer, the tumour suppressor FBW7 exerts its anti-tumour effects by controlling glucose metabolism and oxygen consumption in a TXNIP-dependent manner ${ }^{217}$.

Further understanding reveals one of the molecular mechanisms is the association between TXNIP and GLUT family. The GLUT membrane transporter family is crucial in glucose transportation and includes class I (GLUT1-4), class II (GLUT7, GLUT11)
and class III (GLUT6, GLUT8, GLUT12) transporters ${ }^{218}$. TXNIP inhibits the influx of glucose and lactate production by decreasing the expression of class I glucose transporters such as GLUT1 and GLUT4 via both endocytosis and degradation of protein levels and reduction of messenger RNA levels ${ }^{219,220}$. Recently, a class III transporter, GLUT8, has been identified as a central regulator of metabolism, and exhibits a high degree of interaction with TXNIP to promote hexosamine homeostasis ${ }^{221}$. Extracellular matrix remodelling is another critical factor for metabolic regulation extrinsically, as defects in matrix attachment affect cellular metabolism, resulting in a reduction in glucose uptake and subsequent ATP deficiency ${ }^{222}$. Matrix digestion reportedly destabilises TXNIP and enriches GLUT1 transporter at the plasma membrane to promote glycolysis, which is fundamental for both embryogenesis and tumourigenesis ${ }^{222,223}$. All these observations emphasise the critical role of TXNIP in metabolic reprograming.

### 1.3.3 Immune regulation of TXNIP

The tumour-immune cell composition within the TME plays a critical role in cancer progression and the response of tumours to different drug treatments, including targeted, chemo- and immune- therapies. Immune infiltrates are heterogeneous and dynamic in cancer lesions. Cumulative studies have unveiled the important roles of TXNIP on immune regulation. A pan-cancer study recently reports a correlation between TXNIP and infiltration of immune cells, supporting TXNIP as an essential player in immune reprograming within cancer ${ }^{224}$. In addition to its regulation of immune-related signalling pathways and cytokine production, it is also closely involved in the development and maturation of innate and adaptive immune cells. The levels of TXNIP have recently been reported to be negatively associated with the expression of PD-L1, indicating the potential impacts of TXNIP on immune checkpoint molecules (immune
evasion proteins) ${ }^{225}$. However, whether other immune checkpoints are regulated by TXNIP needs to be further studied.

### 1.3.3.1 TXNIP and NF-KB signalling

TXNIP can exert effects on the immune system in multiple manners. As an intracellular amplifier of oxidative stress and inflammasome activation ${ }^{226}$, TXNIP is detected in different cell types (such as tumour cells, immune cells and stromal cells). In endothelial cells, nuclear translocation of TXNIP leads to NF- $\kappa \mathrm{B}$ activation, which facilitates the expression of pro-inflammatory cytokines such as IL-1 $\beta^{227,228}$. However, in tumour cells, TXNIP suppresses TNF- $\alpha$-induced NF- $\kappa \mathrm{B}$ activity and subsequently inhibits hepatocarcinogenesis ${ }^{229}$.

### 1.3.3.2 TXNIP and NLRP3 inflammasome

Activation of NLRP3 inflammasome has been observed in diverse physiological and pathological conditions, such as caloric restriction ${ }^{136}, \mathrm{~T} 2 \mathrm{D}^{230,231}$, preeclampsia ${ }^{232}$, Alzheimer's disease ${ }^{233}$ and cancer. The NLRP3 inflammasome is known to be closely involved in the cancer-immunity cycle ${ }^{80}$ and has both anti-tumorigenic and protumorigenic roles. On one hand, NLRP3 contributes to various types of cell death, such as pyroptosis, apoptosis, necroptosis, and ferroptosis ${ }^{234}$. Accordingly, pharmacological stimulation of NLRP3 appears to control sphere formation of tumour cell lines ${ }^{235}$. In colitis and colitis-associated colorectal cancer contexts, IL-18 induced by the NLRP3 pathway helps to maintain a normal epithelial barrier and suppress tumour growth ${ }^{236}$. Mechanistically, tumour cell death leads to inflammasome activation and IL-18 secretion in Kuppfer cells, a process required for effective NK-cell-mediated tumour cytotoxity ${ }^{236}$. On the other hand, although inflammasome-inducing IL- $1 \beta$ can activate dendritic cells (DCs) to facilitate adaptive anti-tumour immune activation ${ }^{237}$, it has also been reported to expand MDSCs to drive immunosuppression ${ }^{238}$.

Numerous studies have uncovered a link between TXNIP and NLRP3 inflammasome activation, mostly due to the functions of the Trx 1/ TXNIP axis in ROS regulation ${ }^{231239}$. However, this is not always the case, as Trx1 can lead to NLRP3 inflammasome activation independently of TXNIP ${ }^{240}$. Additionally, STING can also trigger the TXNIP-NLRP3 interaction, leading to NLRP3 inflammasome activation without the involvement of Trx1 ${ }^{241}$. Similarly, CXCR4 can directly bind to TXNIP and induce NLRP3 inflammasome activation without affecting the activity of $\operatorname{Trx} 1^{242}$. The UPR signalling is another player that regulates inflammasome activation via TXNIPdependent mitochondrial dysfunction regulation, rather than through direct modulation of ROS level ${ }^{155}$. Together, these data indicate both Trx1 and TXNIP can also induce the activation of NLRP3 inflammasome independently of the modulation of Trx1/ TXNIP balance and ROS regulation.

### 1.3.3.3 TXNIP regulates innate immune cells

In addition to its roles in NF-kB and the inflammasome-mediated inflammation, TXNIP is also closely involved in regulating the generation, development and functionality of diverse innate immune cells. A study with TXNIP-deficient mice demonstrated the requirement for TXNIP in the normal functions of DCs, including secretion of the proinflammatory cytokines including IL-12 and IL-6 and the further activation of T cells ${ }^{243}$. These findings suggest that TXNIP has a role in modulating the function of innate immune cells.

Several studies have also highlighted the importance of TXNIP in the development of NK cells. In TXNIP ${ }^{-/-}$mice, the number of NK cells is severely reduced, along with the decreased expression of the maturation marker CD122. However, the development of T and B cell populations are not impaired in mice loss of TXNIP ${ }^{244}$. TXNIP ${ }^{-/}$NK cells are also deficient in IFN- $\gamma$ production and cytotoxicity, indicating an indispensable role
of TXNIP in maintaining the function of NK cells ${ }^{244}$. Another study has also demonstrated the similar role of TXNIP required for the differentiation of NK cells ${ }^{245}$. Moreover, TXNIP is essential for tumour-infiltrating NK cells. The core of tumours, where NK cells reside, is with high ROS levels. The underlying mechanism for tumourinfiltrating NK cells to confer resistance to oxidative stress is due to retaining of TXNIP in the nucleus and consequently higher activity of Trx-1 against the damage caused by ROS, which further promotes anti-tumour immune responses ${ }^{246}$.

TXNIP is also reported to regulate myeloid lineage. When comparing gene signatures between non-activated and activated polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) from murine models, TXNIP expression appears to be upregulated in the activated group. These findings indicate that TXNIP may have a role in maintaining immune-suppressive activity ${ }^{247}$. Tumour-associated macrophages (TAMs) are abundant in the TME of solid tumours and promote tumour development by suppressing immune responses. In pancreatic ductal adenocarcinoma, TXNIP expression is upregulated in TAMs, and this is driven by KRAS activity in cancer cells. The high expression of TXNIP in TAMs contributes to metabolic changes which are required for macrophage polarisation and the promotion of pro-tumour responses ${ }^{248}$. Thus, these studies suggest the pro-tumorigenic activity of TXNIP by supporting immune-suppressive immune cells.

### 1.3.3.4 TXNIP and Adaptive immune compartment

The role of TXNIP in adaptive immunity is more complex than in the innate compartment, affecting multiple B and T cell subtypes. TXNIP contributes to the development and secretome of adaptive immune cells. signalling In melanoma for instance, TXNIP expression is enriched in the memory T cell compartment ${ }^{249}$. CPT1a, induced by CD28 signals, is a master of fatty acid oxidation and drive mitochondrial
respiratory functions, which is essential for protective memory T cells generation and future T cell activation ${ }^{250,251}$. However, TXNIP is observed to inhibit CPT1a expression, resulting in the interference of the generation of memory T cells ${ }^{250}$. Collectively, TXNIP-dependent degradation of CPT1a leads to memory T cells metabolically compromised and reduced the formation of memory T cells ${ }^{250}$.

Dual anti-CD3/anti-CD28 stimulation on T cells suppresses TXNIP expression. TXNIP suppression has mainly been attributed to anti-CD3, as anti-CD28 co-stimulation alone has minor effects on the levels of TXNIP expression ${ }^{250,252}$. The activation of T cells is, at least to some extent, due to anti-CD3-mediated suppression of TXNIP; a process potentially abolishes inhibitory impacts of TXNIP on transcriptional activation of targeted genes, especially for genes associated with T cell activation, differentiation, cytokine signalling as well as cell death pathways signalling ${ }^{253}$. Notably, despite T cells showing higher levels of glucose uptake with anti-CD3/anti-CD28 stimulation, these metabolic changes are independent of TXNIP-mediated regulation of glycolysis ${ }^{252}$.

Co-stimulatory signals are required for robust activation of T cells after TCR-MHC complex engagement, including signals from the tumour necrosis factor receptor superfamily (TNFRSF) members. Similar co-stimulatory signals (CD3/CD28 stimulation), TLR2, 4, and 5 agonists inhibit TXNIP expression partially through TNF $\alpha$ production. The reasonable mechanism for induced TXNIP suppression could be that downregulating TXNIP facilitates cell cycle entry and contributes to meet the higher glucose uptake demands, optimal for T cell proliferation and activation ${ }^{159}$. TXNIP also appears to be indispensable in the restriction of T cell (more pronounced in $\mathrm{CD}^{+} \mathrm{T}$ cells) and germinal centre B cell expansion following viral infections, a process that relies on Trx1/TXNIP balance ${ }^{252}$. However, similar to a study by Yang et al ${ }^{246}$, Muri et al also
found that ablation of TXNIP does not affect the development and homeostatic maintenance of T cells, B cells and myeloid cells ${ }^{252}$.

Regulatory T cells (Tregs) are immunosuppressive cells crucial for the inhibition of effector and cytotoxic T cell responses. The roles of Tregs in tumour induction varies depending on the specific subtype of Tregs, and has been shown to predict various clinical outcomes ${ }^{254,255}$. The plasticity and stability of Tregs is regulated by cellular metabolism ${ }^{255}$. A recent study highlights the requirement of MondoA -TXNIP axis in maintaining the identity and functionality of Tregs by repressing glycolysis in colorectal cancer ${ }^{256}$. Inhibition of MondoA or TXNIP in Tregs leads to the upregulation of glycolytic genes and the increase of glycolytic activities. Elevated glycolysis compromises the immuno-suppressive function of Tregs ${ }^{256}$. Mechanistically, glycolysis reduces FOXP3 and ROR $\gamma$ t expression, but promotes a switch to a Th17-like effector phenotype in Tregs producing more IL-17A, which can be reversed by TXNIP activation. Accordingly, intra-tumoral Tregs generally are presented with increased glycolytic pathway, resulting in a pro-tumour immune microenvironment ${ }^{256,257}$.

Germinal centres (GCs) are the sites of antigen-stimulated B cells proliferation and differentiation ${ }^{258}$. In GCs, antigen-activated B cells not only produce high-affinity antibodies through somatic hypermutation (SHM) on immunoglobulin genes, but also produce antibodies with specialized functions via class-switch recombination (CSR). GC B cells express high levels of BCL-6 that help modulate GC formation through several different mechanisms. These mechanisms include inducing the GC to undergo SHM and CSR, supressing premature B cell activation prior to GC formation and inhibiting B cell differentiation ${ }^{259,260}$. TXNIP is reported to promote GCs development by suppressing BCL-6 activity. In support of this, TXNIP ${ }^{-/-}$mice exhibit large secondary follicle with a GC-like structure and a higher population of $\mathrm{Ki}-67^{+} \mathrm{B}$ cells in the
spleen ${ }^{261}$. TXNIP has also been shown to be expressed at different stages of B cell development. As a central metabolic gatekeeper, TXNIP restricts glucose and energy supplies, which are essential for pre-B cell development ${ }^{215}$. Additionally, deletion of TXNIP provides strong survival advantage and rescues prednisolone-induced cell death in pre-B Acute Lymphoblastic Leukemia cells (ALL) as a result of removal of ATP production ${ }^{215}$. Collectively, TXNIP has been shown to be essential in the maintenance and activation of different adaptive immune cell types.

### 1.3.4 TXNIP-targeting therapeutics

As we have discussed, it is clear that TXNIP is closely associated with multiple biological functions, especially for TXNIP-mediated perturbation in thioredoxin antioxidant system, that are critical for the development of several pathological processes. Indeed, a fine regulation of ROS levels is critical for cellular life. Thus, TXNIP-mediated ROS regulation is undoubtedly regarded as an essential therapeutic target. Consequently, there are a number of therapeutic strategies currently aimed at modulating TXNIP for clinical application.

TXNIP can promote diseases by regulating oxidative and glycolytic stress, inflammation, and by inhibiting the cell cycle. These notions are supported by accumulating evidence that loss of TXNIP by pharmacological inhibition or genetic TXNIP deletion show protective roles from neurological diseases and diabetes in murine models ${ }^{262,263}$. TXNIP antagonists have been comprehensively reviewed by Qayyum et al ${ }^{264}$. Briefly, TXNIP antagonists consist of small-molecule drug, phytochemicals and peptides. Two old drugs, verapamil (NCT02372253) and Taurine (NCT01226537), that modulates TXNIP levels are currently being tested in clinical trials for the treatment of type 1 and 2 diabetes in clinical trials. Verapamil, a nondihydropyridine L-type calcium channel blocker traditionally used orally for the
treatment of hypertension, inhibits TXNIP expression ${ }^{265}$. Taurine, used for glycemic control in diabetic patients, is also reported to increase TXNIP expression ${ }^{266}$. A recent high-throughput screening has identified SRI-37330, a small molecule TXNIP inhibitor, which significantly decreased glucagon secretion, hepatic glucose output and efficiently treating diabetes ${ }^{267}$.

In the context of cancer treatment, TXNIP agonists hold great potential as anti-tumour agents. Several studies identified that the induced TXNIP expression mediates different types of cancer treatments. For example, targeted therapies in breast cancer such as trastuzumab, cetuximab and lapatinib -which block HER-1/2 pathway- highly increase TXNIP expression and cause G1 cell cycle arrest and apoptosis ${ }^{145}$. Additionally, in triple-negative breast cancer (TNBC), silibinin, used in the treatment of toxic liver damage, has been shown to upregulate TXNIP, which suppresses glycolysis and cell proliferation in cancer cells ${ }^{268}$. Importantly, TXNIP agonist 3-O-methylglucose has been shown to enhance the cytotoxicity of cisplatin in treating non-small-cell lung cancer ${ }^{269}$. Therefore, TXNIP agonists may have great potential as treatment strategies in cancer.

### 1.4 Growth Differentiation Factor 15 (GDF15)

In this thesis, we explored the downstream target(s) which potentially mediated the immune-regulatory effects of TXNIP after chemotherapy treatment. Since TXNIP is able to regulate the expression of cytokines ${ }^{150,164}$, it is reasonable to hypothesise that secreted factors (cytokines) could mediate its effects. Therefore, we performed proteomic analysis and found out TXNIP was a regulator of Growth Differentiation Factor 15 (GDF15) upon chemotherapy treatment. Further analyses identified the importance of GDF15 in immune regulation.

GDF15, also known as macrophage inhibitory cytokine 1, was first found in 1997 to be expressed in macrophages and required for its activation ${ }^{270}$. Human GDF15 is the product of a simple 2 exon gene, located on chromosome 19p12-13.1, with 309 bp exon I, 891 bp exon II and a single 1820 bp intron ${ }^{271}$. It is a distant member of the TGF- $\beta$ superfamily, consisting of ligands including TGF- $\beta$ s, activins, bone morphogenetic proteins (BMPs) and GDFs. Under quiescent, non-activated conditions, GDF15 expression is at low level in most tissues ${ }^{272}$. However, GDF15 significantly increases upon pathological stresses in various diseases, such as metabolic disease and cancer ${ }^{273,274}$. The following sections detail relevant GDF15 actions in the context of this thesis.

### 1.4.1 Membrane receptors of GDF15

It has been reported that GDF15 can bind to different receptors on the cell surface, including transforming growth factor-beta receptor, GDNF-family receptor a-like (GFRAL) and CD48 receptor.


Figure 1-5. Summarization of membrane receptors of GDF15, including TGF- $\beta$ receptor, GFRAL and CD48, and the downstream signalling pathways.
(Left panel) GDF15 binds to TGF- $\beta$ receptors, leading to the phosphorylation of SMAD2/3 and SMAD1/5/8; (Middle panel) GDF15 binds GFRAL to regulate energy homeostasis and body weight; (Right panel) The binding between GDF15 and CD48 accumulates FOXP3 in Tregs.

### 1.4.1.1 Transforming growth factor-beta (TGF-6) receptor

Dysfunction of TGF- $\beta$ signalling promotes the progression of cancer by exerting different aspects of effects on cancer cells. In addition to its regulation on proliferation and invasion of cancer cells, cancer stem cell properties and drug resistance, TGF- $\beta$ signalling can also modulate tumour microenvironment by suppressing both innate and adaptive immune system ${ }^{275,276}$. The activation of TGF- $\beta$ signalling leads to the heteromeric complex consisting of type I receptors, type II serine/threonine kinase receptors and the subsequent activation of downstream targets, SMAD transcription factors ${ }^{277}$. As a family member of TGF- $\beta$, GDF15 shares the same receptors with TGF$\beta$ and has been reported to modulate several downstream targets of TGF- $\beta$ signalling pathways. For example, in leukocytes, the binding of GDF15 to ALK-5 (type I receptor) results in the transphosphorylation of ALK-5 by TGF- $\beta$ receptor II, which further inactivates leukocyte integrin activity and dampens neutrophil recruitment ${ }^{278}$.

Generally, the binding of GDF15 to TGF- $\beta$ receptors leads to the phosphorylation of SMAD2/3 and SMAD1/5/8, which in turn form complexes with SMAD4 to mediate their transcriptional responses. GDF15-dependent SMADs signalling pathways are crucial in a variety of biological processes. For instance, GDF15-induced activation of SMAD2/3 signals is essential for the regulation of oxidative metabolism and the maintenance of M2-like phenotype in macrophages ${ }^{279}$. During systemic inflammation, GDF15 induction activates SMAD1/5 downstream of the TGF- $\beta$ RI, contributing to the suppressive activity of CD56 ${ }^{\text {bright }} \mathrm{NK}$ cells ${ }^{280}$. Notably, the finding that nuclear GDF15 is also reported to blunt SMAD-DNA binding has shown GDF15 can also decrease

TGF- $\beta$ signalling ${ }^{281}$. However, the effects induced by GDF15-TGF- $\beta$ receptors binding can be SMAD-independent as well. In hypothalamic neurons, instead of regulating classical SMADs regulatory pathway, GDF15-mediating TGF $\beta$ receptor activation subsequently reduces neuropeptide Y mRNA expression and increases proopiomelanocortin (POMC) mRNA, leading to the activation of phosphorylated signal transducer. Consequently, the whole process results in cancer-associated anorexia and weight loss ${ }^{282}$. In addition, AKT/mTOR signalling has also been shown to be activated by GDF15-TGF- $\beta$ RII binding in SMAD-independent manner ${ }^{283}$.

### 1.4.1.2 GDNF-family receptor a-like (GFRAL)

GFRAL is another well-known cognate receptor of GDF15. GFRAL is relatively more expressed in specific brain regions, such as the substantia nigra, the hippocampus and especially hindbrain neurons ${ }^{284}$. Recent observation that ablation of MT1-MMP restored GFRAL expression indicated the negative regulatory role of MT1-MMP in GFRAL expression regulation ${ }^{285}$. Given that the GDNF family members are wellknown neurotrophic factors, supporting the survival of a range of target neurons, GDF15-GFRAL signalling are proposed to be involved in the regulation of brain cells' functions. Accordingly, GDF15-GFRAL signalling axis is reported to regulate energy homeostasis and body weight physiologically. Moreover, activation of this signalling initiates anorexia/cachexia syndrome pathologically in preclinical models ${ }^{286,287}$. Consistently, this finding was supported by the clinical evidence indicating the positive association between serum GDF15 levels with weight loss in patients with cancer ${ }^{288}$. Additionally, pharmacological blocking of GDF15/GFRAL axis alleviates cancer cachexia ${ }^{289,290}$.

GDF15 binding leads to the formation of a complex with GFRAL and a coreceptor RET. The GDNF-like cysteine-rich domain C1-C2 of GFRAL is responsible for GDF15
binding but intact GFRAL protein is required for RET association ${ }^{286}$. Commonly, GFRAL-mediated signal transduction is dependent on engagement with its coreceptors, RET. RET depletion compromises GDF15/GFRAL-mediated signalling ${ }^{286,291}$. However, some studies argued that RET might not be necessary to transmit the signals induced by GDF15-GFRAL binding ${ }^{292}$. Valine 87 or isoleucine 89 in GDF15 are critical residues for binding GFRAL are. Another residue, tryptophan 32 in GDF15, has been revealed to mediate the action of GDF15/GFRAL axis ${ }^{286,293}$. Mutation of the tryptophan at position 32 attenuates GDF15/GFRAL-mediated signalling, but without affecting the interaction between GDF15 and GFRAL ${ }^{286,293}$.

### 1.4.1.3 CD48 receptor (SLAMF2)

A recent study found that CD48 on Tregs is another receptor of GDF15. GDF15-CD48 binding mediates the production of peripherally derived inducible Treg (iTreg) cells and maintains the suppressive function of natural Treg (nTreg) cells ${ }^{294}$. CD48 is a type of surface receptors, belonging to the signalling lymphocyte activation marker (SLAM) family, and plays an important role in regulating immune cells functions. CD48 is reported to be expressed on almost all hematopoietic cells ${ }^{295}$. The classic ligands of CD48 include CD244 and CD2 and the ligand-receptor binding promotes the crosstalk between immune cells and immune cells or other cell types ${ }^{295}$. In hepatocellular carcinoma, GDF15 has been found to interact with CD48. The GDF15-CD48 interaction leads to the downregulation of an E3 ubiquitin ligase STUB1 and accumulation of FOXP3, a lineage specification factor critical for the development of Tregs ${ }^{296}$. Consequently, deletion of CD48 or treatment with GDF15 neutralizing mAbs in hepatocellular carcinoma increases the response of patients to anti-PD-L1 antibody treatment and markedly prolongs survival ${ }^{294}$.

### 1.4.2 Regulation of GDF15

GDF15 is expressed at low levels in most tissues under normal state, yet relatively abundant in liver ${ }^{297}$, intestine ${ }^{298}$, kidney ${ }^{299}$ and placenta ${ }^{271}$. The basal transcriptional regulation of GDF15 is determined by sp1 transcription factors ${ }^{300}$. As a ubiquitous cellular stress signal, endogenous GDF15 could be induced in a variety of cell types under different physiological and pathological stress conditions, including exercise, aging, diabetes, cancer and even drug consumption ${ }^{301,302}$. Molecular mechanisms responsible for modulating the levels of GDF15 in cells include transcriptional and epigenetic regulation and protein degradation ${ }^{303}$.

### 1.4.2.1 GDF15 regulation in Non-cancer contexts

## Exercise and injury

Exercise is observed to significantly increase plasma GDF15 ( $\sim 295 \mathrm{pg} / \mathrm{ml}$ vs $\sim 215$ $\mathrm{pg} / \mathrm{ml}$ at rest). At the end of recovery, GDF15 further increases to $\sim 350 \mathrm{pg} / \mathrm{ml}^{304}$. However, skeletal muscle is not the source of GDF15 induced by exercise although it can release GDF15 under certain conditions ${ }^{304,305}$. Therefore, the responsible organ(s) need to be further studied. Exercise-induced GDF15 observed in circulation works on neurons, contributing to energy homeostasis ${ }^{304,306}$.

Injury is another condition to induce the expression of GDF15. For example, post renal ischemia-reperfusion injury (IRI), GDF15 increases as early as 2-4 hours, and high levels can be remained for a long period (even 12 months) ${ }^{307,308}$. Cardiomyocytes is the source of GDF15 in the infarcted heart, playing cardioprotective roles via activating phosphoinositide 3-OH kinase (PI3K) /AKT signalling pathway ${ }^{309}$. However, GDF15 has been also observed to be activated after acute injury and further induce harmful effects on retinal ganglion cell ${ }^{310}$.

## Diabetes

GDF15 is markedly elevated in patients with obesity ${ }^{311}$. Interestingly, there is no difference in GDF15 mRNA expression in adipose tissue between lean and obese individuals ${ }^{311}$. The activation of the integrated stress response (ISR) by hypoxia, the unfolded protein response (UPR) and inhibition of histidyl tRNA synthetase have been observed to cause the induction of GDF15 in a PERK-ATF4-CHOP signalling dependent manner, indicating the important role of ISR in regulating GDF15 expression ${ }^{312}$. Overexpression of GDF15 in adipocytes by activating ISR results in suppression of appetite and a reduction in the risk of obesity ${ }^{313}$, suggesting a protective role of GDF15 against obesity.

## Mitochondrial functions

AMP-activated protein kinase (AMPK) is a master regulator of mitochondrial function, modulating multiple enzymes involved in mitochondrial homeostasis ${ }^{314}$. One study demonstrated that activation of AMPK in mice resulted in increased GDF15 expression. In contrast, GDF15 expression was blunted in AMPK $\beta 1$-isoform deficient mice, suggesting that GDF15 is a downstream target of AMPK. Importantly, although AMPK activation induces ER stress (especially ATF4/CHOP pathway) and the CHOP/ATF4 signalling is reported to regulate GDF15 expression ${ }^{298,315}$, AMPK-induced GDF15 expression is CHOP-independent ${ }^{316}$. Additionally, peroxisome proliferator-activated receptor $\gamma(\operatorname{PPAR} \gamma)$, another essential factor in maintaining oxidative metabolism and mitochondrial biogenesis, is observed to stimulate GDF15 expression in macrophages ${ }^{317}$. A low ratio of NAD/NADH is also associated with GDF15 induction, further suggesting that GDF15 is a potential mitochondrial stress-induced cytokine ${ }^{318}$. Inflammation and infection

Proinflammatory cytokines, such as TNF $\alpha$, IL1 $\beta$, and IL6, are observed to induce GDF15 expression ${ }^{270}$. In addition, NF- $\kappa$ B, a major regulator of pro-inflammation, can also induce GDF15 expression by binding exon 2 of GDF15 gene to promote transcription ${ }^{319}$. Collectively, these data suggest the close relationship between inflammation and GDF15. During uncontrolled systemic inflammation, elevated levels of circulating GDF15 are associated with enhanced morbidity and an increased risk of septic complications. The potential reason is that GDF15 mediates tolerance to inflammatory damage by regulating hepatic triglyceride production, supporting metabolic demands of the heart and protecting heart from damage ${ }^{320}$. In addition, increased circulating GDF15 is observed in acute inflammatory models of infection and sepsis including lipopolysaccharide (LPS). However, despite the important role of GDF15 in weight loss and anorexia, GDF15-neutralizing antibody do not reverse anorexia induced by LPS ${ }^{321}$. Upregulation of GDF15 by LPS in serum could possibly be explained by its role as an anti-inflammatory regulator, which suppresses inflammation attacks ${ }^{322}$. In support of this, the addition of recombinant human GDF15 protein (rhGDF15) decreases the generation of proinflammatory cytokines, and inhibits the activation of T cells ${ }^{323}$.

Both viral and bacterial infection have also been shown to induce the expression of GDF15, especially in liver and kidney ${ }^{320}$. For example, GDP15 expression is increased in cells infected with the human papillomavirus type 8 E7 oncoprotein (HPV8-E7) ${ }^{324}$. However, upregulation of GDF15 in the body/serum does not affect pathogen control, evidenced by the observation that blockade of GDF15 with neutralizing antibody does not change bacterial titers in peritoneal lavage fluid or viral load in the bronchoalveolar lavage fluid ${ }^{320}$, suggesting that GDF15 does not directly participate in eliminating
pathogens. Indeed, GDF15 promotes the tolerance to inflammatory damage via metabolic reprogramming ${ }^{320}$.

### 1.4.2.2 GDF15 regulation in tumour-relevant condition

Oncogenes and tumour suppressor genes play important roles in regulating GDF15 expression. Aurora kinase A (AURKA), a tumour oncogene, promotes the production of GDF15, while blocking AURKA compromises GDF15 production in cancer cells ${ }^{325}$. Moreover, tumour suppressors, such as p53, GSK- $3 \beta$ and EGR-1, can also induce GDF15 expression ${ }^{303}$. So far, two p53 binding sites have been identified in the promoter region of GDF15 gene ${ }^{277,326}$. In support of this, experiments in HCT116 cells have identified that GDF15 expression is highly dependent on p53 expression. GDF15 expression induced by p53 has been shown to inhibit tumour cell growth ${ }^{277}$, but decreased chemotherapy-induced apoptosis ${ }^{327}$. Additionally, genetic deletion of p53 abolishes the increased serum of GDF15 and GDF15-mediated weight loss upon cisplatin challenge ${ }^{328}$.

Hypoxia is a hallmark of cancer, facilitating the formation, progression and metastasis of tumours ${ }^{329}$. GDF15 expression has also been reported to be induced under anoxia condition. Interestingly, the regulation of GDF15 is independent of on the hypoxia inducible factor 1 , a key mediator of the anoxia response ${ }^{326}$. Until now, the molecular mechanism mediating hypoxia-induced GDF15 is still elusive.

### 1.4.2.3 Drug consumption

GDF15 expression changes in response to exogenous drugs such as metformin, colchicine, AICAR, chemotherapy, chemo-preventive dietary compounds and nonsteroidal anti-inflammatory drugs (NSAIDs) ${ }^{281,301}$. After metformin treatment, GDF15 is increased predominately in the kidney and distal intestine, which contributes
to metformin-mediated improved lifespan in patients with diabetes ${ }^{298,330}$. The mechanism is that GDF15 is responsible for metformin-mediated energy balance and weight loss by binding GFRAL ${ }^{298}$, suggesting GDF15 levels mediate the response to metformin. Notably, increased GDF15 expression following metformin treatment is dependent on ISR signalling, especially ATF4 and CHOP proteins ${ }^{331}$. In addition to metabolic modulating drugs, chemotherapies, such as docetaxel and mitoxantrone, promote GDF15 expression in prostate cancers, which results in decreased drug sensitivity ${ }^{332}$. Additionally, NSAIDs have also been shown to increase the levels of GDF15 protein in a NRF2-dependent manner to suppress inflammation ${ }^{333}$.

### 1.4.3 The functions of GDF15 in cancer

Accumulating studies revealed multifunctional roles of GDF15 in controlling biological events. In the nervous system, GDF15 controls food intake and body mass via GFRAL as previously mentioned. In addition, as a neuronal survival factor, GDF15 also helps to enhance of hippocampal neural stem cell proliferation and neuronal differentiation, the repair of crushed optic nerve and regeneration of the peripheral nervous system ${ }^{334,335}$. In metabolic disorders, such as diabetes and obesity, glucose intolerance is decreased when overexpressing GDF15 or administrating recombinant GDF15 protein in a murine model ${ }^{336}$. Importantly, GDF15 has pleiotropic functions and may differ in various types of cancer ${ }^{337}$. Similar to other TGF $\beta$ family members, although substantial increases in GDF15 expression are observed in cancer cells ${ }^{338,339}$. The roles of GDF15 may differ during different stages of cancer tumorigenesis.


Anti-tumour


Figure 1-6. GDF15 shows both pro-tumour and anti-tumour effects.
(Left panel) On left panel, GDF15 promotes cell survival, metastasis and chemoresistance; (Right panel) On right panel, GDF15 facilitates cell apoptosis and decreases inflammation.

### 1.4.3.1 Pro-tumorigenic effects of GDF15

It is well-documented that elevated GDF15 expression is related to poor prognosis in cancer, suggesting it is pro-tumorigenic. GDF15 has been identified to be involved in different oncogenic processes, including cancer initiation, proliferation, metastasis, drug sensitivity and cancer recurrence. Expectedly, GDF15 has several roles in modulating the response of tumour cells and their surrounding microenvironment.

## GDF15 and tumour cell survival and proliferation

Several studies have identified a role of GDF15 in driving tumour cell proliferation. In prostate cancer, an oligonucleotide microarray screen of more than 8900 genes identified that malignant tissues show higher GDF15 expression compared to normal tissues ${ }^{340}$, indicating the role of GDF15 in malignant transformation. Additionally, GDF15 exhibits increased expression in prostatic androgen-independent cell models compared to androgen-sensitive cell models, suggesting GDF15 is involved in the progression of hormone-refractory behavior ${ }^{341,342}$. Similarly, GDF15 promotes
malignant progression of breast and gastric cancer cells by inducing the activation of AKT/ERK/mTOR signalling ${ }^{343}$. To be noted, GDF15 is found to be expressed in both tumour-associated macrophages (TAMs) and cancer cells in esophageal squamous cell carcinomas, and secreted GDF15 is associated with cancer cells growth and poor prognosis ${ }^{344}$. Moreover, to facilitate hepatocellular carcinoma progression, hepatic stellate cells (HSCs) produce GDF15 to form a pro-tumoral microenvironment ${ }^{345}$. When co-cultured with hepatoma cells, HSCs increase the secretion of GDF15 in an autophagy-dependent manner, resulting in increased proliferation of hepatoma cells by activating ERK/AKT signalling ${ }^{345}$.

## GDF15 and tumour metastasis

In CRC patients, circulating GDF15 concentration has been observed to be elevated, and further increase when metastasis occurs ${ }^{346}$, suggesting GDF15 is positively associated with metastasis of CRC. Similarly, GDF15 induced by NF-кB signalling pathway facilitates metastasis of breast cancer cells to bone tissue, which can be blocked by inhibition of the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) ${ }^{347}$. Additionally, activated GDF15 signalling is observed in metastatic variants, promoting the mobility of tumour cells and the migration of prostate cancer cells ${ }^{348,349}$. To be concordant, overexpression of GDF15 leads to prostate cancer bone metastasis and colonization ${ }^{350}$. Loss of GDF15 has also been shown to prevent EMT phenotype and alleviate invasion through IGF-1R-FoxM1 signalling in breast cancer ${ }^{351}$.

## GDF15 and drug resistance

GDF15 has also been reported to modulate the response of cancer cells to drug treatment. For example, activation of autophagy by challenging breast cancer cell lines with divergent autophagy inducers, such as tamoxifen, trastuzumab, bortezomib or
rapamycin, promotes GDF15 upregulation and high levels of GDF15 is associated with poor prognosis, suggesting that GDF15 is part of an autophagy signature and mediates autophagy-driven chemoresistance ${ }^{352}$. Moreover, GDF15 is positively associated with stemness and chemo-radiotherapy resistant markers in cancer cells. Interestingly, knockdown of GDF15 leads to the decreased expression of these markers ${ }^{353,354}$. Together, these data suggest that GDF15 expression may help promote drug resistance by enabling tumour cells to adapt to their surrounding environment. Potential GDF15 driven adaptation mechanisms include maintenance of cell stemness, activation of oncoproteins and modulation of drug resistance markers.

## GDF15 mediating cross-talk among tumour microenvironment

The tumour microenvironment, which includes an array of components such as adipocytes, immune cells, blood vessels, fibroblasts, signalling molecules, and the extracellular matrix, is indispensable to tumour as a whole ${ }^{355}$. The crosstalk between the different cell types within the TME leads to different outcomes ${ }^{356}$. GDF15 has been shown to modulate the interaction between various cell types within TME. For example, GDF15 derived from cancer cells stimulates vasculature development in melanoma ${ }^{357,358}$. Yet, several studies have also shown secreted GDF15 has potential anti-angiogenic effects in the $\mathrm{TME}^{326}$.

GDF15 is involved in the regulation of different immune cells. High levels of GDF15 are associated with decreased lymphocyte infiltration in tumours, suggesting an association between GDF15 and immune cells ${ }^{359}$. GDF15 released by tumour cells blunts the killing activity of macrophages and suppresses macrophage surveillance during tumourigenesis ${ }^{319}$. The administration of recombinant GDF15 protein significantly reduces T-cell stimulatory activity of tumour-associated macrophages, promoting resistance to anti-PD1 therapy in mice model ${ }^{325}$. Expectedly, GDF15
knockdown in tumour cells deprives of the generation of $\mathrm{CD} 11 \mathrm{~b}^{+} \mathrm{PD} 1^{+}$cells and confers tumour-associated macrophages (TAMs) with enhanced phagocytic activity and T-cell stimulatory activity ${ }^{325}$. Dendritic cells (DCs) are professional antigen-presenting cells to link innate and adaptive immune responses ${ }^{360}$. During DCs maturation, GDF15 treatment leads to surface protrusion retraction, accompanied by decreased expression of maturation and costimulatory markers, suggestive of the inhibitory anti-tumour effects of GDF15 by regulating DCs function ${ }^{361}$. Additionally, GDF15 has also been found to mediate the immune-suppressive effects on NK cells and T cells in glioma ${ }^{362}$. Together, GDF15 has inhibitory effects on different immune cell types.

Cancer-associated fibroblasts (CAFs) are among cell types abundant in the tumour stroma, and have a variety of functions including matrix deposition and remodelling, extensive reciprocal signalling interactions with cancer cells and crosstalk with infiltrating leukocytes ${ }^{363}$. In prostate and pancreatic cancers, CAFs are also found to be another source of GDF15 $5^{339,364}$. Overexpression of GDF15 in fibroblasts stimulates cancer cells to grow and migrate in paracrine signalling ${ }^{339}$. Similar effects of CAFderived GDF15 are also observed on leukemia cells. Indeed, CAFs are found to promote chemo-resistance in acute myeloid leukemia (AML) via secretion of GDF15 ${ }^{364}$. Genetic and pharmacologic deletion of GDF15 in CAFs increases drug-induced cytotoxicity in leukemic cells, suggesting an important contribution of GDF15 in establishing CAFmediated chemoprotective niches ${ }^{364}$. Additionally, GDF15 expressed by bone marrow mesenchymal stem cells facilitates the proliferation of myeloma cells by activating AKT-dependent siganling ${ }^{365}$. Therefore, GDF15 plays an important role in mediating crosstalk among different cell types within the TME.

### 1.4.3.2 Anti-tumorigenic effects of GDF15

Although the role of GDF15 in promoting tumorigenesis has been highlighted in numerous studies, solid evidence has documented that GDF15 also has antitumorigenic effects. GDF15 is shown to affect cancer cell proliferation, leading to high rates of cellular apoptosis and inhibition of tumours growth ${ }^{366,367}$. For example, in glioblastoma, overexpression of GDF15 inhibits tumour growth and decreases tumour volume in nude mice ${ }^{326}$. GDF15 has similar tumour-inhibiting activities in colorectal and bladder cancers ${ }^{303,368}$. In transgenic NAG-1Tg/Lox mice, a model which ubiquitously expresses human GDF15, display reduced inflammatory responses and show resistant to tumour formation ${ }^{369,370}$. Furthermore, GDF15 expression is induced by tumour suppressors and anti-cancer drugs, which helps promote apoptosis and reduce tumorigenicity ${ }^{303,366}$.

### 1.4.4 Circulating GDF15 as a predictive marker for cancer prognosis

Despite the existence of a nucleus-residing form, GDF15 is mostly found in the cytoplasm or the extracellular matrix $(\mathrm{ECM})^{281}$. The unprocessed translated form of GDF15 consists of 308 amino acids with a classical signal sequence ( 29 aa$)^{270}$. Upon cleavage by PACE4 and MMP-26, a matured form is produced at the C-terminus (112 aa $)^{270,371}$. GDF15 can be secreted both in a pro-form and mature form, levels of which can be evaluated in the circulation ${ }^{372}$. The mature protein is secreted as a $\sim 25 \mathrm{kDa}$ homodimer consisting of two 112 amino acid polypeptide chains, linked by disulfide bonds ${ }^{372}$. Similarly to tissues trends, low levels of circulating GDF15 are observed under physiological condition $(0.15-1.15 \mathrm{ng} / \mathrm{ml})^{292}$, but are markedly increased under pathological conditions ${ }^{324}$. Notably, serum GDF15 levels are predictive of all-cause mortality ${ }^{373,374}$. Collectively, circulating GDF15 is suggested to be a potential prognostic marker for diseases.

The levels of circulating GDF15 positively correlates with the expression levels of GDF15 in primary tumours, suggesting GDF15 expressed by tumour cells not restricted in resection and is secreted into the blood stream ${ }^{362}$. Elevated concentrations of GDF15 circulating in blood are associated with cancer incidence, progression, recurrence and cancer-related death ${ }^{359,375,376}$. In line with this, a prospective study has also confirmed that the levels of circulating GDF15 positively correlate with an increase in colorectal cancer incidences ${ }^{274}$. However, a recent EPIC-Heidelberg cohort study reported that GDF15 serum levels negatively correlate with the risk of prostate cancer incidences, in contrast to a positive risk in lung cancer ${ }^{377}$. These studies suggest that the association between tumour incidence and circulating GDF15 levels are dependent on tumour type. A number of clinical studies looking at metastatic disease have identified that the serum levels of GDF15 are elevated in patients with bone metastases ${ }^{378,379}$. Patients with cancerous bone metastases have a 5 -fold increase in circulating GDF15 with an AUC of 0.87 compared to cancer patients without metastatic disease ${ }^{378}$. Moreover, in colorectal cancer models, a metastatic cell line, SW620, secretes more GDF15 protein into conditional media when compared to a paired primary cell line, SW480 ${ }^{380}$. These findings are further supported by the levels of serum GDF15 measured in colorectal patients with metastatic diseases ${ }^{380}$. Higher levels of serum GDF15 are detected in colorectal cancer patients and positively correlate with the occurrence of liver metastasis ${ }^{381}$.

Circulating GDF15 levels have also been shown to correlate with cancer prognosis. A Swedish cohort study suggests that elevated GDF15 serum levels are associated with higher death rates in patients with prostate cancers ${ }^{382}$. In melanoma, a retrospective study with 761 patient samples also identified that high serum GDF15 correlates with shorter OS and recurrence in stage III and unresectable stage IV patients ${ }^{383}$. GDF15
secretion also increases following chemotherapy, suggesting a role for GDF15 in predicting drug sensitivity and efficacy in cancer patients ${ }^{384,385}$.

### 1.5 Summary

It is well accepted that tumours are not restricted to their tissue of origin and that the TME is crucial in modulating the induction and malignant transformation of tumour cells ${ }^{67,386}$. The clinical successes of immunotherapies (such as immune checkpoint blockade) highlight the crucial role of the immune system in controlling malignant cells and promoting long-term anti-cancer effects ${ }^{77,387,388}$.

Chemotherapy agents, such as oxaliplatin, are capable of both inducing cytotoxicity and promoting immune activation in tumours. Several mechanisms have been reported to mediate the activation of anti-tumour immune responses. For instance, chemotherapy-induced immunogenic cell death (ICD) leads to cells exposing or releasing DAMPs (HSP70, calreticulin, ATP, high-mobility group box 1, type I IFN, cancer cell-derived nucleic acids and annexin A1) ${ }^{389}$, and these signals mediate antitumour immune responses dependent on a crosstalk between innate cells (dendritic cells, macrophages and NK cells) and adaptive immune cells (T and B cells). Additionally, chemotherapies have been shown to promote upregulation of HLA expression and change the spectrum of peptides presented on MHC class I molecules (immunopeptidome), which facilitates the activation of antigen presenting cells, such as DCs, and ultimately favours T cell anti-tumour response. Other mechanisms include the manipulation of immune checkpoint molecules (like PD-L1) ${ }^{390}$ and "immune modulation" independent of classic $\mathrm{ICD}^{391}$. However, despite advances in the understanding of the interaction of chemotherapy with immune responses, these mechanisms have not produced major clinical benefit in solid tumours, and an exact role of the involvement of chemotherapy in immunogenicity is still elusive. This
highlights the urgent need for understanding the mechanisms which drive changes in immune cell response by chemotherapy.

In this thesis, we aim to study the underlying molecular mechanisms involved in oxaliplatin-mediated immune activation in colorectal cancer. We, firstly, identified the induced TXNIP expression post drug treatments by RNA sequencing analysis. TXNIP is a stress-response gene, that plays an important role in inhibiting the genesis and progression of cancers. In support of this, decreased expression is observed in many types of cancers, suggesting that TXNIP has tumour-suppressive activities ${ }^{102,392-394}$. Despite studies reporting the involvement of TXNIP in different molecular processes including drug sensitivity, metastasis, angiogenesis, glycolysis and NLRP3 inflammasome activation ${ }^{107,188,207,220,231}$, we failed to recapitulate these phenotypes in our system. Further analyses revealed that TXNIP can affect the function of Tregs and NK cells by regulating the expression and secretion of GDF15, a cytokine belonging to TGF- $\beta$ family. Moreover, the relevance and clinical implication of TXNIP/GDF15 axis was also investigated.

### 1.6 Overall aim of the study

### 1.6.1 Hypothesis

The null hypothesis of this thesis is that chemotherapies, such as oxaliplatin, is beneficial to cancer patients, at least to some extent, by inducing the immune activation. This effect can be achieved by modulating the expression of target proteins in cancer cells. Thus, we hypothesise that one of differentially expressed genes mediates oxaliplatin-induced immune modulation.

### 1.6.2 Aims

The aims of the thesis were as followed:

- To explore the differentially expressed genes upon chemotherapy treatment in colorectal cancer by RNA sequencing analysis and further verify the target by immuno-blotting and qPCR analyses;
- To explore the upstream regulator using CRISPR/Cas9 gene editing technique combined with immune-blotting assay;
- To identify the functional impact of TXNIP modulation in colorectal cancer cells by viability, wound-healing and metabolic analysis assays;
- To analyse the downstream target of TXNIP by proteomic analysis, and its effects on immune cells (such as Tregs and NK cells) by performing co-culture experiments; To explore the effects of the newly discovered signalling on chemotherapeutic drug resistance by establishing oxaliplatin-resistant cell models and analysing publicly-available datasets.

Chapter II. Materials and Methods

### 2.1 Reagents \& Materials

### 2.1.1 Cell lines

Human colon adenocarcinoma cell lines DLD1, DiFi, and SW48 were purchased from American Type Culture Collection.

LIM1215 is a generous gift from Prof. Sabine Tejpar from the Department of Oncology (University Leuven, Belgium).

HT29 and HCT15 are generous gifts from Dr. Juan Jose Garcia Gomez from the Department of Medical Physics and Biomedical Engineering (University College London).

HUVEC (Human Umbilical Vein Endothelial Cells) was purchased from PromoCell (GmbH).

### 2.1.2 Cell culture

"Complete media", RPMI and DMEM media (Life Technologies Ltd, US) were supplemented with $10 \%$ heat inactivated Fetal bovine serum (FBS, Sera Laboratories International Ltd), $1 \%$ Penicillin/streptomycin (Life Technologies Ltd, US) and Lglutamine (Life Technologies Ltd, US). In this study, FBS from new batches would be tested before use. The tests include whether it will affect cell morphology, cell growth and drug sensitivity. If FBS from new batches showed no variability, it was warranted to use for cell culture.

Endothelial Cell Growth Medium 2 (PromoCell GmbH, Germany) supplemented with Supplement-Mix (PromoCell GmbH, Germany)

Trypsin/EDTA (PAA Laboratories, Germany)

Oxaliplatin (Ebewe) were obtained from the hospital pharmacy at the Guys' hospital (London, UK); 5-fluorouracil (5-FU, S1209-SEL-100mg) was purchased from Selleck Chemicals, US

PBS (Gibco, US)

6, 12, 24 and 96 well cell culture plates (Costar Corning)

15 and 50ml falcon tube (SARSTEDT)

Cryovials (SARSTEDT)

Mr. Frosty ${ }^{\text {TM }}$ Freezing Container (Thermo Scientific)

Biosafety cabinet

Centrifuge (Labnet Prism)

P1000, P200 and P20 pipette filtered
$37^{\circ} \mathrm{C}$ water bath
$37^{\circ} \mathrm{C}$ incubator
$-80^{\circ} \mathrm{C}$ freezer

### 2.1.3 Organoids

Dulbecco's Modified Eagle Media - DMEM Advance/F12 (Life Technologies Ltd)

Pen-Strep (Thermo Fisher Scientific)

B27 (Life Technologies Ltd)

HEPES (Thermo Fisher Scientific)

N2 (Life Technologies Ltd)

N -acetylcysteine (NAC, Sigma)

Anit-Anti (Life Technologies Ltd)
nicotinamide (Sigma-Aldrich)

GLutaMAX (Thermo Fisher Scientific)

Rspondin (PeproTech)

Noggin (PeproTech)

EGF (Life Technologies Ltd)

A83-01 (Tocris)

SB20 (Sigma-Aldrich)

PGE2 (Tocris)

Gastrin (Sigma-Aldrich)

Y-27632 (RhoKi)

TrypLE ${ }^{\text {TM }}$ Express Enzyme (Gibco)

Basement Membrane Extract (BME) BME-2 (Cultrex)

GentleMACS C Tube (Miltenyi Biotec)

ACK lysis buffer (Thermo Fisher Scientific)

### 2.1.4 Cell viability

Deep Blue Cell Viability ${ }^{\text {TM }}$ Kit (BioLegend)

CellTiter-Glo® 3D Cell Viability Assay kit (Promega)

Low-attached U-bottom 96 well plate (Costar)

Black-sided/ White-sided, flat-bottomed plates (Corning B.V. Life Sciences)

CLARIOstar Plate Reader (BMG LABTECH)

### 2.1.5 CRISPR-CAS9 genome engineering

Cas9 Nuclease Expression plasmid (Horizon)

Edit-R synthetic crRNA and tracrRNA oligos (Horizon)

Edit-R crRNA Non-targeting Control (Horizon)

DharmaFECT Duo Transfection Reagent (Horizon)

Flow cytometer (BD Biosciences)

10 mM Tris buffer solution

Neon® Transfection System (Thermo Fisher Scientific)

### 2.1.6 Generation of CRISPRa Constructs

Edit-R CRISPRa Lentiviral dCas9-VPR particles (Horizon)

### 2.1.7 Western blotting

NE-PER ${ }^{\text {TM }}$ Nuclear and Cytoplasmic Extraction Reagent (Thermo Fisher Scientific)

Mitochondria Isolation Kit (Thermo Fisher Scientific)

TBS: Tris-buffered saline ( 25 mM Tris, $100 \mathrm{mM} \mathrm{NaCl}, \mathrm{pH} 7.5$ )

Tween-20 (Sigma-Aldrich)
Bovine Serum Albumin (BSA) (BioSera)

PVDF transfer membrane (Immobillon)

Pierce ECL Western Blotting substrate (Thermo Scientific)

Pierce ${ }^{\text {TM }}$ BCA Protein Assay Kit

Table 2-1 Primary antibodies

| Antibody | Species | Company | Dilution for WB |
| :---: | :---: | :---: | :---: |
| TXNIP | Rabbit | Cell Signaling Technology | 1:1000 |
| Actin | Mouse | Protein-tech | 1:5000 |
| MondoA | Rabbit | Cell Signaling Technology | 1:1000 |
| Lamin A | Rabbit | Cell Signaling Technology | 1:1000 |
| GAPDH | Mouse | Protein-tech | 1:5000 |
| IRE-1 $\alpha$ | Rabbit | Cell Signaling Technology | 1:1000 |
| ATF6 | Rabbit | Cell Signaling Technology | 1:1000 |
| BIP | Rabbit | Cell Signaling Technology | 1:1000 |
| PERK | Rabbit | Cell Signaling Technology | 1:1000 |
| ATF4 | Rabbit | Cell Signaling Technology | 1:1000 |
| eif $2 \alpha$ | Rabbit | Cell Signaling Technology | 1:1000 |
| p-eif2 $\alpha$ | Rabbit | Cell Signaling Technology | 1:1000 |
| Tubulin | Mouse | Protein-tech | 1:5000 |
| C-MYC | Rabbit | Abcam | 1:1000 |


| IL-1 $\beta$ | Rabbit | Cell Signaling <br> Technology | $1: 1000$ |
| :---: | :---: | :---: | :---: |
| GLUT1 | Rabbit | Cell Signaling <br> Technology | $1: 1000$ |
| Caspase 1 | Rabbit | Cell Signaling <br> Technology | $1: 1000$ |
| GDF15 | Rabbit | Abcam | $1: 1000$ |
| Cas9 | Mouse | Santa Cruz | $1: 1000$ |
| Foxp3 | Rabbit | Abcam | - |

Table 2-2 Secondary antibodies

| Antibody | Species | Company | Dilution for <br> WB |
| :---: | :---: | :---: | :---: |
| HRP conjugated anti <br> mouse | Goat | Protein-tech | $1: 3000$ |
| HRP conjugated anti <br> rabbit | Goat | Protein-tech | $1: 3000$ |
| AlexaFluor® 647 anti <br> mouse | Goat | Invitrogen | - |
| AlexaFluor® 569 anti <br> rabbit | Goat | Invitrogen | - |

### 2.1.8 RNA isolation and quantitative real-time PCR

Trizol Reagent ${ }^{\mathrm{TM}}$ (Invitrogen)

Rneasy Mini Kit (Qiagen)

Rnase-free Dnase (Qiagen)

SuperScript ${ }^{\text {TM }}$ II Reverse Transcriptase kit (Thermo Fisher scientific)

QuantStudio 7 Flex Real-Time PCR System (Biosystems)

Power SYBR green PCR master mix (Biosystems)

Table 2-3 Primers used for qRT-PCR

| Name | Forward | Reverse |
| :---: | :---: | :---: |
| $E I F 2 A K 3$ | CACCTGGACCCCAACCATAC | TGCATGAGGTCCAGCAAAGT |
| $E R N 1$ | TGAGGACGACGTGGACTACA | CTCCCGCTGCCAGACATAAA |
| $H S P A 5$ | CAACGCCAAGCAACCAAAGA | ACACGCTGGTCAAAGTCTTCT |
| $G A P D H ~$ | CTCCTGTTCGACAGTCAGCC | CCCAATACGACCAAATCCGTTG |
| $T X N I P ~$ | GACCTGCCCCTGGTAATTGG | GGGAGGAGCTTCTGGGGTAT |
| $M Y C ~$ | GGCTGATACGTCTTATGTCATCC | GAGGCTCCACAAGGTGTGA |
| $A R R D C 4$ | GCCAGCCAGTTCAGTATGGA | GCATAATTTGGTGGTGCTTCAGG |
| $M L X I P ~$ | ACGGCTCTGTGGACGTAGA | GGCTCTTCCAGTACTTCCCTTC |

Primers were designed by Universal Probe Library (Roche life science, https://lifescience.roche.com/en_gb/brands/universal-probe-library.html\#assay-design-center). Primers with the top ranking were further analysed by Net Primer website (Premier Biosoft, http://www.premierbiosoft.com/netprimer/) and Umelt Quartz (https://dna-utah.org/umelt/quartz/). Selected oligonucleotides pairs were then tested by q-PCR (Melting curves for each primer were shown in Appendix Figure 1 to prove primer specificity). All the primers showed a single pick representing a single amplicon; therefore, they have been used throughout this study.

### 2.1.9 Glucose Uptake assay

Glucose Uptake Assay Kit (Promega)

White multi-well plates (Corning)

### 2.1.10 Lactate Detection Assay

Lactate-GloTM assay kit (Promega)

### 2.1.11 ELISA

Human GDF15/ IL-1 $\beta$ / IFN $\gamma /$ TNF $\alpha$ Quantikine ELISA Kit (R\&D Systems)

### 2.1.12 siRNA transfection

OPTi-MEM-1 (Gibco)

Lipofectamine ${ }^{\text {TM }}$ RNAiMAX Transfection Reagent (Thermo Fisher Scientific)
siRNA oligonucleotides (Horizon)

Table 2-4 Sequence of siRNA oligonucleotides

| Reagent or Resource | Source | Identifier |
| :---: | :---: | :---: |
| siRNAs |  | Dharmacon |
| ON-TARGETplus non-targeting pool <br> siRNA | D-001810-10-05 |  |
| ON-TARGETplus SMARTpool siRNA <br> Human EIF2AK3 | Dharmacon | L-004883-00-0005 |
| ON-TARGETplus SMARTpool siRNA <br> Human MLXIP | Dharmacon | L-008976-00-0005 |

### 2.1.13 Extracellular acidification rate

XF96 Extracellular Flux Analyzer (Bioscience)

Seahorse XF Glycolysis Stress Test Kit (Agilent)

### 2.1.14 Immunohistochemical staining

3\% hydrogen peroxidise (Sigma-Aldrich)

EnVision Chem Detection Kit (DaKo Cytomation)
$100 \%$ and $70 \%$ ethanol (Tennants)

Haematoxylin (VMR)

Eukit mounting media (Sigma-Aldrich)

Leica BOND refine polymer detection kit (DS9800).

### 2.1.15 Immunofluorescence staining

Pierce ${ }^{\text {TM }} 16 \%$ Formaldehyde (w/v), Methanol-free (28906, Thermo Fisher scientific, USA)

Blocking solution: 1\% BSA in PBS

Heat inactivated goat serum (Invitrogen)

Triton X-100 (Thermo Fisher scientific)

DAPI (Cell Signalling Technology)

NIS Elements software (Nikon Eclipse)

Donkey Serum (Sigma-Aldrich)

MitoTracker ${ }^{\text {TM }}$ Red CMXRos (Thermo Fisher scientific)

### 2.1.16 Tube formation

Matrigel ${ }^{\mathrm{TM}}$ (BD Biosciences)

### 2.1.17 Proteome profiler antibody arrays

Human XL Cytokine Array Kit (Cat\# ARY022B, R\&D systems, Minneapolis, MN, USA)

### 2.1.18 ROS production

DHE (Dihydroethidium) Assay Kit—Reactive Oxygen Species (ab236206, Abcam)

### 2.1.19 Chromatin Immunoprecipitation-Quantitative Polymerase Chain Reaction (ChIP-PCR)

Chromatin Extraction Kit (Abcam)

QIAquick PCR Purification Kit (Qiagen)

ChIP Kit Magnetic One -Step (Abcam)

IgG control (Cell Signalling Technology)

### 2.1.20 Mass Spectrometry

NuPAGE ${ }^{\text {TM }}$ LDS Sample Buffer (Thermo Fisher scientific)

Imperial protein stain (Thermo Fisher scientific)

TMTpro reagents (Thermo Fisher scientific)

### 2.1.21 Immune cell isolation and differentiation

Ficoll-Paque (GE Healthcare)

### 2.1.22 Flow cytometry

live/dead dye (Thermo Fisher scientific)

Trustain (Biolegend)

Intracellular fixation and permeabilization kit (ebioscience)

### 2.1.23 Proliferation assays

eFluorTM 670 dye (ebioscience)
2.1.24 CD48-CD244 binding assay

Recombinant human CD48-Fc (R\&D Systems)
recombinant human GDF15(R\&D Systems)
recombinant human CD244-Avitag (R\&D Systems)

### 2.2 Methods

### 2.2.1. Cell culture

DLD1, HCT15, HT29 and LIM1215 were maintained in complete RPMI media at $37^{\circ} \mathrm{C}$ with $5 \% \mathrm{CO}_{2}$. DIFI, and SW48 were grown in complete DMEM media at $37{ }^{\circ} \mathrm{C}$ with 5\% CO2. HUVEC were cultured in Endothelial Cell Growth Medium 2 at $37^{\circ} \mathrm{C}$ with 5\% CO 2 . Media were changed every three days to remove dead cells and to refresh nutrients. Cells were split once the confluency reached $80-90 \%$. For experiments we conducted, cells were used from passage 4 and no longer used after passage 15. CRC cell lines have been authenticated by short tandem repeat (STR) profiling (Appendix Figure 2) and were routinely tested for mycoplasma (MycoSEQ ${ }^{\text {TM }}$ Mycoplasma Detection Kit) throughout the study.

### 2.2.2. Organoids

## CRC tissue processing

Colonic tissues from colorectal cancer patients were provided by University College Hospital London (UCLH) and were used to isolate CRC cells as using the method described by Sato et al ${ }^{33}$. Biobank ethical approval were covered under HTA licence 12055 and REC reference 15/YH/0311. Informed consent forms were signed by all the participants in the study. Patient consent can be withdrawn at any time.

Briefly, specimens were washed with 10 ml of PBS and then cut into small pieces (1-2 mm ) in digestion buffer (Table 2-5). Tissue and digestion buffer were transferred to a gentleMACS C Tube and incubated at $37^{\circ} \mathrm{C}$ for 1 h . Samples were filtered through 100 $\mu \mathrm{m}$ strainers into 50 ml falcon tubes and centrifuged at 800 g for 2 min . The supernatant was removed and cell pellets were incubated in ACK lysis buffer at room temperature (RT) for 5 min . Cells were then washed twice with PBS and resuspended in appropriate volumes of Matrigel (roughly $300 \mu \mathrm{l}$ ). In a 6 -well plate, $7 \times 40 \mu \mathrm{l}$ Matrigel droplets
containing cells were plated per well. After incubation at $37^{\circ} \mathrm{C}$ for $10-20 \mathrm{~min}, 2 \mathrm{ml}$ of organoids complete media (Table 2-6), supplemented with the ROCK Inhibitor Y27632, were added to each well. Media was changed twice a week until the cultures were ready for passaging.

Table 2-5 Digestion buffer

| Reagent | Volume (10 ml) |
| :---: | :---: |
| Organoid Media | 9.5 ml |
| Collagenase II $(100 \mathrm{mg} / \mathrm{mL})$ | 0.5 ml |
| Primocin $(0.1 \mathrm{mg} / \mathrm{mL})$ | 0.02 ml |
| Pen/Strep $(100 \times)$ | 0.1 ml |
| RevitaCell Supplement $(100 \times)$ | 0.01 ml |

Table 2-6 Complete Medium

| DMEM+++ |  |
| :---: | :---: |
| Reagent | Volume ( 500 ml ) |
| DMEM Advance/F12 | 485 ml |
| Pen-Strep 1× | 5 ml |
| HEPES 10 mM | 5 ml |
| GLutaMAX $1 \times$ | 5 ml |
| Basel Media |  |
| Reagent | Volume ( 50 ml ) |
| DMEM+++ | 47 ml |
| B27 (50×) | 1 ml |
| Anti-Anti (100×) | $500 \mu \mathrm{l}$ |
| N2 (100×) | $500 \mu \mathrm{l}$ |
| N -acetylcysteine ( 1.25 mM ) | $125 \mu 1$ |
| Nicotinamide ( 10 mM ) | $500 \mu \mathrm{l}$ |
| Complete media |  |
| Reagent | Volume ( 50 ml ) |
| Basel medium | 35 ml |
| Rspondin ( $100 \mu \mathrm{~g} / \mathrm{ml}$ ) | 10 ml |
| Noggin ( $100 \mu \mathrm{~g} / \mathrm{ml}$ ) | 5 ml |
| EGF ( $50 \mathrm{ng} / \mathrm{ml}$ ) | $50 \mu \mathrm{l}$ |


| A83-01 $(500 \mathrm{nM})$ | $50 \mu \mathrm{l}$ |
| :---: | :---: |
| SB20 $(10 \mu \mathrm{M})$ | $16.6 \mu \mathrm{l}$ |
| PGE2 $(0.01 \mu \mathrm{M})$ | $5 \mu \mathrm{l}$ |
| Gastrin $(10 \mathrm{nM})$ | $5 \mu \mathrm{l}$ |

## Human CRC organoid culture and treatment

Organoids were routinely passaged once a week. Briefly, organoids were collected by suspending Matrigel domes in 1 ml of ice-cold DMEM+++ media (Table 2-6). After centrifugation at 300 g for 5 min , dense organoids dissociation was accomplished by resuspending organoids in 2 ml TrypLE ${ }^{\mathrm{TM}}$ Express Enzyme, incubation for 20 min at $37^{\circ} \mathrm{C}$ and mechanical dissociation by pipetting. FBS was then added to cells resuspended in TrypLE, and centrifuged at 1200 rpm for 3 min . Cell pellets were resuspended in cold Matrigel at 1:1 to 1:6 ratios and then reseeded into culture plates. Media was changed every 2-3 days. Every line of CRC organoids was cultured in separate plates and a laboratory management system was implemented to prevent misidentifications and cross-contaminations. Organoids were routinely tested for mycoplasma throughout the study.

For qPCR and immunoblotting analyses, organoids were seeded in 6 -well plates and collected after 48 h of treatment with $10 \mu \mathrm{M}$ oxaliplatin, which is clinically relevant concentrations ${ }^{395}$. Chemotherapies were pre-diluted in complete medium. After 48 hrs , organoids were collected for experiments.

## Organoids freezing

Organoids were harvested as described in section Human CRC organoid culture and treatment. Cell pellets were resuspended in $500 \mu \mathrm{l}$ of Recovery Cell freezing media (12648010, Invitrogen) and aliquoted into 2 ml cryovials. Cryotubes were placed into Cool Cell freezing pots and placed into $-80^{\circ} \mathrm{C}$ freezer.

## Organoid viability assays

$10 \mu \mathrm{l}$ of Matrigel was dispensed into 96 -well plates and allowed to polymerise. Organoids cells were harvested as described in section Human CRC organoid culture and treatment, and dispensed into wells containing Matrigel. After 24 hrs , organoids were treated with oxaliplatin $(10 \mu \mathrm{M})$ treatment, a clinically relevant drug concentration ${ }^{395}$. After 48 h , cell viability was assayed by using CellTiter-Glo® 3D cell viability assay kit at $1: 1$ ratio (e.g. add $100 \mu \mathrm{l}$ reagent buffer to $100 \mu \mathrm{l}$ of media containing cells). An extensive quality control process was implemented on all screening plates, and a Z-factor score was calculated to compare the negative (nontreatment group) and positive control (Etoposide-treated group) wells.

### 2.2.3 Spheroids

## Generation and analysis of tumour spheroids

DLD1 and HCT15 cell spheroids culture were performed with a requirement of a minimum confluence of $90 \%$. Cells were trypsinised and centrifuged before being assessed for cell viability. Cells with at least $90 \%$ viability were taken for the generation of spheroids. The spheroid formation was performed with 1,000 vital cells in $100 \mu \mathrm{l}$ per well in a low-attached 96-well plate under standard culture conditions. DLD1 spheroids formed within 24 hrs of seeding, whereas HCT15 spheroids formed after 48 hrs .

## Cell viability assay (for 3D spheroids)

Spheroids were generated as described in section Generation and analysis of tumour spheroids. To measure cell viability in spheroids, CellTiter-Glo® 3D cell viability reagents were used. The three-dimensional (spheroids) cultures were treated with 10 $\mu \mathrm{M}$ oxaliplatin and incubated for 48 hrs . They were then subsequently transferred to black-sided, flat-bottomed plates after incubation with CellTiter-Glo® 3D cell viability reagents at 1:1 ratio for 30 min . A CLARIOstar Plate Reader was used to measure luminescence intensity.

### 2.2.4 Cell viability (For 2D cells)

Deep Blue Cell Viability ${ }^{\text {TM }}$ Kit, which is based on the resazurin reagent, was used to measure the cytotoxicity of chemotherapy. Similar to other resazurin-based reagents, Deep Blue Cell Viability ${ }^{\text {TM }}$ Kit can be used to analyse cell number of live cells by measuring the extent of resazurin reduction and resorufin production. After cells were seeded ( 5000 cells/well), oxaliplatin was added to the wells at several doses for the indicated time (such as 48 hrs and 72 hrs ). The plate was incubated at $37^{\circ} \mathrm{C}$ for 3 hrs following the addition of $1: 10$ volume ratio of Deep Blue Cell Viability ${ }^{\text {TM }}$ reagent to each well. A CLARIOstar Plate Reader (Excitation: 530-570 nm, Emission $=590-620$ nm ) was used to detect the reduction of resazurin into resorufin and the OD value was used to calculate cell viability.

### 2.2.5 CRISPR-CAS9 genome engineering

## Cell gene editing

Experiments were conducted with the CRISPR/Cas9 system to knockout TXNIP, GDF15 and MLXIP. Targeting cells were accomplished using the Edit-R CRISPR/Cas9 gene engineering protocol (Horizon Discovery). Guide RNAs for TXNIP (Edit-R CRISPR (knockout) Human TXNIP crRNA, Catalog ID:CM-010814-01-0002); for GDF15 (Edit-R CRISPR (knockout) Human GDF15 crRNA, Catalog ID:CM-019875-01-0002), and for MondoA (Edit-R CRISPR (knockout) Human MLXIP crRNA, Catalog ID:CM-008976-01-0002) were purchased from Horizon Discovery.

In details, CRC cells were seeded at an appropriate density $\left(70 \times 10^{4}\right.$ cells/well for DLD1 cells and $30 \times 10^{4}$ cells/well for HCT15 cells) in 6 -well plates after trypsinisation, washing, and resuspension with antibiotic-free complete media. $2 \mu \mathrm{l}$ of Cas 9 mRNA stock solution $(1 \mu \mathrm{~g} / \mu \mathrm{l})$ was diluted with $18 \mu \mathrm{l}$ of Tris buffer to produce a Cas 9 mRNA working solution. A transfection complex ( $2 \mu \mathrm{M}$ ) was prepared by mixing $2 \mu \mathrm{l}$ of
crRNA $(10 \mu \mathrm{M})$ with $2 \mu \mathrm{l}$ of tracrRNA $(10 \mu \mathrm{M})$. Cas 9 mRNA and synthetic guide RNA transfection complexes were then transferred into an Eppendorf tube as described in Table 2-7 (row 2-4). DharmaFECT Duo working solution was gently mixed with 2 ml of serum-free media in a separate Eppendorf tube. Following 5 min of incubation at RT, $200 \mu \mathrm{l}$ DharmaFECT Duo working solution was added to each sample tube as shown in Table 2-7 (row 5). The mixer was incubated at RT for 20 min after pipetting gently up and down. Transfection media was prepared (row 6 and 7 ) and added into the 6 -well plate. Cell sorting was performed after 72 hrs of transfection by a BD Aria Fusion cell sorter. DAPI staining was performed to assess cell viability. The levels of TXNIP, GDF15 and MondoA expression in each clone were determined after 4 weeks in culture. According to previous publications ${ }^{396,397}$, the following knockout clones were chosen: Three TXNIP knockout clones, three MondoA knockout clones, and four GDF15 knockout clones. The heterogenous knockout cell lines were generated by mixing the knockout clones of each gene and they were used for subsequent functional evaluation ${ }^{396,397}$. Two gRNAs were simultaneously used for transfection to generate TXNIP ${ }^{-/ /}$GDF15 $5^{-/}$double knockout cell model. The stability of each knockout cell line/organoid was checked every five passages using PCR and western blotting analyses.

Table 2-7 CRISPR CAS9 gene editing experiment in a 6-well plate format

| Sample Name | Non-targeting <br> control (NTC) <br> synthetic guide <br> RNA | Gene-specific <br> synthetic guide <br> RNA | Untransfected |
| :---: | :---: | :---: | :---: |
| Serum-free media | $135 \mu \mathrm{l}$ | $135 \mu \mathrm{l}$ | $400 \mu \mathrm{l}$ |
| Working guide RNA <br> solution <br> $(2 \mu \mathrm{M})$ | $25 \mu \mathrm{l}$ | $25 \mu \mathrm{l}$ | 0 |
| Working Cas9 mRNA <br> solution (100 ng/ l$)$ | $40 \mu \mathrm{l}$ | $40 \mu \mathrm{l}$ | 0 |
| DharmaFECT Duo <br> solution | $200 \mu \mathrm{l}$ | $200 \mu \mathrm{l}$ | 0 |


| $(60 \mu \mathrm{~g} / \mathrm{ml})$ |  |  |  |
| :---: | :---: | :---: | :---: |
| Growth media | $1600 \mu \mathrm{l}$ | $1600 \mu \mathrm{l}$ | $1600 \mu \mathrm{l}$ |
| Total volume per 6-well | $2000 \mu \mathrm{l}$ | $2000 \mu \mathrm{l}$ | $2000 \mu \mathrm{l}$ |

## Organoid Gene editing

Neon® Transfection System was used for CRISPR Editing of organoids. Briefly, the ribonucleoprotein (RNP) Complex Mix was prepared in the order listed in Table 2-8 and incubated at RT for 20 min . Culture media was carefully removed and discarded from each well without disturbing the Matrigel dome. 2 ml TrypLE ${ }^{\text {TM }}$ Express Enzyme was used to dissociate organoids into single cells.

Table 2-8 Preparation of Reagents for Neon® Electroporation

| Component | (Volume per Reaction $(\mu \mathbf{l})$ |
| :---: | :---: |
| Resuspension Buffer R | 6 |
| Working guide RNA solution $(100 \mu \mathrm{M})$ | 0.6 |
| Working Cas9 mRNA solution $(4 \mathrm{ug} / \mu \mathrm{L})$ | 0.9 |
| Total | 7.5 |

After neutralisation and centrifugation for 3 min at 1200 rpm , supernatant was discarded and cell pellets were resuspended in 1 ml DMEM containing 1\% BSA. Cells were counted after running the suspension through a $40 \mu \mathrm{~m}$ strainer. $1 \times 10^{5}$ cells were prepared for each electroporation reaction. For each electroporation condition, cells were suspended in $7.5 \mu \mathrm{l}$ of resuspension buffer and transferred to $7.5 \mu \mathrm{l}$ of RNP Complex Mix; gently pipetting up and down the mix, avoiding air bubbles.

The mixture was electroporated using the settings described in Table 2-9. Following electroporation, cells were centrifuged at 1200 rpm for 3 min and resuspended in $25 \mu \mathrm{l}$ Matrigel. Cells were then mixed and seeded. Cells were then replaced with fresh
complete media every 2 days and harvested for genome editing evaluation after 7-10 days of culture.

Table 2-9 Electroporation Conditions

| Electroporation Parameter |  |
| :---: | :---: |
| Electrical potential | 1600 V |
| Pulse width | 20 ms |
| Number of pulses | 2 |

### 2.2.6 Generation of CRISPRa Constructs

## Generation of stable DLD1 cell line expressing dCas9-VPR

$5 \times 10^{4}$ DLD1 cells were seeded and incubated overnight. The Edit-R CRISPRa Lentiviral dCas9-VPR particles was thawed on ice and the calculated volume $(\mathrm{MOI}=$ 0.3 ) was pipetted into 0.25 ml of the basal media (no serum) to create the transduction media. Culture media was removed and replaced with the transduction media. 6 h after transduction, 0.75 ml of growth media (containing serum) was added. After 48 h , selection media (complete media containing puromycin) was used to select stable dCas9-VPR cell lines.

## Transfection of stable dCas9-VPR expressing cell lines with synthetic guide

## RNAs

Stable dCas9-VPR cell lines were successfully established, they can be used for endogenously expressing genes of interest. Cells were seeded and cultured until >50\% confluency. Transfection was carried out after media was removed and replaced with 1.6 ml of fresh culture media. Transfection reagents were prepared in two separated tubes (A and B): Tube A (195 $\mu \mathrm{l}$ Serum/antibiotic-free media and $5 \mu \mathrm{l} 10 \mu \mathrm{M}$ guide RNA mix) and Tube B (195 $\mu \mathrm{l}$ Serum/antibiotic-free media and $5 \mu \mathrm{l}$ DharmaFECT
reagent). Tubes A and B were mixed thoroughly and incubated at RT for 20 min before adding to the cells. Guide RNAs were purchased from Horizon:

Table 2-10 Guide RNAs for CRISPRa

| Reagent or Resource | Source | Identifier |
| :---: | :---: | :---: |
| CRISPRmod CRISPRa (activation) Human <br> MLXIP Synthetic crRNA (SMARTpool) | Horizon | P-008976-01-0005 |
| CRISPRmod CRISPRa (activation) Human <br> TXNIP Synthetic crRNA (SMARTpool)) | Horizon | P-010814-01-0005 |
| CRISPRmod CRISPRa (activation) Human <br> GDF15 Synthetic crRNA (SMARTpool) | Horizon | P-019875-01-0005 |
| CRISPRmod CRISPRa (activation) Human <br> MYC Synthetic crRNA (SMARTpool) | Horizon | P-003282-01-0005 |
| CRISPRmod CRISPRa (activation) Human <br> ERN1 Synthetic crRNA (SMARTpool) | Horizon | P-004951-01-0005 |
| CRISPRmod CRISPRa synthetic crRNA <br> non-targeting controls | Horizon | U-009500-10-05 |

### 2.2.7 Western blotting

## Protein-lysate preparation

Cells were seeded into 6 -well plates $\left(3 \times 10^{5}-5 \times 10^{5}\right.$ cells per well). The next day, cells were replaced with fresh complete media for 1 h before the treatment as indicated in certain experiments. Following two washes with PBS, cells were lysed in 150-200 $\mu \mathrm{l}$ $1 \times$ sample lysis buffer (Table 2-11, $5 \times$ sample lysis buffer diluted in $\mathrm{ddH}_{2} \mathrm{O}$ ) at $75^{\circ} \mathrm{C}$ for 15 min. Protein concentrations in lysates were measured using BCA protein quantification kit. Samples were diluted to $1-2 \mu \mathrm{~g} / \mu \mathrm{l}$ in 5 X loading buffer (to a 1 X working concentration) (Table 2-12) and boiled for 10-15 min.

Table 2-11 5X sample lysis buffer

| Reagent | Volume |  |
| :---: | :---: | :---: |
| 1 M Tris PH6.8 | 2.5 ml |  |
| SDS | 1 g |  |
| Glycerol | 5 ml |  |
| Hit up to 60-70 degree |  |  |

Table 2-12 5X Loading buffer

| Reagent | Volume |
| :---: | :---: |
| 1 M Tris PH6.8 | 3 ml |
| $10 \%$ SDS | 10 ml |
| $100 \%$ Glycerol | 25 ml |
| $\beta-\mathrm{ME}$ | 2.5 ml |
| $1 \%$ Bromophenol blue | 0.025 g |
| ddH2O | Up to 100 ml |

For the nucleus and cytoplasm fractionation, NE-PER ${ }^{\text {TM }}$ Nuclear and Cytoplasmic Extraction Reagent was used. In detail, cells were trypsinised by trypsin-EDTA and then harvested for centrifugation at 500 g for 5 min . The cell pellet was washed twice with PBS and then ice-cold CER I was added. After vigorous vortex, the tube was incubated on ice for 1 h . Ice-cold CER II was then added and the supernatant (cytoplasmic extract) was collected in a pre-chilled Eppendorf tube after vortex. The pellet was washed another twice with PBS and further suspended in ice-cold NER buffer. The volume ratio of CER I: CER II: NER reagents was maintained at 200:11:100 $\mu$ l. The supernatant fraction (nuclear extract) was collected after a 40 min vortex. Store the extracts at $-80^{\circ} \mathrm{C}$ until they are needed.

Mitochondria isolation was performed with the Mitochondria Isolation Kit. Cells were lysed in Mitochondria isolation Reagent A, thoroughly vortexing and incubation on ice for 2 min , before adding $10 \mu \mathrm{l}$ of Reagent B. After an additional 5 min incubation on ice, $800 \mu \mathrm{l}$ of Reagent C was added. The supernatant (cytosol fraction) was then collected. After washing with $500 \mu \mathrm{l}$ of Reagent C, the pellets were collected after centrifugation at $12,000 \mathrm{~g}$ for 5 min as the mitochondrial fraction.

## Gel electrophoresis and immunoblotting

Immunoblotting was performed using general methods. Proteins were separated by SDS-PAGE in 1X Running buffer (Table 2-13) and electro-transferred to a PVDF transfer membrane in 1X transfer buffer (Table 2-14). The membrane was blocked for covering non-specific binding by incubating it with blocking solution for 1 h (TBS-T containing $4 \%$ BSA), followed by an overnight incubation with the primary antibody (See the dilution of primary antibodies in Reagents \& Materials chapter) at $4^{\circ} \mathrm{C}$. Following the washing with TBS-T buffer, the blots were incubated with secondary antibodies (See the dilution of primary antibodies in Reagents \& Materials chapter) for 2 h at RT, then washed 3 times with TBS-T and imaged using a chemiluminescence kit (G: BOX F3, SYNGENE). Western blotting analysis and normalization was conducted using Quantity One software (Bio-Rad Ltd) and all western blotting images shown are representative of 3 independent replicates.

Table 2-13 10× Running buffer

| Reagent | Volume (1000 ml) |
| :---: | :---: |
| Glycine | 144 g |
| Tris | 30 g |
| SDS | 10 g |
| ddH2O | Up to 1000 ml |

Table 2-14 10× Transfer buffer

| Reagent | Volume (1000 ml) |
| :---: | :---: |
| Glycine | 143 g |
| Tris | 30 g |
| ddH2O | Up to 1000 ml |

### 2.2.8 RNA isolation and quantitative real-time PCR

## RNA isolation

RNA was extracted from cells using the Qiagen Rneasy Mini kit following the manufacturer's guidelines. After drug treatment, treated and untreated cells were washed in PBS and lysed in 0.7 ml of QIAzol Lysis Reagent for 5-10 min at RT. 140 $\mu 1$ of chloroform then was added to tubes and lysates were vigorously shaken for 15 s and placed on the bench for 3 min at RT. After centrifugation for 15 min at 12000 rpm , the upper aqueous phase was collected and transferred to a new Eppendorf tube. $525 \mu \mathrm{l}$ of $100 \%$ ethanol was added to tubes, mixed with samples and then pipetted onto a RNeasy MinElute spin column. RNA was eluted with $14 \mu 1$ RNase-free water, following washes with RWT Buffer, RPE Buffer and $80 \%$ ethanol. RNA quantification was performed using a Nanodrop.

## Quantitative real-time PCR (qRT-PCR)

cDNA was synthesized by reverse transcription using a SuperScript ${ }^{\text {TM }}$ II Reverse Transcriptase kit. The mixture listed in Table 2-15 was added to a nuclease-free microcentrifuge tube, incubated for 5 min at $65^{\circ} \mathrm{C}$ and cooled on ice. After brief centrifugation, components were added as listed in Table 2-16, mixed gently and then incubated at $25^{\circ} \mathrm{C}$ for $2 \mathrm{~min} .1 \mu \mathrm{l}$ of SuperScript ${ }^{\mathrm{TM}} \mathrm{II}$ was added and incubated at $25^{\circ} \mathrm{C}$ for 10 min . After further incubation at $42^{\circ} \mathrm{C}$ for 50 min and $70^{\circ} \mathrm{C}$ for $15 \mathrm{~min}, 480 \mu \mathrm{l}$ of RNAase free water was used to dilute RNA samples to $2 \mathrm{ng} / \mathrm{ml}$ for qRT -PCR.

Table 2-15 cDNA preparation reagents 1

| $50-250$ ng random primers | $1 \mu \mathrm{l}$ |
| :---: | :---: |
| 1 ng to $5 \mu \mathrm{~g}$ total RNA or $1-500 \mathrm{ng}$ of mRNA | $\mathrm{X} \mu \mathrm{l}$ |
| $1 \mu \mathrm{ldNTP}$ Mix $(10 \mathrm{mM}$ each $)$ | $1 \mu \mathrm{l}$ |
| Sterile, distilled water | To $12 \mu \mathrm{l}$ |

Table 2-16 cDNA preparation reagents 2

| $5 \times$ First-Strand Buffer | $4 \mu \mathrm{l}$ |
| :---: | :---: |
| RNaseOUT $^{\text {TM }}(40$ units $/ \mu \mathrm{L})$ (optional) | $1 \mu \mathrm{l}$ |
| 0.1 M DTT | $2 \mu \mathrm{l}$ |

qRT-PCR was performed using a SYBR green PCR master mix in a $10 \mu \mathrm{l}$ volume (Table 2-17). The reaction was performed following the conditions described in Table 2-18. Data analysis was conducted with the QuantStudio 6 Flex Real-Time PCR System. Relative mRNA levels were calculated with normalization to the housekeeping gene GAPDH. (See primers used in this study in Reagents \& Materials chapter)

Table 2-17 $\mathbf{q P C R}$ preparation reagent

| Volume | $10 \mu \mathrm{l}$ |
| :---: | :---: |
| Master Mix | $5 \mu \mathrm{l}$ |
| Primer | $0.5 \mu \mathrm{l}$ |
| Sample | $4.5 \mu \mathrm{l}$ |

Table 2-18 qPCR reaction condition

|  | $95^{\circ} \mathrm{C}$ | 10 min |
| :---: | :---: | :---: |
| 40 cycles | $95^{\circ} \mathrm{C}$ | 15 s |
|  | $56^{\circ} \mathrm{C}$ | 20 s |
|  | $72^{\circ} \mathrm{C}$ | 40 s |
| $0.05^{\circ} \mathrm{C} / \mathrm{s}$ | $95^{\circ} \mathrm{C}$ | 15 s |
|  | $60^{\circ} \mathrm{C}$ | 1 min |
|  | $95^{\circ} \mathrm{C}$ | 15 s |

### 2.2.9 Glucose Uptake assay

A Glucose Uptake Assay Kit was used to measure glucose uptake. Cells were seeded in white, opaque plates at a density of 5000 cells each well. After 24 hrs, cells were replaced with fresh media with or without drug. Media was removed at indicated timepoints (48h post drug treatment) and cells were washed with PBS and $50 \mu \mathrm{l}$ of 1 mM 2 DG was added per well. After incubating samples for 10 min at RT, $25 \mu \mathrm{l}$ of Stop buffer was added to stop the reaction. Neutralization Buffer and 2DG6P Detection Reagent were then added one after another following brief shaking. Luminescence was recorded using the CLARIOstar Plate Reader after 1 h of incubation.

### 2.2.10 Lactate Detection Assay

Lactate production was qiuantified using a Lactate-GloTM assay kit. 5000 cells were plated into 96-well plates and then replaced with fresh media with or without drug after 24 hrs . The media was collected at indicated timepoints (48hrs post drug treatment) and $50 \mu \mathrm{l}$ of sample or lactate control was transferred into the 96 -well plate. The background
of the assay was determined by a negative control (buffer only). After $50 \mu \mathrm{l}$ of Lactate Detection Reagent was added, the plate was incubated for 60 min at RT. Luminescence was recorded using the CLARIOstar Plate Reader.

### 2.2.11 ELISA

Supernatant GDF15/ IL-1 $\beta$ / IFN $\gamma /$ TNF $\alpha$ levels were measured using the Human ELISA Kits. All reagents were warmed to room temperature before use. Within 15 min of use, Colour Reagents A and B were mixed in equal volumes to prepare the Substrate Solution. For Human GDF15/ IL-1 $\beta$ / IFN $\gamma /$ TNF $\alpha$ Standard, the dilution series were produced by the stock solution. The $1500 \mathrm{pg} / \mathrm{ml}$ standard serves as the high standard and Calibrator Diluent serves as the zero standard ( $0 \mathrm{pg} / \mathrm{mL}$ ). $50 \mu \mathrm{l}$ of standard, control, or samples were added per well. Following 2 hrs of incubation at RT, liquid was removed and washing buffer was used to wash the plate three times. Each well was incubated with $200 \mu \mathrm{l}$ of Human GDF15/ IL-1 $\beta$ / IFN $\gamma /$ TNF $\alpha$ Conjugate for 1 h at RT. Substrate Solution was then added after 4 times washing. Plates were then kept at RT for 30 min and protected from light. A CLARIOstar Plate Reader ( 450 nm , being corrected against 570 nm ) was used to measure the OD value within 30 min following the addition of $50 \mu \mathrm{l}$ of Stop Solution. Data was analysed using MARS software and excel.

### 2.2.12 siRNA transfection

For transient transfection, siRNA was transfected into cells with Lipofectamine ${ }^{\mathrm{TM}}$ RNAiMAX Transfection Reagent. Cells were plated 16-18 hrs before transfection in antibiotic-free complete media. $5 \mu \mathrm{l}$ of Lipofectamine ${ }^{\mathrm{TM}}$ RNAiMAX Transfection Reagent and 25 pM siRNA (Table 2-4) were mixed thoroughly and incubated for 20 min at RT before added to cells. Western blotting and PCR analyses were performed to assessed knockdown efficiency after 48 hrs.

### 2.2.13 Extracellular acidification rate

Cell bioenergy testing is to analyse the metabolic activities of the living cells by measuring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). ECAR is an indicator of glycolysis. The assay was performed using the Seahorse XF Glycolysis Stress Test Kit and the XF96 Extracellular Flux Analyzer. Briefly, $3 \times 10^{4}$ cells were seeded onto Seahorse XF Microplates and incubated overnight. Meanwhile, a sensor cartridge in Seahorse XF Calibrant was hydrated in Seahorse XF Calibrant at $37^{\circ} \mathrm{C}$ in a non- $\mathrm{CO}_{2}$ incubator overnight. During the assay, cells were replaced with assay media. For the preparation of assay media, Seahorse XF Base Medium was diluted with 2 mM glutamine and pH was adjusted to 7.4 with 0.1 N NaOH . Compounds were equilibrated to room temperature and each compound was resuspended in assay medium (Table 2-19). In a hydrated sensor cartridge, glucose, oligomycin, and 2-DG were added into Port A, Port B and Port C, separately. The extracellular acidification rate (ECAR) was measured following 1 h incubation in warmed assay media in a $37^{\circ} \mathrm{C}$ non- $\mathrm{CO}_{2}$ incubator.

Table 2-19 ECAR measurement preparation

| Compound | Volume of assay medium | Resulting stock concentration |
| :---: | :---: | :---: |
| Glucose | $3000 \mu \mathrm{l}$ | 100 mM |
| Oligomycin | $720 \mu \mathrm{l}$ | $100 \mu \mathrm{M}$ |
| 2-DG | $3,000 \mu \mathrm{l}$ | 500 mM |

### 2.2.14 Human samples

Two sets of patient samples were used for clinical validation (mainly for immunohistochemistry experiment) in this study, namely cohort 1 and cohort 2.

Cohort 1 was a retrospective cohort collected in Peking university Third Hospital by Dr. Gang Li. This study was approved by Peking university Third Hospital Medical Science Research Ethics committee (Reference number IRB00006761-M2022237) and was performed in accordance with the principle of the Helsinki Declaration II. A total of 35 CRC tissues were retrospectively collected from patients before chemotherapy (32 CRC tissues) and after oxaliplatin-based chemotherapy (3 CRC tissues, with treatment of FOLFOX6, FOLFOX6 and Xelox6, respectively) from May 2014 to March 2021. Notably, these 3 tissue samples (after oxaliplatin-based treatment) were collected when patients were on treatment.

Cohort 2 was a human colorectal cancer tissue microarray (TMA) purchased from Shanghai Outdo Biotech Company Ltd (Shanghai, China). All tissue samples were collected before chemotherapy treatment. The TMA contained 97 colorectal cancer samples and paired adjacent normal tissues collected from patients between 2009 and 2018 and were accompanied by patient clinical data. Patient information of TMA is provided in Appendix Table 1.

### 2.2.15 Immunohistochemical staining (IHC)

The expression of TXNIP and GDF15 protein in patient tissue samples (including 2 cohorts detailed in 'Human samples' of Method chapter) was assessed by immunohistochemistry $(\mathrm{IHC})^{398}$. Freshly cut $4-\mu \mathrm{m}$ sections from Formalin Fixed Paraffin Embedded (FFPE) tissue samples were used for the immunohistochemical assessment. IHC staining was performed as previous publications ${ }^{399,400}$. To begin with, FFPE slides were dewaxed and rehydrated. After antigen retrieval in 0.01 M sodium citrate buffer ( PH 6.0 ) in a microwave for 20 min , slides were treated with peroxidase block for 5 min and protein block solution for another 5 min at RT. Then Slides were incubated with primary antibody against TXNIP (Abcam, ab188865; 1:250), GDF15
(Protein-tech, 27455-1-AP; 1:500) and FOXP3 (Abcam, ab215206; 1:1000) overnight at $4^{\circ} \mathrm{C}$. The specificity of both TXNIP and GDF15 antibodies were initially confirmed by western blotting with HCT15 genomic editing cell models established in this study (Appendix Figure 3C, D). Post primary antibody incubation, tissues were incubated with secondary antibodies (EnVision Chem Detection Kit, DaKo Cytomation) for 30 min at RT, followed by incubation with horseradish enzyme-labelled streptavidin solution for 10 min and then visualised with $3,3^{\prime}$-diaminobenzidine and counterstained with haematoxylin. Slides were then dehydrated and fixed before mounting. Controls were performed: human liver and placenta tissue slides were included as positive controls, and negative controls omitted primary antibodies (Appendix Figure 3A, B, E). The stained tissues were interpreted by two pathologists (Dr. Xingang Zhou from Department of Pathology, Beijing Ditan Hospital, Capital Medical University and Dr. Nan Zhang from Department of Pathology, Beijing Children's Hospital Medical University) independently in a blinded manner. Staining intensity of samples was semiquantitatively evaluated using the H -score method, which is determined by both the staining extent and intensity. The H-score is calculated as the sum of the percentage of staining multiplied by an ordinal value corresponding to the intensity level $(0=$ none, $1=$ weak, $2=$ moderate, $3=$ strong). Thus, the H -score ranged from 0 to 300 , indicating no staining to diffuse intense staining. The intraclass correlation coefficient (ICC) analysis was used for assessing the level of agreement between independent reviewers. The ICC scores were $0.896,0.907$ and 0.887 for samples stained with anti-TXNIP, antiGDF15 and anti-FOXP3 antibodies, respectively.

### 2.2.16 Immunofluorescence staining (IF)

Immunofluorescence staining (IF) was performed as previously outlined ${ }^{401}$. A total of $5 \times 10^{3}$ DLD1 cells were seeded. $10 \mu \mathrm{M}$ oxaliplatin was then applied to the cells the
following day. After 48 h of treatment, tissue cultures were rinsed with PBS, fixed with 4\% PFA for 20 min , and then rinsed with PBS three times, followed by permeabilization for 10 min with $0.1 \%$ Triton-X100. After PBS wash, tissue cultures were incubated for 1 h in blocking buffer (5\% BSA and 5\% Donkey Serum), and further incubated overnight at $4^{\circ} \mathrm{C}$ with the primary antibodies (TXNIP, ab188865, 1:250; Calreticulin, ab22683, 1:250) or phalloidin (Phalloidin-iFluor 488 Reagent kit, ab176753) diluted in 5\% BSA. After further washing with PBS, secondary antibodies (AlexaFluor® 647 anti-rabbit, 1:500; AlexaFluor® 488 anti-mouse, 1:500) were applied for 1 h in 5\% BSA to stain the cells. DAPI was stained with 1:1000 for 15 min and examined using a spinning disk confocal microscope. For Mitochondria staining, cells were incubated with MitoTracker ${ }^{\mathrm{TM}} \operatorname{Red} \mathrm{CMXRos}(500 \mathrm{nM})$ for 15 min at $37^{\circ} \mathrm{C}$ and rinsed with PBS before fixation.

### 2.2.17 wound-healing migration assay

A wound-healing migration assay was used to estimate cell migratory ability. $5 \times 10^{4}$ DLD1 cells (non-targeting control and TXNIP-KO cells) were seeded and grown to $100 \%$ confluence in 6 well cell culture dish. Wounds were scraped across each cell monolayer using a sterile $200 \mu \mathrm{l}$ micropipette tip. Non-adherent cells were removed by PBS washes for three times. Cells were treated with oxaliplatin ( $10 \mu \mathrm{M}$ oxaliplatin diluted in FBS-free media to reduce cell proliferation) was performed and incubated at $37^{\circ} \mathrm{C}$ for the indicated time periods. A camera-equipped inverted microscope (Leica DM IL LED microscope) was used to measure the distance of migration by cancer cells. The average width of the wound was calculated using ImageJ software. The wound healing rate $=100 \% \times([$ wound width at $0 \mathrm{~h}-$ width at other time point $] /$ width at 0 h$)$.

### 2.2.18 Tube formation assay

NTC or TXNIP-overexpressing (TXNIPa) DLD1 cells were seeded and replaced with fresh media after 24 hrs . After 48 hrs of treatment, the supernatant (tumour-conditioned media, TCM) was then collected after centrifugation to remove cell debris. The wells of a 96 -well cell culture plate were pre-coated with $100 \mu 1$ of Matrigel. HUVECs $\left(1 \times 10^{5}\right.$ /well) were then added to plates in $100 \mu \mathrm{TCM}$ and then imaged using a microscope equipped with a camera (Leica DM IL LED microscope) after 8 hrs . Complete tubular structures were calculated using ImageJ software.

### 2.2.19 Proteome profiler antibody arrays

Human cytokine array kit was used to evaluate the expression of 105 human cytokines secreted from DLD1 cells (non-targeting control and TXNIP-KO cells) and all the procedures were performed according to the manufacturer's instructions. In details, cells were plated at $4 \times 10^{5} /$ well in 6 -well plates. After 24 hrs of culture, cells were treated with oxaliplatin, and cultured for a further two days. Then the media was collected as tumour-conditioned media (TCM) after centrifugation to remove cells and debris. 1 ml of TCM was added to the Human XL Cytokine Array membranes and incubated overnight at $4^{\circ} \mathrm{C}$. Membranes were washed three times and then incubated with Detection Antibody Cocktail for 1 h at RT, followed by incubation with Streptavidin-HRP for 30 min at RT. After three times washes, Chemi Reagent Mix was added on each membrane and incubated for 1 to 10 min . Membranes were then imaged. An image and a table were provided for coordinate reference (Appendix Figure 4, Appendix Table 2).

### 2.2.20 bulk RNA sequencing (RNA-seq) analysis

The RNA-Sequencing experiments were used to analyse the differentially expressed genes in colorectal cancer cells (DLD1 and HCT15 cells) after oxaliplatin treatment
and performed by Novogene (Cambridge, UK). Samples were warranted for Total RNA from CRC cells was isolated using RNeasy Mini Kit, followed by quality control to check purity (by Nanodrop), quantity (by Nanodrop) and RIN (by Agilent 2100) (Appendix Figure 5). Messenger RNA was purified from total RNA using poly-T oligoattached magnetic beads. The purified messenger RNA was the fragmented by fragmentation reagents. After fragmentation, the first strand cDNA was synthesized using random hexamer primers followed by the second strand cDNA synthesis. The library was ready after end repair, A-tailing, adapter ligation, size selection, amplification, and purification. Workflow of RNA library preparation was presented in Appendix Figure 6. The library was then validated with Qubit and qPCR for quantification and bioanalyzer for size distribution detection. Quantified libraries were pooled and sequenced on Illumina platforms, according to effective library concentration and data amount. For the data analysis, base calls were performed using CASAVA. Reads were aligned to the genome using the split read aligner TopHat (v2.0.7) and Bowtie2, using default parameters. HTSeq was used to estimate abundance. To identify involved biological processes post treatment, Gene ontology (GO) analysis was performed with all the downregulated differentially expressed genes (DEGs), with 2607 genes for DLD1 cells and 1950 genes for HCT15 cells.

Gene set enrichment analysis (GSEA) was performed using GSEA software version 4.2.2 following guideline. Gene sets database was set to h.all.v2022.1.Hs.symbols.gmt and number of permutations was set to 1000 .

### 2.2.21 ROS production

The ROS level in the live cancer cells was measured using DHE (Dihydroethidium) Assay Kit- Reactive Oxygen Species. DHE was used as a fluorescent probe for ROS detection, specific for superoxide and hydrogen peroxide. Thus, ROS generation was
represented by total DHE fluorescence intensity. Around $5 \times 10^{3}$ cells were added to a 96-well plate. Oxaliplatin treatment $(10 \mu \mathrm{M})$ was performed the next day. After 48 h , culture media was aspirated and $150 \mu 1$ cell-based assay buffer was used for wash. 130 $\mu \mathrm{l}$ of ROS staining buffer was added and incubated for 1.5 hrs protected from light for staining. Three wells of cells were designed as positive controls and another three wells of cells were designed as negative controls. N -acetyl cysteine (NAC) reagent, as a reduced glutathione (GSH) precursor, was used as a negative control and Antimycin A, an inhibitor of complex III of the mitochondrial electron transport chain, as a positive control. Following washing steps, a CLARIOstar Plate Reader (Excitation: 480-520 nm, Emission: $570-600 \mathrm{~nm}$ ) was used to measure the fluorescence intensity.

### 2.2.22 Chromatin immunoprecipitation coupled with qPCR (ChIP-qPCR) assay

Chromatin immunoprecipitation (ChIP) assay, an antibody-based technology, was used to study the binding between MondoA protein and the DNA promoter sequence of the TXNIP gene. DLD1 cells were treated with Oxaliplatin $(10 \mu \mathrm{M})$ with/without NAC pretreatment. After 48 hrs of treatment, cells were harvested and cross-linked with $1 \%$ formaldehyde (10 min at RT). The fixation was stopped by adding glycine ( 5 min at RT) and the cells were then washed twice with cold PBS (10 min at $4^{\circ} \mathrm{C}$ ). Chromatin extraction was performed using the Chromatin Extraction Kit (ab117152, Abcam) followed by sonication. The sonication conditions were optimised by applying increasing number of pulses for 30 s with 30 s pauses on a Sonics Vibracell sonicator (75\% power). DNA was reverse cross-linked at $65^{\circ} \mathrm{C}$, digested with Proteinase K, purified using QIAquick PCR Purification Kit (28104, Qiagen) and loaded on 1\% agarose gel to assess DNA fragmentation. Optimal DNA shearing was achieved using two rounds of 40 cycles for 30 s with 30 s pauses (Appendix Figure 7A, B).

The sonicated samples were divided for input samples and ChIP samples. The sonicated samples were divided for input samples and ChIP samples. Input DNA was reverse cross-linked, purified as described above and quantified by Nanodrop. ChIP pull-down assays were performed using the ChIP Kit Magnetic One-Step according to the manufacturers' instructions. $1.6 \mu \mathrm{~g}$ of sonicated chromatin and $2 \mu \mathrm{~g} \operatorname{IgG}$ control (2729, Cell signalling Technology) or anti-MondoA (13614-1-AP Protein-tech) were employed. Anti H3K4me3 antibody (ab8580, Abcam) was used as ChIP positive control for open chromatin.

Recovered DNA was amplified by PCR using GoTaq Hot start master mix (Promega) and primers specific for TXNIP promoter region (forwardCACAGCGATCTCACTGATTG; reverse- GTTAGTTTCAAGCAGGAGGC). Thermocycling was performed at $95^{\circ} \mathrm{C}$ for 10 min , followed by 40 cycles of $95^{\circ} \mathrm{C}$ for $30 \mathrm{~s}, 60^{\circ} \mathrm{C}$ for 30 s and $72^{\circ} \mathrm{C}$ for 10 s , with an additional extension at $72^{\circ} \mathrm{C}$ for 10 min . PCR products were loaded on 1.5\% agarose gel (Appendix Figure 7C). Specificity of the PCR product was assessed by Sanger sequencing using both forward and reverse primers. Alignment with the reference sequence was performed using Blastn (https://blast.ncbi.nlm.nih.gov/).Quantification of TXNIP promoter amplicons in all the experimental samples was performed by Syber green qPCR.

### 2.2.23 Liquid chromatography-mass spectrometry (LC-MS/ MS) analysis

LC-MS/MS analysis was used in this study to screen the secreted soluble factors (secretome) of the supernatants in an unsupervised manner. The procedures included several steps detailed below:

## Step1: Preparing Secreted Protein Pellets for Mass Spec

DLD-1 cells were seeded with a density around $70-80 \%$ in 6 -well plates. On second day, cells were washed with PBS and replaced with 2 ml of FBS-free media (RPMI+1\%
penicillin/streptomycin $+1 \%$ Glutamin). After 48 hrs (day 4), supernatants from cell culture were collected, centrifuged ( $300 \mathrm{~g} / 5 \mathrm{~min}$ ) to get remove debris, followed by adding cold acetone at a ratio of $1: 3$. The mix was shaken thoroughly and stored at $20^{\circ} \mathrm{C}$ overnight. Protein pellets were collected after a centrifugation at 10000 g for 15 $\mathrm{min})$. Keep the pellets in $-80^{\circ} \mathrm{C}$ freezer for storage till mass spectrometry analysis.

Step2: Purification of Protein Pellets by Running a short length ( $\sim 2 \mathrm{~cm}$ ) of 1D SDSPage Gels

Each protein pellet was resuspended in $20 \mu \mathrm{l}$ of 8 M urea, followed by adding $2.5 \mu \mathrm{l}$ of 200 mM dithiothreitol (DTT) for 1 h at $56^{\circ} \mathrm{C} .2 .5 \mu \mathrm{l}$ of 550 mM Iodoacetamide (IAA), an alkylating agent reacting with free sulfhydryl groups, was then added for 30 min at RT in the dark. $5 \mu \mathrm{l}$ of $4 \times$ NuPAGE ${ }^{\text {TM }}$ LDS Sample Buffer was added and then vortex. The samples were then kept for at $90^{\circ} \mathrm{C}$ for 5 min . Samples were then loaded into a $10 \%$ Bis-Tris gel, resolved for about 1 cm ( 80 volts; $63 \mathrm{~mA} ; 8$ watts) before being stained with Imperial protein stain (Appendix Figure 8). This procedure was to remove contaminated or toxic factors from buffers.

Step 3: In-gel Enzymatic Tryptic Digestion
In-gel reduction, alkylation and digestion with trypsin was performed according to a routine digestion protocol prior to subsequent analysis by mass spectrometry. Cysteine residues were reduced with DTT and derivatised by treatment with IAA to form stable carbamidomethyl derivatives. Trypsin digestion was carried out overnight at room temperature after initial incubation at $37^{\circ} \mathrm{C}$ for 2 hrs . The peptides were exacted from gels with acetonitrile, followed by a speedVac to dry the peptides.

## Step 4: TMTpro labelling

Digested peptides were labelled with TMTpro tags based on Thermo user guide protocol (https://assets.thermofisher.com/TFS-Assets/ LSG/ manuals/ MAN0018773_TMTproMassTagLabelingReagentsandKits_UG.pdf). Basically, 500 $\mu \mathrm{g}$ of TMTpro reagents in $10 \mu \mathrm{l}$ acetonitrile were added to $50 \mu \mathrm{~g}$ peptides in 100 mM TEAB (triethylammonium bicarbonate) buffer and incubated at room temperature for 1 h . TMTpro tags corresponding to samples are listed in the table below (TKO short for TXNIP-KO).

| Sample ID | TMTpro_10ul |
| :---: | :---: |
| DLD1_NTC_rep1 | 126 |
| DLD1_NTC_rep2 | 127 N |
| DLD1_NTC_rep3 | 127 C |
| DLD1_TKO_rep1 | 128 N |
| DLD1_TKO_rep2 | 128 C |
| DLD1_TKO_rep3 | 129 N |

Step 5: MS Check Point_2 (TMT labelling efficiency)
5ul per sample was analysed by a 60 min-gradient collision-induced dissociation (CID)_MSMS method. The label efficiency was calculated below based on PD searching outcomes.

|  |  |  | PD outcome |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Sample ID | TMTpro $1 \overline{0} \mathrm{ul}$ |  | protei <br> n | $\begin{gathered} \text { peptid } \\ \text { e } \end{gathered}$ | $\begin{gathered} \text { PSM } \\ \mathbf{S} \end{gathered}$ | TMEpept | TMT label efficiency (\%) | total pept intensity | CV\% |
| $\begin{gathered} \text { DLD1 } \\ \text { NTC rep } 1 \end{gathered}$ | 126 | TMT <br> label efficienc y and total ion intensity | 990 | 4012 | 4682 | 3995 | 99.576271 | $6.91 \mathrm{E}+09$ | $\begin{gathered} 18.1841 \\ 9 \end{gathered}$ |
| $\begin{gathered} \text { DLD1 } \\ \text { NTC rep } 2 \\ \hline \end{gathered}$ | 127N |  | 880 | 3616 | 4317 | 3601 | 99.585177 | $6.74 \mathrm{E}+09$ |  |
| $\begin{gathered} \text { DLD1 } \\ \text { NTC rep } 3 \\ \hline \end{gathered}$ | 127C |  | 970 | 3891 | 4491 | 3875 | 99.588795 | $9.22 \mathrm{E}+09$ |  |
| $\begin{gathered} \text { DLD1 } \\ \text { TKO rep } 1 \\ \hline \end{gathered}$ | 128N |  | 806 | 3428 | 4120 | 3418 | 99.708285 | $8.50 \mathrm{E}+09$ | $\begin{gathered} 33.2130 \\ 3 \end{gathered}$ |
| $\begin{gathered} \text { DLD1 } \\ \text { TKO rep } 2 \\ \hline \end{gathered}$ | 128C |  | 641 | 2376 | 2767 | 2371 | 99.789562 | $4.77 \mathrm{E}+09$ |  |
| $\begin{gathered} \text { DLD1 } \\ \text { TKO rep } 3 \end{gathered}$ | 129 N |  | 850 | 3529 | 4237 | 3520 | 99.74497 | $9.61 \mathrm{E}+09$ |  |

Step 6: Clean up by Pierce high pH C18 spin column
After the labelling efficiency was checked out, the reaction was quenched with hydroxylamine to a final concentration of $0.3 \%(\mathrm{v} / \mathrm{v})$ for 15 min and all individual tags were combined as one. The sample was vacuum centrifuged to near dryness and subjected to C18 solid-phase extraction (SPE, Sep-Pak) for a clean-up. The cleaned peptides are dried by speed vacuumed and for LCMS analysis.

Step 7: LC-MS/MS tandem mass spectrometry
The TMT set sample was resuspended in re-suspension buffer ( $2 \%$ acetonitrile in 0.05\% Formic acid) to be analysed by LC-MS/MS with triply injections. Chromatographic separation was performed using an Ultimate 3000 NanoLC system equipped with an Ultimate 3000 RSLC nano pump (Thermo Fisher Scientific, UK). Peptides were resolved by reversed phase chromatography on a $75 \mu \mathrm{~m} * 50 \mathrm{~cm}$ C18 column using a three-step gradient of water in $0.1 \%$ formic acid (A) and $80 \%$ acetonitrile in $0.1 \%$ formic acid (B). The gradient was delivered to elute the peptides at a flow rate of $250 \mathrm{nl} / \mathrm{min}$ over 120 min .

The eluate was ionised by electrospray ionisation using an Orbitrap Fusion Lumos (Thermo Fisher Scientific, UK) operating under Xcalibur v4.1. The instrument was programmed to acquire using a "Synchronous Precursor Selection with MultinotchMS3" method (SPS). Synchronous Precursor Selection is a process of selecting multiple MS2 precursors using a single fill and single waveform in a collision-induced dissociation (CID) or higher energy collision dissociation (HCD) cell, while MultinotchMS3 is to reduce co-isolated interference from MS2 in an ion-trap cell. This method allows for accurate and sensitive quantitation based on isobaric TMT tags.

Step 9: Database Searching
Raw mass spectrometry data were processed into peak list files within Proteome Discoverer (ThermoScientific v2.5). The workflow was presented in Appendix Figure 9. Processed data was then searched using Mascot search algorithm (www.matrixscience.com) and Sequest search engine embedded in a Proteome Discoverer software (version 2.4), against the current version of the reviewed Swissprot Homo Sapiens (Human) database downloaded from Uniprot (http://www.uniprot.org/uniprot/), plus enhanced GFP sequence.

### 2.2.24 Immune cell isolation and differentiation

Leucocyte cones (NC24 Leukocyte cone) were ordered from the National Health Service Blood and Transplant Service (NHSBTS) (The NHSBTS obtains informed consent from the donors and has internal ethical approval under the terms of HTA licence). Cells were mixed 1:1 with PBS and layered on Ficoll-Paque (GE Healthcare; 1714402). Cells were spun at 800 g for 30 min , with the brake off, and the Human peripheral blood mononuclear cells (PBMCs) were taken from the buffy layer above the Ficoll-Paque. CD14 ${ }^{+}$cells, naïve CD4 T cells, or NK cells were isolated from PBMCs using the MACS system as per manufacturer's instructions (Miltenyi Biotech; 130-050-201, 130-094-131, 130-092-657. LS Columns; 130-042-401). Purity was checked using anti-CD14, anti-CD4 and anti-CD45RA, or anti-CD56 antibodies (concentration as per manufacturer's instructions) and seen to be $>95 \%$. If purity was below $95 \%$, the cells were disposed of.

### 2.2.25 Flow cytometry

$1-2 \times 10^{5}$ cells were stained with a live/dead dye in PBS for 10 min on ice in the dark, before being washed twice in FACS buffer ( $0.5 \%$ BSA in PBS +2 mM EDTA). Cells were then Fc blocked with Trustain in FACS buffer for 10 min on ice in the dark. Cells
were washed and then stained using a variety of antibodies $\pm$ secondary reagents described in table 2-20, using concentrations recommended by the manufacturer, on ice for 30 min in the dark. Cells were washed and either read immediately or fixed using $1 \%$ PFA in FACS buffer and read within 3 days. Cells were read using a BD Accuri C6 Plus flow cytometer, with analysis carried out using BD Accuri C6 Plus software. All cells were gated as follows: (a) Forward scatter and side scatter (SSC) to exclude cellular debris (whilst also adjusting threshold), (b) live/dead (only live cells carried forward) and (c) SSC-A vs. SSC-H—only singlets carried forward. All MFIs were corrected against an appropriate isotype control. Intracellular flow cytometry was carried out using the intracellular fixation and permeabilization kit according to manufacturer's instructions.

Table 2-20 Antibodies for flow cytometry

| Antibodies | Source | Identifier |
| :---: | :---: | :---: |
| LIVE/DEAD ${ }^{\text {TM }}$ Fixable Red Dead Cell Stain Kit | ThermoFisher | Cat\# L23102 |
| Human TruStain FcX․․ (Fc Receptor Blocking Solution) | Biolegend | Cat\# 422302 |
| PE Mouse IgG1, k Isotype Ctrl Antibody | Biolegend | Cat\# 400112 |
| FITC Mouse IgG1, k Isotype Ctrl (FC) Antibody | Biolegend | Cat\# 400110 |
| PerCP Mouse IgG1, k Isotype Ctrl Antibody | Biolegend | Cat\# 400148 |
| APC Mouse IgG1, k Isotype Ctrl Antibody | Biolegend | Cat\# 400120 |
| FITC anti-human CD56 (NCAM) Antibody | Biolegend | Cat\# 304604 |
| PE anti-human CD107a (LAMP-1) Antibody | Biolegend | Cat\# 328608 |
| Ultra-LEAF ${ }^{\text {TM }}$ Purified Rat IgG2a, k Isotype Ctrl Antibody | Biolegend | Cat\# 400544 |
| Purified Rat IgG2a, k Isotype Ctrl Antibody | Biolegend | Cat\# 400502 |
| FITC anti-human CD279 (PD-1) Antibody | Biolegend | Cat\# 329904 |
| APC anti-human CD279 (PD-1) Antibody | Biolegend | Cat\# 329908 |
| FITC anti-human CD48 Antibody | Biolegend | Cat\# 336706 |
| FITC anti-human HLA-DR Antibody | Biolegend | Cat\# 327006 |
| APC anti-human CD86 Antibody | Biolegend | Cat\# 374208 |
| APC anti-human CD274 (B7-H1, PD-L1) Antibody | Biolegend | Cat\# 329708 |
| PE anti-human CD40 Antibody | Biolegend | Cat\# 334308 |
| PerCP anti-human CD4 Antibody | Biolegend | Cat\# 317432 |
| FITC anti-human CD3 Antibody | Biolegend | Cat\# 317306 |
| PE anti-human CD8 Antibody | Biolegend | Cat\# 344706 |
| PerCP anti-human CD163 Antibody | Biolegend | Cat\# 333626 |
| PerCP/Cyanine5.5 anti-human CD206 (MMR) Antibody | Biolegend | Cat\# 321122 |
| PE anti-human CD14 Antibody | Biolegend | Cat\# 301806 |
| PE anti-human FOXP3 Antibody | Biolegend | Cat\# 320108 |
| PE anti-human CD45RA Antibody | Biolegend | Cat\# 304108 |
| FOXP3 Fix/Perm Buffer Set | Biolegend | Cat\# 421403 |

### 2.2.26 Proliferation assays for immune cells

96 -well tissue culture stimulation plates were prepared the night before by adding 100
$\mu \mathrm{l} /$ well $1 \mu \mathrm{~g} / \mathrm{ml}$ anti-CD3 in PBS. PBMCs were stained using an eFluor ${ }^{\text {TM }} 670$ dye according to manufacturer's instructions and plated at $2 \times 10^{5}$ cells in $100 \mu \mathrm{l} .100 \mu \mathrm{l}$ of supernatant or other factor (in certain experiments) was added and cells were cultured
for 4 days. After culture cells were harvested and analysed using flow cytometry. Stained unstimulated cells were used as a control.

### 2.2.27 CD48-CD244 binding assay

All products, including ELISA plates (DY990), blocking buffer (DY995), streptavidinHRP (DY998) and substrate solution (DY999), were purchased from Biotechne. Recombinant human CD48-Fc was plated at $1 \mu \mathrm{~g} / \mathrm{ml}$ in PBS overnight at $4^{\circ} \mathrm{C}$. Plates were washed 3 times with wash buffer and then blocked with blocking buffer. Plates were subsequently incubated for 2 hrs at room temperature. Plates were washed and wells treated with the following in quintuplets; PBS, recombinant human GDF15 at 1 $\mu \mathrm{g} / \mathrm{ml}$, isotype control at $10 \mu \mathrm{~g} / \mathrm{ml}$, anti-CD48 at $10 \mu \mathrm{~g} / \mathrm{ml}$ and supernatant from NTC or GDF15 (a) cell lines. Plates were incubated for 2 hrs at $4^{\circ} \mathrm{C}$. Plates were then washed 3 times and incubated for 4 hrs with $1 \mu \mathrm{~g} / \mathrm{ml}$ recombinant human CD 244 -Avitag at $4^{\circ} \mathrm{C}$. Plates were washed 3 times and Streptavidin-HRP, substrate and stop solution added as per manufacturer's instructions. Plates were read on a CLARIOstar instrument at 450 nm , being corrected against 570 nm , and analysed using MARS software and excel.

### 2.2.28 NK degranulation assays

Recombinant human CD48-Fc, anti-CD2 and anti-NKp46 were plated at $1 \mu \mathrm{~g} / \mathrm{ml}$ in PBS in 96-well round-bottomed plates and incubated overnight at $4^{\circ} \mathrm{C}$. Plates were washed with PBS once before being incubated with (in RPMI $+10 \% \mathrm{FBS}$ media [R10] unless otherwise stated) isotype control or anti-CD48 (both at $10 \mu \mathrm{~g} / \mathrm{ml}$ ), media alone or $1 \mu \mathrm{~g} / \mathrm{ml}$ rhGDF15, or NTC or GDF15 (a) supernatant for 1 h at $4^{\circ} \mathrm{C} .1 \times 10^{5} /$ well NK cells were added in R10 and incubated for 18 hrs at $37^{\circ} \mathrm{C}$. Cells were spun down, washed once in FACS buffer before being stained with anti-CD107-PE or isotype control. \% CD107a positive cells were determined by gating on the isotype control for each condition.

### 2.2.29 Functional Treg assay

Anti-CD3 was plated at $1 \mu \mathrm{~g} / \mathrm{ml}$ in PBS and incubated overnight at $4^{\circ} \mathrm{C}$. Supernatant was removed and $2 \times 10^{5}$ /cell isolated naïve CD4 cells were added in the presence of 1 $\mu \mathrm{g} / \mathrm{ml}$ anti-CD28 in the presence of NTC or GDF15 (a) supernatant $+/$ - isotype control $(10 \mu \mathrm{~g} / \mathrm{ml})$ or anti-CD48 $(10 \mu \mathrm{~g} / \mathrm{ml})$. Cells were cultured at $37^{\circ} \mathrm{C}$ for 4 days. On day 3 , anti-CD3 was plated at $1 \mu \mathrm{~g} / \mathrm{ml}$ in PBS and incubated overnight at $4^{\circ} \mathrm{C}$. Allogeneic PBMCs were isolated, stained with eFluor ${ }^{\text {TM }} 670$ proliferation dye and plated at $1 \times 10^{5}$ cells/ well. $1 \times 10^{5}$ Tregs were added at a 1:1 ratio and the co-culture was run for 4 days. Cells were then harvested and stained with anti-CD3, anti-CD8 and anti-CD4 antibodies. The proliferation dye MFI in the responder population was normalized against matched cells stimulated in media alone.

### 2.2.30 scRNA-seq analysis for colorectal cancer patients

For comparing TXNIP and GDF15 expression in colorectal cancer tumour samples, we used log transformed-normalized single-cell RNA sequencing data derived from 63 colorectal cancer patients ${ }^{19}$ deposited at the Synapse (syn26844071) and extracted only tumour cells. Tumour cells are identified using Reference Component Analysis version $2(\mathrm{RCA})^{402}$, using Pearson correlation with reference dataset, and filtered low-quality cells for the number of expressed genes (>2,200) and Unique Molecular Identifier (UMI) count $>1,000$.

To identify intrinsic CMS (iCMS) for each tumour samples, we used 715 iCMS associated genes, followed a previously described method ${ }^{19}$. Scaled data for each cohort was used to avoid batch effect from each cohort and used iCMS metagene score to define iCMS type for each cell. iCMS metagene score were calculated using mean expression of iCMS2/3 specifically up and down genes, respectively.

### 2.2.31 Public dataset analysis

TCGA dataset was used to compare the differential expression of TXNIP/GDF15 between adjacent normal samples and cancer patient samples. Gene expression data from TCGA was downloaded from GDC data portal ((https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas). Both colon adenocarcinoma COAD and rectal adenocarcinoma (READ) cohorts were included as colorectal cancer cases.

Four public datasets were used in this study for prognostic analyses, including GSE29621, GSE38832, GSE6988, and GSE52735. Detailed information of these datasets was presented in Appendix Table 3-6. These datasets were generated from Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo). For the survival analysis, the continuous variables were dichotomized via the survminer R package, and the Kaplan-Meier curves were performed using the survival R package.

### 2.2.32 Establishment of oxaliplatin-resistant (OXAR) cell lines

To test the response of the studied signalling pathway in drug resistant models, human colorectal cancer cell lines were established, named as oxaliplatin-resistant cells (OXAR) cells, by treatment with constant high oxaliplatin concentration in vitro. Oxaliplatin was diluted in RPMI complete media before treating cancer cells. Briefly, Cells were grown in T 75 flasks at a high concentration for a period of 12 months, with $50 \mu \mathrm{M}$ for DLD1 cells and $25 \mu \mathrm{M}$ for HCT15 cells. Finally, cell lines that can grow exponentially in RPMI with high concentrations of oxaliplatin were identified as drug resistant cell lines. The IC50 values of cells to oxaliplatin are shown in table 2-21. Experiments on resistant cell lines were performed after culturing in the medium without oxaliplatin for at least 2-3 weeks.

Table 2-21 The IC50 values for oxaliplatin in CRC cell lines

| CRC cell lines | IC $_{\mathbf{5} \mathbf{0}}(\boldsymbol{\mu M})$ | Standard <br> deviation | $\mathbf{9 5 \%}$ CI |
| :---: | :---: | :---: | :---: |
| DLD1 parental | 13.37 | 0.0274 | $11.76-15.17$ |
| DLD1 OXAR | 105.5 | 0.02947 | $92.06-121.7$ |
| HCT15 parental | 6.729 | 0.1113 | $3.232-13.72$ |
| HCT15 OXAR | 36.45 | 0.0849 | $25.66-52.23$ |

Abbreviations: IC50, The inhibitory concentrations of cell growth by 50\%; OXAR: Oxaliplatin resistant cells.

### 2.2.33 Statistical analysis

All in vitro experiments were performed in three times independently from one another. All quantitative data are presented as mean $\pm$ standard deviation (SD). Data was analysed using GraphPad Prism 9.0 and the SPSS version 22.0. The mean values of the two groups were compared using paired t-tests. One-way ANOVA was used to evaluate multiple independent groups. Non-parametric data were analysed with the MannWhitney U test. The chi-squared, Yates' continuity corrected chi-Square or the Fisher tests were applied to compare categorical variables. Kaplan-Meier analyses were performed via the survival package and the log-rank test was used to analyse the $P$ value. All probability values were two-sided. Spearman's rank-order correlation was used to determine the correlation calculated in this study. $P$-value $<0.05$ was considered as statistically significant.

Chapter III. TXNIP was induced by Chemotherapy treatment in CRC

### 3.1 Introduction

CRC is the third most diagnosed cancer and the second ranking in terms of leading cause of cancer death, with increasing incidence in younger people (https://www.cancer.net/cancer-types/colorectal-cancer/statistics). CRC is a complex disease, characterised by strong aggressiveness and heterogeneity ${ }^{1,403}$. Chemotherapy was initially developed at the early 20th century and still remains the predominant choice for treating most cancer types, even though immune checkpoint blockade therapy has revolutionised cancer therapy in some cancer types. Randomized trials have clearly established that the application of chemotherapy results in improved clinical outcomes ${ }^{404,405}$.

Platinum (Pt)-based drugs are widely used to treat different cancer types ${ }^{406}$. Cisplatin is the first anti-cancer drug, accidentally discovered in the late 1960s and approved by the US Food and Drug Administration (FDA) in 1978 to treat testicular cancer ${ }^{406}$. Oxaliplatin (OXA), a 3rd generation diaminocyclohexane (DACH) platinum analogues, is the only platinum-based anti-cancer drug approved by FDA to treat $\mathrm{CRC}^{407}$ and commonly used to treat patients unresponsive to $5-\mathrm{FU}^{408}$. In advanced colorectal carcinoma, oxaliplatin has been reported to produce response rates $2-24 \%$ in untreated patients and even $\sim 10 \%$ in patients with relapse ${ }^{409}$. It binds to DNA to form oxaliplatinDNA adducts and induces single strand breaks ${ }^{407}$.

Platinum-DNA adducts are formed by oxaliplatin to promote the activation of several biological processes, including DNA damage and reactive oxygen species (ROS) production, leading to cell cycle arrest and cell death ${ }^{410-412}$. It is well established that oxaliplatin-induced DNA damage, which is responsible for cytotoxicity properties of drugs ${ }^{413}$. Even though fewer Pt-DNA adducts, defined by inter-strand DNA cross-links (ISC) and DNA-protein cross-links (DPC), are formed by oxaliplatin when compared
to cisplatin, oxaliplatin is more potent in the induction of DNA damage and cellular apoptosis ${ }^{413,414}$. Clearly, increased ROS production has been observed by most chemotherapeutics, including oxaliplatin ${ }^{415-417}$. ROS is reactive oxygen-containing molecules, mediating drug-induced cell injury and death ${ }^{417}$. Consistently, inhibition of glutathione helps to increase the levels of ROS, enhancing oxaliplatin chemosensitivity ${ }^{418}$. Chemotherapy-induced ROS is involved in different types of cell death, including apoptosis, autophagy and necroptosis, by activating several signalling pathways ${ }^{419}$. For example, oxaliplatin can trigger apoptosis by activation of Bax/caspase cascade and PERK/ATF4/CHOP pathways ${ }^{68}$.

Oxaliplatin treatment has been observed to induce the activation of tumour suppressors, such as $\mathrm{p} 53^{420}$. Oxaliplatin-induced tumour suppressors mediates the activation of cell death and the remodelling of tumour microenvironment. Additionally, the view that chemotherapy regimens are an immunologically silent process is increasingly being challenged, as chemotherapies have been reported to function as immunotherapies that can rearrange the tumour microenvironment, which potentiates the enhanced efficacy for the following immunotherapies ${ }^{421}$. This concept has been supported by observations that conventional chemotherapy showed superior anti-tumour effects in syngeneic immunocompetent as opposed to immunodeficient hosts mouse models, dependent on innate and adaptive immune activation ${ }^{56,57,67}$. Clinical trials have also proved that combining neoadjuvant chemotherapy and immune checkpoint inhibitors has a superior response than chemotherapy alone in different types of cancers ${ }^{422-426}$. Immunogenicity induced by chemotherapy has been reported to involve immunogenic cell death via the release of DAMPs and cytokines, and upregulation of HLA expression changes in the spectrum of peptides presented on MHC class I molecules. Moreover, oxaliplatin has been already validated to induce immunogenicity, especially to induce HMGB1 release
and CRT exposure ${ }^{56,57,427}$. However, whether and how tumour suppressive genes are involved in chemotherapy-induced immune response need to be explored.

### 3.2 Aims and Objectives

The aim of the work described in this chapter was to identify tumour suppressive genes which are induced in colorectal cancer by chemotherapy treatment. As ROS plays an important role in mediating drug effects, we also aimed to identity whether ROS was involved in the regulation of target genes. These aims have been addressed by the following specific objectives:

1. To identify tumour suppressive gene(s) by an unsupervised screening method such as RNA sequencing in tumour cell lines (DLD1 and HCT15 cells) upon chemotherapy treatment;
2. To verify the target gene(s) (induced by chemotherapy treatment) by immunoblotting and qPCR in different cell models and patient samples, including 2D tumour cell lines, 3D tumour cell models, patient derived organoids and patient tissue samples;
3. To study whether ROS was involved in the regulation of target gene(s) by using antioxidant agent treatment, such as N -acetylcysteine (NAC);
4. To investigate the regulatory signalling pathway of gene of interest using CRISPR-KO cell models.

### 3.3 Results

### 3.3.1 TXNIP was induced by Chemotherapy treatment in colorectal cancer

To investigate dysregulated protein coding genes in CRC post chemotherapy, we performed RNA-seq in two human CRC cell lines (DLD1 and HCT15) after 48 hrs of oxaliplatin treatment. These two cell lines were selected for two different reasons: 1) Based on CMS classification, both DLD1 and HCT15 belong to CMS1 subtype ${ }^{428}$, which is defined as an "immune" subtype with high prevalence of MSI (Detailed characteristics in Table 3-1). Specifically, CMS1 subtype is well characterised by
increased immune infiltrate phenotype, mainly comprising of cytotoxic T and TH1 cells.
2) In CMS1 samples, genes copy number counts were consistently lower in oncogenes and higher in tumour suppressors ${ }^{14}$. These models were therefore thought to potentially induce the expression of tumour suppressive genes to mediate immune activation.

Table 3-1 Cell line characteristics ${ }^{428}$

| Cell <br> Lines | CMS <br> status | Molecular <br> phenotype | SNV/Indel | Morphology |
| :---: | :---: | :---: | :---: | :---: |
| DLD1 | CMS1 | MSI | APC/TP53/KRAS/PI3KCA | undifferentiated |
| HCT15 | CMS1 | MSI | APC/TP53/KRAS/PI3KCA | undifferentiated |

After oxaliplatin treatment with a clinical relevant concentration $(10 \mu \mathrm{M})^{395}$, cells underwent robust changes, with 2500-3000 genes significantly altered (Appendix Table 7, 8). Aiming at exploring potential tumour suppressive genes, we focused more on increased genes induced by chemotherapy. Among these upregulated differentiated genes (DEGs), we observed that the expression of a commonly known tumour suppressive gene, TXNIP, was markedly increased after oxaliplatin treatment in both DLD1 and HCT15 cell lines (Figure 3-1A-B). We then compared the upregulated genes in both cell lines (Figure 3-1C). The analysis employed the adjusted $\mathrm{P}<0.05$ and $\mid \log (2)$ (fold change) $\mid>2$ as the cut-off criteria, and showed that 23 protein-coding targets ( $7.3 \%$ ) shared by both cell lines were found to be upregulated by oxaliplatin (Figure 3-1C). Specifically, TXNIP showed the most significant difference with highest abundance among the upregulated genes (Table 3-2). TXNIP has been reported to exert antitumour effects in various cancer types (including colorectal cancer) and low TXNIP expression correlates with poor prognosis ${ }^{102,429-431}$.

A


B


HCT15
C
HCT15
Upregulated DEGs post Oxa


Figure 3-1. Differential gene expression (assessed by RNA-seq) between oxaliplatintreated group and control group.

After 48 hrs treatment with $10 \mu \mathrm{M}$ oxaliplatin, cells were collected for RNA-seq analysis. A volcano plot ( $\log 2 \mathrm{FC}$ versus negative $\log$ of P value) was used to visualize statistically
significant gene expression changes (fold change $\geq 1.5$ and adjusted P value $<0.05$ ). TXNIP gene is labelled. $\mathrm{n}=3$ biological replicates per group (A) DLD1 cells; (B) HCT15 cells. (C) 23 overlapped upregulated genes (7.3\%) induced > 4-fold (Padj<0.05) after oxaliplatin treatment between DLD1 and HCT15 cells were determined by RNA sequencing analysis. Abbreviation: Ctrl: Control; Oxa: Oxaliplatin; DF: Different; FC: Fold Change; p-adj: p-adjust; NS: no significant.

Table 3-2 List of top upregulated genes post oxaliplatin

| Gene symbols (Protein <br> coding) | Ctrl (FPKM) | Oxaliplatin <br> (FPKM) | Log2 Fold <br> change | P-Adgj |
| :---: | :---: | :---: | :---: | :---: |
| PRR35 | 0 | 28.54605 | 7.266649 | $4.05 \mathrm{E}-07$ |
| $L C N 10$ | 0.348552 | 19.8151 | 5.777981 | 0.000165 |
| KCNB2 | 0 | 9.706757 | 5.710984 | 0.000944 |
| MSLNL | 1.404126 | 67.71865 | 5.648547 | $1.39 \mathrm{E}-10$ |
| ARHGDIG | 0 | 8.572541 | 5.535994 | 0.002144 |
| LCN6 | 0 | 7.722649 | 5.382577 | 0.003533 |
| DIRAS1 | 0.358471 | 14.16814 | 5.291237 | 0.001478 |
| AZU1 | 0.348552 | 13.53987 | 5.224396 | 0.001382 |
| CCDC27 | 0.606003 | 20.50235 | 4.952012 | 0.00037 |
| TXNIP | $\mathbf{2 6 9 . 1 3 1 5}$ | 5656.84 | 4.393907 | $3.23 \mathrm{E}-05$ |
| TBXA2R | 2.287421 | 39.23884 | 4.07954 | $4.03 \mathrm{E}-07$ |
| KRTAP3-1 | 1.736888 | 26.77862 | 3.986304 | $8.66 \mathrm{E}-05$ |
| $C 16 o r f 90$ | 1.404126 | 20.14336 | 3.886849 | 0.000405 |
| LYPD1 | 0.697103 | 9.959529 | 3.878697 | 0.02032 |
| ATAD3C | 0.651553 | 9.393553 | 3.819505 | 0.020046 |
| FCGRT | 0.707023 | 9.525459 | 3.815109 | 0.018535 |
| PAX5 | 0.606003 | 8.417741 | 3.690189 | 0.032801 |
| RGS22 | 4.4838 | 52.87831 | 3.584577 | $2.38 \mathrm{E}-08$ |
| LYPD5 | 0.716943 | 8.107734 | 3.567269 | 0.040775 |
| IGF2 | 1.010025 | 11.52926 | 3.521304 | 0.009887 |

Data was retrieved from RNA-seq analysis from DLD1 cells, summarizing the top 20 upregulated genes post oxaliplatin treatment. TXNIP was labelled in red as the most significant altered gene with highest abundance.

| Gene symbols <br> (Protein coding) | Ctrl (FPKM) | Oxaliplatin <br> (FPKM) | log2 FoldChange | P-Adj |
| :---: | :---: | :---: | :---: | :---: |
| KRTAP2-3 | 0 | 125.2869734 | 9.346411215 | 0.000822836 |
| CYP24A1 | 0.645985892 | 73.91566603 | 6.735820341 | $2.60 \mathrm{E}-08$ |
| VSTM1 | 0.322992946 | 38.76174837 | 6.697601482 | $3.47 \mathrm{E}-05$ |
| RFPLAA | 0 | 13.31136649 | 6.101070502 | 0.00062468 |
| NPPB | 1.982261228 | 122.4772137 | 5.923907619 | 0.000154238 |
| LCK | 0.345144722 | 22.4735449 | 5.901918684 | 0.0001421 |
| BIRC7 | 0 | 11.39585598 | 5.880086644 | 0.001313292 |
| PRR35 | 0.345144722 | 21.92623207 | 5.86539495 | 0.000187016 |
| KRT9 | 0 | 10.86855432 | 5.814285504 | 0.001184268 |
| HS3ST6 | 0 | 9.642396919 | 5.640915916 | 0.002780822 |
| SSTR3 | 1.013282389 | 45.82666816 | 5.456949584 | $7.27 \mathrm{E}-07$ |
| $T M P R S S 7$ | 0 | 7.836157053 | 5.353880062 | 0.006101127 |
| ADAMTS2 | 0.38081625 | 15.21411853 | 5.33938626 | 0.001615086 |
| SRRM4 | 0 | 7.34284595 | 5.257292063 | 0.012565035 |
| EIF4E1B | 0 | 7.230008502 | 5.22289714 | 0.017273012 |
| LCN10 | 0.322992946 | 12.19816562 | 5.027935484 | 0.004747616 |
| HSPB8 | 0.725960971 | 21.13577096 | 4.908199231 | 0.000947597 |
| FLT4 | 0.345144722 | 9.85969415 | 4.711884638 | 0.009902761 |
| CHRNA6 | 0.322992946 | 9.405088523 | 4.634463318 | 0.018943818 |
| XAF1 | 0.690289443 | 16.50837613 | 4.568367934 | 0.010104646 |
| MATK | 2.040084531 | 46.98371948 | 4.496302136 | $2.01 \mathrm{E}-08$ |
| PHF21B | 0.322992946 | 8.392757488 | 4.476010289 | 0.020318371 |
| NXPH3 | 0.322992946 | 8.072125448 | 4.420445965 | 0.025793578 |
|  |  |  |  |  |


| ATP1A4 | 0.38081625 | 8.029853169 | 4.413252593 | 0.023099204 |
| :---: | :---: | :---: | :---: | :---: |
| RTP4 | 0.38081625 | 7.798576551 | 4.387449964 | 0.027914431 |
| HCAR3 | 0.345144722 | 7.740984883 | 4.369117289 | 0.02452052 |
| FAM92B | 0.322992946 | 7.754964271 | 4.355803974 | 0.04006894 |
| C4orf54 | 0.690289443 | 14.08672325 | 4.343227528 | 0.009454433 |
| PRSS42 | 0.38081625 | 7.582404294 | 4.334104743 | 0.028220147 |
| DRGX | 0.322992946 | 7.452116596 | 4.322380286 | 0.034623455 |
| APOL3 | 10.50305893 | 208.2544095 | 4.314170911 | $6.98 \mathrm{E}-22$ |
| DYDC2 | 0.645985892 | 13.04497435 | 4.256247912 | 0.007933229 |
| SLC15A3 | 2.514395612 | 46.94254903 | 4.254588477 | $1.82 \mathrm{E}-07$ |
| CACNG8 | 1.832738192 | 33.40182175 | 4.231699872 | $5.38 \mathrm{E}-05$ |
| IGFL1 | 2.155731138 | 38.27056813 | 4.185045954 | $1.39 \mathrm{E}-05$ |
| KRT17 | 3.850670948 | 68.95377886 | 4.172827901 | $3.03 \mathrm{E}-11$ |
| EBI3 | 14.83487788 | 266.0035139 | 4.15521294 | $4.57 \mathrm{E}-37$ |
| C16orf90 | 0.703809196 | 11.90929734 | 4.101257861 | 0.017437336 |
| IGF2 | 0.703809196 | 11.95379642 | 4.09722856 | 0.014115672 |
| COL24A1 | 0.725960971 | 11.99965864 | 4.096047544 | 0.011797236 |
| EDN2 | 6.955024248 | 113.4347255 | 4.072292564 | $2.95 \mathrm{E}-13$ |
| NYAP2 | 1.084625445 | 17.74741109 | 4.066588654 | 0.001891278 |
| GCNT4 | 1.523264998 | 23.60117836 | 4.050536826 | 0.000364396 |
| REN | 4.231487197 | 68.31979062 | 4.030919015 | $2.42 \mathrm{E}-09$ |
| ITGAM | 1.048953917 | 16.93258115 | 4.027097243 | 0.002851174 |
| HBA1 | 0.645985892 | 11.00846375 | 4.020184502 | 0.021304122 |
| IL2RG | 1.832738192 | 28.61641862 | 4.019125292 | 0.000344523 |
| LRRC36 | 0.703809196 | 10.80983768 | 3.94970852 | 0.026958678 |
| FAM71E2 | 0.690289443 | 10.38587083 | 3.900474734 | 0.037724297 |
| WFDC1 | 2.169250891 | 31.24933696 | 3.891210709 | $1.48 \mathrm{E}-05$ |
| MYL9 | 29.9329762 | 436.3212348 | 3.86698279 | $3.81 \mathrm{E}-27$ |
| ELF5 | 0.725960971 | 10.26139989 | 3.866506692 | 0.02582918 |
| ZFR2 | 0.690289443 | 9.980694236 | 3.844324484 | 0.035209322 |
| HOXD1 | 0.761632499 | 9.872667651 | 3.795635882 | 0.026157866 |
| TMEM40 | 10.85683567 | 147.2144137 | 3.764734464 | $9.07 \mathrm{E}-15$ |
| AZU1 | 1.465441695 | 19.09803945 | 3.748475391 | 0.001746411 |
| ZFP28 | 0.725960971 | 9.157486628 | 3.710785603 | 0.041477085 |
| CREB3L3 | 1.336275335 | 17.89904996 | 3.701912394 | 0.001550174 |
| GNAO1 | 0.703809196 | 9.099775873 | 3.695245462 | 0.039404822 |
| LRRC15 | 1.013282389 | 12.81001184 | 3.626272077 | 0.009022534 |
| ANO2 | 1.810586416 | 20.1612586 | 3.518297597 | 0.004383479 |
| RNF113B | 1.013282389 | 11.87272272 | 3.511094279 | 0.014796324 |
| SCN2B | 1.071105693 | 11.91387003 | 3.498138024 | 0.024626459 |
| TXNIP | $\mathbf{8 9 9 . 8 8 3 0 4 3 6}$ | 10036.04559 | 3.479143186 | 4.63E-06 |
| PTPN7 | 17.09648016 | 188.901704 | 3.467242815 | $1.52 \mathrm{E}-19$ |
| TPSD1 | 1.048953917 | 11.02478902 | 3.395584352 | 0.017021385 |
| GZMM | 4.182295917 | 43.14589896 | 3.372146633 | $5.79 \mathrm{E}-05$ |
| HRC | 1.659268282 | 16.78685498 | 3.296420599 | 0.003711629 |
| SCUBE1 | 4.36928558 | 41.52237034 | 3.287034387 | 4.63E-06 |

Data was retrieved from RNA-seq analysis from HCT15 cells, summarizing the top 70 upregulated genes post oxaliplatin treatment. TXNIP was labelled in red as the most significant altered gene with highest abundance.

To validate the expression pattern of TXNIP, we treated colorectal cancer cells with oxaliplatin for 48 hrs at various concentrations. Correspondingly, the result showed 5 $\mu \mathrm{M}$ oxaliplatin was already capable of significantly upregulating TXNIP mRNA levels and the increased expression was more pronounced at increased drug dosage (Figure 3-

2A, B). Moreover, $10 \mu \mathrm{M}$ oxaliplatin was the minimum drug concentration to trigger
optimum TXNIP expression. Further, cells were collected at different time points post $10 \mu \mathrm{M}$ oxaliplatin. Induction of TXNIP expression was observed at later time points (Figure 3-2C, D). 48 hrs of treatment induced the highest increase. After 48 hrs of treatment with 10uM oxaliplatin, the induction of TXNIP reached to approximately 1015 times fold at mRNA level (Figure 3-2A-D).


Figure 3-2. Assessment of TXNIP expression treated with oxaliplatin by quantitative polymerase chain reaction ( $q-P C R$ ) analysis.
(A-B) q-PCR analysis of TXNIP mRNA in DLD1 cells (A) or HCT15 cells (B) treated with oxaliplatin for 48 h at various concentrations. (C-D) q-PCR analysis of TXNIP gene expression in DLD1 (C) or HCT15 cells (D) treated with $10 \mu \mathrm{M}$ oxaliplatin at different time points. Results shown are representative of three independent experiments. All values were expressed as mean $\pm$ SD. ${ }^{*} \mathrm{p}$ value $(\mathrm{p})<0.05,{ }^{* *} \mathrm{p}<0.01,{ }^{* * *} \mathrm{p}<0.001, * * * * p<0.0001$, vs. Control (PBS). Abbreviation: 2D: Two-dimensional.

Immunoblotting was used to assess TXNIP expression at the protein level. The results were consistent with the qPCR data (Figure 3-3A-H). The TXNIP protein expression levels were upregulated significantly compared with control group, in both dose and time dependent manners (Figure 3-3A-H). Taken together, these results demonstrate that oxaliplatin can promote the transcriptional upregulation of TXNIP in the colorectal cancer models, DLD1 and HCT15 cells.


Figure 3-3. Western blotting analysis of TXNIP expression in colorectal cancer cells treated with oxaliplatin.
(A-B) Assessment of TXNIP in DLD1 cells post oxaliplatin treatment at different time points (A); or with different dosages (B); (E-F) Assessment of TXNIP in HCT15 cells post oxaliplatin treatment at different time points (E); or with different dosages (F); (C, D, G, H) The mean and standard errors were then calculated for each group and statistical analysis was performed. $\beta$ ACTIN was used as an internal reference. Each experiment is run in triplicate. Bars represent mean $\pm$ SD. ${ }^{*} \mathrm{p}<0.05,{ }^{* *} \mathrm{p}<0.01,{ }^{* * *} \mathrm{p}<0.001$, vs. Control (PBS). (E, F) Western blotting analyses of TXNIP with oxaliplatin of different dosages or at different time points.

Compared to 2D (two-dimensional) monolayers, 3D (three-dimensional) cell models are more accurate at mimicking in vivo features such as cell-to-cell interactions, tumour growth and drug responses ${ }^{30,432}$. Spheroids are one of the most commonly used 3D cell models, in which the cells are closely packed with high density. Previous reports showed DLD1 and HCT15 cells have been widely used to establish spheroids model for cancer studies, including drug combinations efficacy ${ }^{433}$, tumour-immune interaction ${ }^{434-435}$, cell-cell adhesion properties ${ }^{436}$ and cancer metastasis and growth ${ }^{437}$. To generate uniformly sized spheroids, ultra-low attachment culture plates were used, and multicellular spheroids were generated (Figure 3-4A). As shown, optimal spheroids
development was observed at 24 and 48 hrs in DLD1 and HCT15, respectively. Oxaliplatin treatment decreased the viability and volume of CRC spheroids (Figure 34A).

Given that 3D structures have been reported to show better performance for drug testing and cellular signalling than 2D cultures, we measured the expression of TXNIP after treating CRC spheroids using the same conditions tested in 2D cultures. Similar results were observed. Specifically, higher expression of TXNIP was seen after longer treatment condition at both mRNA and protein levels in DLD1 as well as HCT15 spheroids (Figure 3-4B-G). For DLD1 spheroids, increased TXNIP was observed from 24 hrs of drug treatment. But 24 h of treatment was not able to induce significant increase of TXNIP at protein level in the HCT15 spheroids model even though the mRNA level was already significantly upregulated (Figure 3-4B-G).


Figure 3-4. The induction of TXNIP expression post oxaliplatin treatment in 3D spheroids models.
(A) Representative images of the morphology of CRC cell lines cultured as 3D tumour spheroids in non-adherent 96 -well plates. Cells were seeded on day 0 . Spheroids were formed after 24 h for DLD1 and 48 h for HCT15 cells. On day $3,10 \mu \mathrm{M}$ of oxaliplatin was added. Photographs were taken on day $0,1,2,3,4,5$ and 6 after plating. (B-C) qPCR analysis of TXNIP mRNA in (B) DLD1 and (C) HCT15 spheroids treated with oxaliplatin at 0, 24 and 48 h ; (D-G) Western blotting analyses of TXNIP at different time points post oxaliplatin treatment in DLD1 and HCT15 cells. (D-E) Western blotting of TXNIP after treatment of oxaliplatin at 0,24 and 48 h in (D) DLD1, (E) HCT15 spheroids; Results shown are representative of three independent experiments. (F-G) The statistical analyses were performed in (F) DLD1 spheroids,
(G) HCT15 spheroids. All values were expressed as mean $\pm$ SD. ${ }^{*} \mathrm{p}<0.05,{ }^{* *} \mathrm{p}<0.01$, $* * * \mathrm{p}<0.001$, vs. Control (PBS). Abbreviation: 3D: Three-dimensional.

Patients-derived organoids (PDTOs) have been reported to be a very useful tool in biomedical research ${ }^{50}$. Other than research, PDTOs provide the potential for translational medicine to present an individualized platform for treatment prognosis prediction ${ }^{25}$. Several methods are available for the culture of organoids, including the submerged method ${ }^{33}$ and the air-liquid interface(ALI) method ${ }^{438}$. Here, we generated colorectal cancer organoids from patient's resected tumour tissue and used a general submerged method to maintain organoids in culture (Figure3-5A). Two PDTOs were challenged with $10 \mu \mathrm{M}$ oxaliplatin and showed similar trends of increased TXNIP expression at the mRNA level (Figure 3-5B-C), but very marginal at the protein level (Figure 3-5D-E). Collectively, these data demonstrate that oxaliplatin induces the expression of TXNIP and the drug response shows difference between 2 D and 3D cultures.


Figure 3-5. The induction of TXNIP expression post oxaliplatin treatment in 3D PDTOS models.
(A) Schematic of generation and maintenance of patient-derived colorectal cancer organoids; (B-C) qPCR analyses of TXNIP post oxaliplatin treatment in two different PDTOs, (B) CRC001,
(C) CRC002. (D-E) Western blotting analyses of TXNIP post oxaliplatin treatment in two different PDTOs, (D) CRC001, (E) CRC002; All values were expressed as mean $\pm$ SD.
$* \mathrm{p}<0.05, \quad * * \mathrm{p}<0.01, \quad * * * \mathrm{p}<0.001, \quad * * * * \mathrm{p}<0.0001$, vs. Control. Abbreviation: CRC: Colorectal cancer.

5-FU is another chemotherapeutic agent for colorectal cancer treatment. To test whether TXNIP induction was specific to oxaliplatin or whether other chemotherapies could also induce TXNIP expression, we treated DLD1 and HCT15 cells with $10 \mu \mathrm{M}$ of 5FU and observed the significantly increased expression of TXNIP in HCT15 cells, but marginal increase in DLD1 cells (Figure 3-6). These data suggested that TXNIP induction could be a general response to chemotherapies.


Figure 3-6. The induction of TXNIP expression post 5-FU treatment in colorectal cancer cell lines by Western blotting analyses.
(A) DLD1 cells; (B) HCT15 cells. Abbreviation: 5-FU: Fluorouracil.

### 3.3.2 TXNIP was accumulated in cytosol post oxaliplatin treatment

TXNIP is an alpha-arrestin protein (also named as ARRDC6), which is a member of the arrestin-clan family proteins. In humans, this family is comprised of true arrestins (visual and $\beta$-arrestins), the arrestin domain-containing proteins (ARRDCs), isoforms of the retromer subunit VPS26 and DSCR3 ${ }^{439}$.

True arrestin proteins are scaffolding proteins regulating G-protein-coupled receptor (GPCR)-dependent signalling ${ }^{440}$. GPCRs transduce signals through a conformational change in response to agonist binding ${ }^{441}$. Arrestins can bind to activated receptors to promote their internalisation, destabilisation and degradation.

Novel arrestin-related proteins have been found and include six proteins: ARRDC1ARRDC6 ${ }^{439}$. To date, only a few studies have been conducted to understand the molecular function of ARRDCs. These studies report that ARRDCs may modulate
extracellular vesicle biogenesis and protein trafficking ${ }^{442-444}$, cancer metastasis ${ }^{445}$, insulin resistance ${ }^{446}$ and glucose metabolism ${ }^{201}$.

TXNIP is predominately found in the cytoplasm ${ }^{100,447}$. However, accumulating evidence have shown that TXNIP also localises to plasma membranes ${ }^{448}$ and/or diverse intracellular organelles, including mitochondria and the nucleus ${ }^{499}$. The localisation of TXNIP is critical for its roles in biological processes ${ }^{107,246}$. Specifically, TXNIP translocation from the nucleus into mitochondria under oxidative stress leads to the activation ASK1 and mitochondrial pathway of apoptosis ${ }^{449}$.

Thus, we decided to assess the distribution of TXNIP under oxaliplatin treatment condition. Firstly, we treated DLD1 cells with $10 \mu \mathrm{M}$ of oxaliplatin and, consistent with previous results, observed increased TXNIP expression by confocal imaging (Figure 37A). Consistent with other reports ${ }^{100}$, cell fractionation into nuclear and cytoplasmic fractions confirmed that induced TXNIP following drug treatment mostly accumulated in the cytoplasm in both DLD1 and HCT15 cells (Figure 3-7B-C). Mitochondria isolation also revealed that oxaliplatin caused TXNIP enrichment in mitochondria (Figure 3-8A), which was confirmed by confocal imaging (Figure 3-8B). However, confocal images showed that oxaliplatin induced TXNIP expression was not fully overlapped with a mitochondria stain, MitoTracker, suggesting TXNIP may localise to other organelles (Figure 3-8B). TXNIP has previously reported to localise to the ER and interact with protein disulfide isomerase (PDI) to regulate the activity of $\mathrm{PDI}^{156}$. In our study, TXNIP was also observed to partially overlap with calreticulin, an ER chaperone (Figure 3-8C). Altogether, these data suggest that TXNIP primarily accumulates in the cytosol organelles, including the mitochondria and ER, following oxaliplatin treatment.


Figure 3-7. The accumulation of induced TXNIP in cytosol.
(A) Immunofluorescent detection of TXNIP by confocal microscopy in DLD1 cells. DAPI (blue), Phalloidin (green), TXNIP (deep red); (B-C) effects of oxaliplatin on subcellular localization of TXNIP assessed by cell fractionation and immunoblotting in both (B) DLD1 and (C) HCT15 cells. LAMIN A - a nucleus marker, GAPDH - a cytoplasm marker.
A

Ctrl
C


Figure 3-8. The localization of TXNIP in both mitochondria and ER after oxaliplatin treatment.
(A) Effects of oxaliplatin on mitochondria localization of TXNIP assessed by mitochondria fractionation and immunoblotting. Tom20 - a mitochondria marker; (B-C) confocal imaging of subcellular localization of TXNIP in response to oxaliplatin in DLD1 cells. (B) After 48 hrs
treatment, merged images were taken: DAPI (blue), Phalloidin (green), TXNIP (deep red) and MitoTracker Red (red); overlap between red and deep red was showed as white. (C) Colocalization between TXNIP (red) and Calreticulin (green) in DLD1 cells.

### 3.3.3 TXNIP expression was decreased in colorectal cancer

The previous results strongly suggested that oxaliplatin induces TXNIP upregulation in CRC models. Therefore, to further investigate the role of TXNIP as a tumour suppressive gene, we analysed TCGA-COAD dataset. Consistent with other studies ${ }^{103,107,135,394,450}$, the expression of TXNIP was downregulated in tumour samples (Figure 3-9A); moreover, its expression positively correlates with the colon tumour suppressor APC expression and negatively correlates with oncogene MYC expression analysed in TCGA database (Figure 3-9B), indicating its potential anti-tumour function in colorectal cancer. Notably, these correlations were relatively weak.


Figure 3-9. Decreased TXNIP expression in TCGA colorectal cancer cohort.
The Cancer Genomic Atlas (TCGA: COAD and READ) database analysis: (A) Comparative analysis of substantial expression of TXNIP between adjacent normal tissue and cancer tissues, $\mathrm{P}<2.2 \mathrm{e}-16$; (B) Co-expression analysis for TXNIP in colorectal cancer versus MYC and APC. Plotted data are $\log 2 \mathrm{mRNA}$ expression from RNA-seq RPKM.

In addition, the levels of TXNIP expression were also quantified in archived tissues from a retrospective cohort of 32 patients with colorectal cancer. Samples included tissues isolated from tumour resection and biopsies. All the samples in the cohort were collected before chemoradiotherapy except for 3 patient samples. For these 3 patients, samples were collected from biopsies before treatment and resection after oxaliplatin-
based neo-adjuvant chemotherapy treatment. The clinical characteristics of all patients are listed in Table 3-3. An immunohistochemical assay was conducted to compare the expression of TXNIP between tumour lesion and adjacent normal tissue (ANT). TXNIP expression was mainly observed in the cytoplasm across all samples, and the staining intensity varied from weak to median in patient samples without treatment. The staining showed tumour lesions presented lower expression of TXNIP compared with normal tissues (Figure 3-10A-B). We then measured the expression of TXNIP in the biopsy samples collected before and after oxaliplatin-based neo-adjuvant chemotherapy treatment. Consistent with previous results in cell line models, TXNIP expression in all 3 patient tissues was increased in tumour resection samples post-chemotherapy compared with pre-chemotherapy tumour biopsies (Figure 3-10C-E). Therefore, clinical samples supported our in vitro data, which showed oxaliplatin-based chemotherapy can induce the expression of TXNIP.

Table 3-3 The clinical characteristics of all patient samples from Peking university
Third Hospital

| Patient No. | Sex | Collect |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| procedure |  |  |


| B0042815 | Female | resection | right hemicolon | adenocarcinoma | 66 | T3N1M0 | No |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| B0045868 | Female | resection | left hemicolon | adenocarcinoma | 55 | T3N0M0 | No |
| B0046985 | Male | resection | left hemicolon | adenocarcinoma | 57 | T3N1M0 | No |
| B0055650 | Male | resection | transverse colon | adenocarcinoma | 54 | T4aN0M0 | No |
| B0056913 | Male | resection | transverse colon | adenocarcinoma | 47 | T3N1M1 | No |
| B0058974 | Female | resection | ileocecum | adenocarcinoma | 64 | T4N2M0 | No |
| B0060127 | Male | resection | right hemicolon | adenocarcinoma | 49 | T2N0M0 | No |
| B0060644 | Female | resection | sigmoid colon | adenocarcinoma | 65 | T3N1cM0 | No |
| B0062970 | Male | resection | right hemicolon | adenocarcinoma | 53 | T4bN2bM1a | No |
| B0063214 | Female | resection | ileocecum | adenocarcinoma | 65 | T2N2M1 | No |
| B0063782 | Female | resection | rectosigmoid | adenocarcinoma | 51 | T3N2M1 | No |
| B0063918 | Male | resection | sigmoid colon | adenocarcinoma | 71 | T4NOMO | No |
| B0066989 | Female | resection | colon | adenocarcinoma | 40 | T3N0M0 | No |
| B0027766 | Female | resection | right hemicolon | adenocarcinoma | 50 | T4N1cM0 | No |
| B0033322 | Male | biopsy | sigmoid colon | adenocarcinoma | 57 | T2N2aM1a | No |
| B0044089 |  | resection | sigmoid colon | adenocarcinoma |  | T2N2aM1a | Yes |
| B0050898 | Male | biopsy | rectum | adenocarcinoma | 50 | T4N1M1 | No |
| B0053926 |  | resection | rectum | adenocarcinoma |  | T4N1M1 | Yes |
| B0058435 | Male | resection | sigmoid colon | adenocarcinoma | 56 | T4N2M0 | No |
| B0060820 |  | resection | sigmoid colon | adenocarcinoma |  | T4N2M0 | Yes |



Figure 3-10. TXNIP expression pattern in our clinical study cohort by immunohistochemistry (IHC) analysis.
TXNIP expression was decreased in colorectal cancer tissue, but upregulated after neo-adjuvant chemotherapy treatment. (A) Detection of TXNIP protein levels in both Tumour and adjacent
normal tissue (ANT) samples from 32 patients with primary colorectal cancer. HE, EnVision, serial sections, original magnification $\times 200$; (B) Statistical analysis of TXNIP IHC score between adjacent normal tissue and Tumour tissue specimen. The semi-quantitative scoring of each specimen was calculated by "expression intensity $\times$ expression area", all values were expressed as mean $\pm$ SD. ${ }^{* * * *} \mathrm{p}<0.0001$; (C-E) Detection of TXNIP protein levels of adjacent normal tissue (ANT), treatment-naïve Tumour samples and oxaliplatin-based neo-adjuvant chemotherapy (FOLFOX6, FOLFOX6 and Xelox6, respectively). HE, EnVision, serial sections, original magnification $\times 400$. Abbreviation: Hematoxylin and eosin stain.

### 3.3.4 TXNIP upregulation is induced by reactive oxygen species (ROS) production dependent on MondoA

A fine cellular redox balance is maintained by ROS and a companion antioxidant system, which can scavenge and therefore control $\operatorname{ROS}^{451}$. One of the key antioxidant systems is the thioredoxin (Trx) system, which is composed of NAPDH, Trx and thioredoxin reductase (TrxR). The antioxidant function of Trx relies on its disulfide reductase activity (providing the electrons to Prxs, methionine sulfoxide reductases, and some redox-sensitive transcription factors) ${ }^{97}$. TXNIP is essential for redox homeostasis due to its ability to bind to thioredoxin (Trx) and inhibit Trx function and expression ${ }^{97,99}$. Oxaliplatin has been reported to induce ROS generation in CRC models ${ }^{68,412,452}$. In CRC, synergistical anti-cancer effects were observed when of oxaliplatin treatment was combined with piperlongumine (PL), a molecule promoting ROS production, via a manner dependent on induction of an ROS-mediated mitochondrial dysfunction and ER stress apoptotic pathways ${ }^{68}$.

Given that oxaliplatin anti-tumour activity is associated with ROS induction ${ }^{453}$ and oxidative stress is also associated with TXNIP expression ${ }^{454}$, the increase in TXNIP expression after oxaliplatin treatment were hypothesised to be mediated by ROS generation. Thus, we tested ROS production using DHE assay.

Consistent with previous studies ${ }^{455,456}$, oxaliplatin increased ROS generation in DLD1 and HCT15 cells (Figure 3-11A-B). Next, when combining NAC, a ROS inhibitor, and oxaliplatin, TXNIP induction was supressed (Figure 3-11C-F). Specifically, the
increase in TXNIP mRNA by oxaliplatin was abolished by the addition of NAC (Figure 3-11C-D), suggesting that ROS generation is required for oxaliplatin-induced TXNIP by transcriptional regulation.


Figure 3-11. ROS production responsible for the activation of TXNIP induced by oxaliplatin.
(A-B) Oxaliplatin induced the overproduction of ROS in both (A) DLD1 cells; (B) HCT15 cells. Cells were treated for 48 h with oxaliplatin ( $10 \mu \mathrm{M}$ ) followed by Dihydroethidium (DHE) staining and fluorescence detection. Results are presented as fold-increase in mean fluorescence intensity normalized to untreated and mean $\pm \mathrm{SD}(\mathrm{n}=3)$. (C-D) qPCR analysis of TXNIP
mRNA in DLD1 cells (C) or HCT15 cells (D) treated with N-acetyl Cysteine or oxaliplatin or the combinational treatment. Two-tailed Student's $t$ test. All values were expressed as mean $\pm$ SD. ${ }^{*} \mathrm{p}<0.05, * * \mathrm{p}<0.01, * * * \mathrm{p}<0.001, * * * * \mathrm{p}<0.0001$. (E-F) Immunoblot analysis of TXNIP in DLD1 cells (E) or HCT15 cells (F) treated with N-acetyl Cysteine or oxaliplatin or the combinational treatment.

Then we further analyse RNA-seq dataset of both DLD1 and HCT15 cells. The result showed 23 upregulated differentially expressed genes (DEGs) shared in both cell lines, including TXNIP (Figure 3-1C, Figure 3-12A). We also observed that another arrestin family member, arrestin domain-containing protein $4(A R R D C 4)$, was increased as well (Figure 3-12A). It was interesting for several reasons: 1) ARRDC4 and TXNIP are members of the same family group (arrestin family) ${ }^{457}$. Importantly, they are paralogs showing $63 \%$ similarity over their entire ORFs ${ }^{458}$. 2) They have always been shown to be regulated under same conditions, even by the same regulator ${ }^{457-459}$. Thus, we selected ARRDC4 for further analysis. Consistently, qPCR analysis showed the increased mRNA level of ARRDC4 (Figure 3-12B). Notably, the induction of ARRDC4 was also blunted by the combined treatment with NAC (Figure 3-12B).


Figure 3-12. Increased $A R R D C 4$ expression post oxaliplatin treatment in colorectal cancer.
(A) heatmap showing overlapped 23 regulated genes induced by oxaliplatin in (Left panel) DLD1 cells, (Right panel) HCT15 cells. The order of DEGs was placed up to fold change of upregulation. Higher differentially expressed genes were put on the top and lower ones on the bottom. (B) qPCR analysis of $A R R D C 4$ mRNA in (left panel) DLD1 cells and (right panel) HCT15 cells treated with N-acetyl Cysteine (NAC) or oxaliplatin or the combinational treatment. All values were expressed as mean $\pm$ SD. ${ }^{* * *} \mathrm{p}<0.001, * * * * \mathrm{p}<0.0001$.
Both TXNIP and ARRDC4 are the most highly MondoA-dependent genes ${ }^{109,458}$. To identify whether MondoA is responsible for the induction of TXNIP, MondoA expression was assessed after treatment and showed no change at transcript and protein levels (Figure 3-13A-C). MondoA has been shown to induce the expression of target genes when it is shuttled into the nucleus ${ }^{109,458}$. After oxaliplatin treatment, the translocation of MondoA into the nucleus was observed (Figure 3-13D). Next, the transient knockdown of MLXIP (gene name of MondoA) in cells led to the compromised effects on induced TXNIP and ARRDC4 expression upon oxaliplatin treatment (Figure 3-13E-F), which was further confirmed by permanent MondoA gene knock-out using a CRISPR-Cas9 system (Figure 3-13G-H). Notably, previous study showed that c-Myc is reported to be regulate TXNIP expression in breast cancer. The molecular mechanism is competing with MondoA to bind TXNIP promoter ${ }^{111}$. Then we analysed c-Myc expression in RNA-seq dataset and, interestingly, observed to be downregulated post oxaliplatin treatment (Figure 3-14A). Thus, we hypothesised that c-Myc expression could be required to supress TXNIP expression.

CRISPR/Cas9-based transcriptional activation (CRISPRa) system has recently emerged as a powerful and scalable technique for genetic overexpression ${ }^{460-464}$. In this system, the dead Cas9 (dCas9), a CRISPR protein variant lacking its endonuclease ability, has been fused with various gene activation domain, such as dCas9-VP64, Synergistic Activation Mediator (SAM), SunTag and VPR (VP64-p65-Rta) ${ }^{465-467}$. Here, we generated dCas9-VPR DLD1 cells. To identify the involvement of c-Myc in TXNIP regulation, we endogenously overexpressed c-Myc using the CRISPR-cas9 activation
system. Then we treated non-targeting control and c-Myc overexpressing cells with oxaliplatin and then analysed TXNIP expression. The results showed that overexpressing c-Myc did not abolish oxaliplatin-induced TXNIP expression (Figure 3-14B), suggesting that in our system, the decrease of c-Myc is not required to drive the increased TXNIP expression after chemotherapy treatment. Taken together, these results suggested MondoA activation is required for chemotherapy-induced TXNIP upregulation, independently of decreased c-Myc levels.

We further used ChIP-PCR to verify the dependence of MondoA on TXNIP regulation. Relative to control, the amount of MondoA on the TXNIP promoter was significantly increased after oxaliplatin treatment, which was compromised after combined treatment with NAC (Figure 3-14C). The specificity of the PCR product was assessed by Sanger sequencing. Altogether, these findings demonstrate that ROS production is responsible for oxaliplatin-induced TXNIP overexpression, possibly by activating transcriptional activity of MondoA.


Figure 3-13. MondoA translocation into nucleus responsible for the activation of TXNIP induced by oxaliplatin.
(A-B) qPCR analysis of MLXIP mRNA in (A) DLD1 cells and (B) HCT15 cells treated with oxaliplatin at indicated time points; (C) Immunoblot analysis of MondoA expression in DLD1 cells after oxaliplatin treatment; (D) effects of oxaliplatin on subcellular localization of MondoA assessed by cell fractionation and immunoblotting in DLD1 cells. LAMIN A -a nucleus marker, GAPDH - a cytoplasm marker; (E-F) Assessment of MLXIP, TXNIP and ARRDC4 mRNA in (E) DLD1 cells and (F) HCT15 cells upon knockdown of MondoA with oxaliplatin treatment by q-PCR analysis. (G-H) Immunoblot analysis of TXNIP expression in both (G) MondoA-knockout DLD1 cells and (H) MondoA-knockout HCT15 cells after oxaliplatin treatment. All values were expressed as mean $\pm$ SD. ${ }^{* *} \mathrm{p}<0.01,{ }^{* * *} \mathrm{p}<0.001$, $* * * * \mathrm{p}<0.0001$. Abbreviation: MKO: MondoA knockout.


Figure 3-14. c-Myc was not involved in oxaliplatin-induced TXNIP expression.
(A) MYC mRNA level was analysed in our RNA sequencing data; (B) Immunoblot analysis of TXNIP expression in c-Myc-overexpressing DLD1 cells after oxaliplatin treatment; (C) ChIPPCR was used to validate MondoA occupancy on the promoters of TXNIP gene in DLD1 cells treated with oxaliplatin or the combinational treatment with NAC. Results shown are representative of three independent experiments. All values were expressed as mean $\pm \mathrm{SD}$. Two-tailed Student's t test; ${ }^{* *} \mathrm{p}<0.01,{ }^{* * *} \mathrm{p}<0.001$. Abbreviation: NTCa: Non-targeting control CRISPR activation. C-MYCa: C-MYC CRISPR activation.

### 3.3.5 ER stress signalling was involved in oxaliplatin-mediated TXNIP regulation

One of the most studied organelles is the ER, the largest intracellular organelle in cells which spans from the nuclear envelope to the cell membrane ${ }^{468}$. Alterations in the function of ER can lead to the accumulation of unfolded or misfolded proteins. The ER activates different signals to restore ER homeostasis in response to the burden of unfolded or misfolded proteins, a process collectively termed the unfolded protein response (UPR) ${ }^{469,470}$.

Chemotherapy has been reported to modulate ER stress ${ }^{471,472}$. To identify whether oxaliplatin modulates ER stress in CRC, we analysed RNA sequencing dataset. Gene ontology (GO) is a well-acknowledged gene functional enrichment database and is a tool for the unification of biology ${ }^{473}$. Interestingly, GO analysis biological processes (BP) terms of RNA-seq data manifested that oxaliplatin-suppressed genes are enriched at ER stress-responsive genes as well as translation-related genes. DEGs were highly clustered in related signalling pathways, such as "tRNA aminoacylation for protein translation", "translation initiation", "SRP-dependent co-translational protein targeting
to membrane", "response to endoplasmic reticulum stress", "protein targeting to membrane", "protein targeting to ER", "protein targeting", "protein localization to endoplasmic reticulum" and "co-translational protein targeting to membrane" (Fugure3-15A-B), suggesting the involvement of ER stress. The UPR-dependent PERK-eIF2a axis is reported to be involved in the synthesis of the secreted proteome ${ }^{474}$, suggesting this axis might be, to a greater extend, modulated by oxaliplatin. Correspondingly, Gene set enrichment analysis (GSEA) further showed the downregulation of unfolded protein responses in the post-treatment group (Figure 3-15C-D). Based on the details in introduction section (1.3.1.3 ER stress signalling), we tested UPR-related markers and observed the downregulated expression of UPR markers, including BiP, IRE-1a, PERK and its downstream targets ATF4, but not ATF6 at RNA level (Figure 3-16A). The immunoblotting assay also showed the decreased expression of BiP and p-eIF2a, but no obvious change for IRE-1a, PERK and ATF4 at protein level (Figure 3-16B). Collectively, oxaliplatin decreased unfolded response signalling in our CRC models.


Figure 3-15. Oxaliplatin suppressed ER stress signalling in CRC.
(A-B) Functional enrichment analysis of RNA sequencing dataset shows the top enriched downregulated gene ontologies after 48h of oxaliplatin treatment in (A) DLD1 cells, (B) HCT15 cells. ER stress-responsive genes signalling and translation-related genes signalling were highlighted. adjusted $p$-value $(\mathrm{padj})=p$-value $*($ total number of hypotheses tested $) /($ rank of the p-value), gene ratio $=$ the number of differentially expressed genes in each GO term/ all differentially expressed genes available in GO database. (C-D) Gene set enrichment analysis (GSEA) for unfolded protein response signature using downregulated transcriptomic data after oxaliplatin treatment. NES $\geq 1$ and false discovery rate $(\mathrm{FDR}) \mathrm{q}$ value $<0.05$.


Figure 3-16. Oxaliplatin decreased unfolded response signalling in CRC.
(A) qPCR analysis of UPR-related genes (HSPA5, ERN1, EIF2AK3, ATF4, ATF6) in DLD1 cells post oxaliplatin; (B) Immunoblot analysis of the expression of UPR-related proteins (IRE1a, ATF6, BiP, PERK, ATF4, t- eIF2a and p-eIF2a) in DLD1 cells after oxaliplatin treatment. All values were expressed as mean $\pm \mathrm{SD}$. NS=non-significant, $* * \mathrm{p}<0.01$, $* * * \mathrm{p}<0.001$, vs. Control. Abbreviation: NES: Normalized enrichment score. HSPA5: Heat shock protein family A member 5. ERN1: endoplasmic reticulum to nucleus signalling 1. EIF2AK3: eukaryotic translation initiation factor 2 alpha kinase 3.

Recent studies emphasise the requirement of ER stress for TXNIP activation, and in particular the major sensors IRE1a and PERK ${ }^{150,154,155}$. For instance, knockout of either PERK or IRE-1a supresses the upregulation of TXNIP expression upon ER stress in $\beta$ cells ${ }^{150}$. Given the observed decrease in IRE-1a and PERK signalling genes following oxaliplatin treatment, the role of ER stress in modulating TXNIP expression was further investigated. To this end, different genetically modified cell models were established to identify if these pathways are required for TXNIP induction by oxaliplatin. We found that knock-down of EIF2AK3, encoding PERK, enhanced TXNIP expression (Figure 3-17C-D). In contrast, overexpression of EIF $2 A K 3$ inhibited TXNIP expression after oxaliplatin treatment (Figure 3-17A-B). Together, this suggests that PERK signalling
could negatively regulate TXNIP expression under oxaliplatin treatment (Figure 3-17A-D). No changes in TXNIP expression were observed in the ERN1 (encoding IRE-1a)-overexpressing condition, suggesting IRE-1a does not regulate TXNIP expression (Figure 3-17E-F). To verify whether PERK-eIF2a signalling was also modulated by ROS, cells were subjected to combinational treatment with NAC. The results showed that treating cells with NAC reversed the decreased expression of p-eIF2a (a downstream target of PERK) following oxaliplatin treatment (Figure 3-17G). To further identify whether MondoA is the major regulator of TXNIP expression, we knocked-down PERK expression in MondoA-KO cell model and observed that reduced PERK signalling was not able to induce TXNIP expression after chemotherapy treatment when depleting MondoA (Figure 3-17H). These results suggested that TXNIP upregulation in response to chemotherapy treatment was indirectly by PERK mediated ER stress signalling, however this could be a secondary consequence of excessive ROS damage of the ER, resulting on PERK/eIF2a general translation, a possibility that would require further investigation. These results therefore highlight a major role for MondoA in mediating TXNIP overexpression.


Figure 3-17. PERK signalling was involved in TXNIP overexpression.
(A, C, E) Immunoblot analysis of TXNIP after oxaliplatin treatment in (A) PERKoverexpressing DLD1 cells, (C) PERK-knockdown DLD1 cells, (E) IRE1a-overexpressing DLD1 cells; (B, D, F) The statistical analysis was performed, respectively. (G) Immunoblot analysis of p-eIF2a and t-eIF2a in the presence and absence of oxaliplatin or NAC. (H) Immunoblot analysis of MondoA, PERK and TXNIP after oxaliplatin in MondoA-knockout or EIF2AK3-knockdown DLD1 cells. All values were expressed as mean $\pm$ SD. NS $=$ nonsignificant, $* \mathrm{p}<0.05, * * \mathrm{p}<0.01, * * * \mathrm{p}<0.001, * * * * \mathrm{p}<0.0001$, vs. Control. Abbreviation: NTCa: Non-targeting control CRISPR activation. C-MYCa: C-MYC CRISPR activation. EIF2AK3a: EIF2AK3 CRISPR activation. ERN1a: ERN1 CRISPR activation.

### 3.4 Overview

Recently, chemotherapy has been reported to induce immune activation in cancer, which is critical for the maintenance of long-term anti-tumour effects. Except for already identified theories including the induction of ICD and adjuvanticity, we hypothesised the involvement of tumour suppressive genes in promoting tumour immunogenicity. The experiments in this chapter aimed to identify a potential tumour suppressive gene which may mediate chemotherapy-induced anti-cancer immune effects. Moreover, as oxidative stress and ROS are main contributors for chemotherapyinduced effects, we aimed to understand the role of ROS in the regulation of target protein. The results are summarized here in Figure 3-18. This chapter is the foundation for the subsequent functional studies.


Figure 3-18. Schematic illustration of molecular mechanism of oxaliplatin-induced TXNIP expression.
Consistent with previous study, ROS was increased after oxaliplatin treatment in colorectal cancer cells. The increased ROS induced TXNIP expression via two different pathways: MondoA activation and ER stress signalling. Abbreviation: ER: Endoplasmic reticulum.

In this chapter, to start with, we used RNA-seq analysis to find out the potential candidate, TXNIP, upon oxaliplatin treatment. The upregulation of TXNIP by oxaliplatin in CRC is time- and dose-dependent. These results were further verified in 3D models (cell line-derived spheroids and patients-derived organoids), which have been proposed as more suitable in-vitro models for cancer studies ${ }^{432}$. Increased TXNIP expression following oxaliplatin treatment was observed at both the protein and mRNA levels, suggesting its expression is transcriptionally induced. Next, due to the close relationship between its function and cellular localisation, we analysed its expression pattern by multiple assays. TXNIP can translocate to different intracellular positions, such as cytosol, nucleus, mitochondria and even cell surface ${ }^{475}$, leading to various biological effects ${ }^{449}$. For example, in pancreatic beta cells, TXNIP resides primarily in the nucleus and shuttles to mitochondria upon oxidative stress, whereby TXNIP promotes the phosphorylation and activation of ASK1 by binding to $\mathrm{Trx}^{449}$. In endoplasmic reticulum, TXNIP is reported to bind to protein disulfide isomerases and promotes their enzymatic activity to fold proteins ${ }^{156}$. Therefore, we explored the cellular localisation of TXNIP after drug treatment. Consistent with other studies ${ }^{447}$, TXNIP expression induced by oxaliplatin primarily accumulates in the cytoplasm. Further studies pointed out upregulated TXNIP was especially enriched in mitochondria and endoplasmic reticulum. However, whether TXNIP was enriched in other organelles is unknown. Collectively, these data suggest that TXNIP may play a role in redox balance or unfold protein response relevant effects.

Secondly, the mechanism of oxaliplatin-induced TXNIP induction was explored. From previous publications, ROS is reported to regulate the expression of TXNIP ${ }^{476}$. Moreover, we observed the increased ROS levels after oxaliplatin treatment, leading us to investigate whether ROS is a regulator of TXNIP expression. Using antioxidant
compounds, NAC, we observed oxaliplatin-induced TXNIP expression dramatically diminished, suggesting that the generation of ROS was responsible for the increased TXNIP by oxaliplatin. Several factors have been reported to regulate TXNIP mRNA expression and can be broadly divided into four classes: transcription factors ${ }^{111}$, microRNAs and circular RNAs ${ }^{127,133}$, epigenetic regulators ${ }^{134}$ and regulators of mRNA and protein stability ${ }^{136}$ (like LncRNAs). Among them, MondoA is the most studied one ${ }^{109,256}$. Especially, another arrestin family member ARRDC4 was also observed to be upregulated by oxaliplatin from our RNA seq data analysis. As they are both highly MondoA-dependent genes, this result emphasises that MondoA could be the possible regulator for the ROS-mediated TXNIP and ARRDC4 upregulation. MondoA knockout was shown to abrogate TXNIP expression induced by oxaliplatin. Correspondingly, we observed more MondoA enriched on TXNIP promoter after oxaliplatin, which was reversed by the addition of NAC, confirming that MondoA was required for oxaliplatininduced TXNIP expression. Whereas, c-Myc, a metabolic regulator of the MondoATXNIP axis ${ }^{111}$, was proved not to be involved in TXNIP regulation by applying CRISPR-activation endogenous overexpression system.

Given the recent studies pointing out the close relationship between TXNIP and ER stress, in addition to the localization of TXNIP in ER, we tested whether TXNIP and ER stress is linked in our system. Thus, we analysed RNA-seq dataset and observed the downregulated ER signalling, especially IRE-1a and PERK-eIF2a pathways. Further studies provided the evidence that PERK-eIF2a axis was more important for TXNIP expression upregulation, which was also modulated by ROS production ${ }^{150,477}$. In our study, we observed the PERK-eIF2a axis was able to regulate TXNIP expression. However, when we knocked down PERK in MondoA-KO cells, oxaliplatin was unable to induce TXNIP expression, highlighting the importance of the MondoA signalling of

TXNIP regulation post chemotherapy. Notably, in our experiment (Figure 3-17H), the levels of PERK knock-down achieved were not substantial. This may raise concerns that there wasn't sufficient PERK knockdown to overcome the impact of MondoA-KO. Thus, PERK knockouts could be established in the future to confirm this finding.

Chapter IV. Induction of TXNIP suppressed GDF15 expression

### 4.1 Introduction

In chapter III, we identified the upregulation of TXNIP after oxaliplatin treatment. Therefore, we aimed to understand the biological functions of TXNIP in this chapter. The hallmarks of cancer according to Bob Weinberg and Douglas Hanahan summarise the shared features of all cancer types. These hallmarks include common phenotypic, molecular and inter-cellular mechanisms, and are grouped into eight acquired capabilities, two enabling characteristics and four prospective new hallmarks and enabling characteristics. These four features are unlocking phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes and senescent cells ${ }^{478-480}$.

One of the acquired capabilities of cancer cells is metabolic reprogramming, which increases the ability of cancer cells to acquire nutrients, in particular glucose and glutamine ${ }^{479}$. One of the reasons that activated oncogenes (e.g., RAS, MYC) and mutant tumour suppressors (e.g., TP53) drive malignant transformation is to increase glucose metabolism ${ }^{481}$. Under aerobic conditions, to support cell division and many biological functions, intracellular glucose is metabolised to pyruvate which enters the mitochondrial tricarboxylic acid (TCA) cycle to produce the majority of ATP ${ }^{482}$. In solid tumours, poorly formed vasculature causes hypoxia and acidosis microenvironment, with low levels of $\mathrm{O}_{2}$ and nutrients. Consequently, tumour cells shift the metabolic pattern to aerobic glycolysis identified by Otto Warburg ${ }^{483}$. In this manner, glucose is catabolised anaerobically to lactate contributing to tumour growth and the immunosuppression in the $\mathrm{TME}^{484-486}$. Importantly, this metabolic alteration relies on the alterations of a series of enzymatic reactions ${ }^{487}$.

Cancer cells prefer aerobic glycolysis, even though aerobic glycolysis is 18 -fold less efficient at producing ATP compared to mitochondrial oxidative phosphorylation.

Interestingly, cancer cells can partially compensate the increasing need by upregulating GLUTs, especially GLUT1 ${ }^{488}$. Glucose transporters (GLUTs), encoded by the $\operatorname{SLC} 2$ genes, play an important role in regulating glycolysis by mastering cellular uptake of various hexoses and derivatives ${ }^{489}$. GLUT1 is a key rate-limiting factor responsible for glucose transport in cancer cells. Accordingly, GLUT1 expression is low in normal epithelial tissues and benign epithelial tumours, yet highly expressed in human carcinomas ${ }^{490}$. Notably, GLUT1 can also transport galactose, mannose, glucosamine and DHA ${ }^{489}$. Increased GLUT1 expression has been demonstrated as a useful biomarker for monitoring colorectal adenoma-to-carcinoma progression ${ }^{491}$ and is also associated with enhanced proliferation, metastasis and drug resistance in CRC and other cancer types ${ }^{482,492-494}$. Therefore, several studies have proposed GLUT1 as a potential prognostic biomarker in colorectal cancer ${ }^{495,496}$. The regulation of GLUT1 expression relies on key proliferation and pro-survival pathways, including hypoxia (HIF-1a) ${ }^{497}$, c-Myc ${ }^{498}$, tumour suppressors (APC) ${ }^{499}$ and p53 pathways. Regulation of GLUT1 expression has been observed at both the transcriptional and translational level. Specifically, GLUT1 expression is transcriptionally regulated by several factors including activated oncogenes (e.g., $R A S^{500}, M Y C^{501}$ ), suppression of tumour suppressors (e.g., P53 ${ }^{502}$, TXNIP ${ }^{219}$ ) and microRNAs (miR-144 ${ }^{503}$, miR-132 ${ }^{504}$ and miR- $150^{505}$ ). In addition, TXNIP ${ }^{220}$ and Derlin- $3^{506}$ have been demonstrated to mediate GLUT1 degradation.

As a major part of redox process, TXNIP regulates ROS levels by inhibiting the activity of thioredoxin ${ }^{96}$. Consequently, TXNIP exerts tumour-suppressive abilities in a range of tumour types ${ }^{450}$. In Chronic Lymphocytic Leukemia (CLL), TXNIP is reported to induce the production of ROS and apoptosis by inactivating $\operatorname{Trx}{ }^{172}$. Similarly, TXNIP reverses doxorubicin-induced chemotherapy resistance by increasing ROS synthesis
and DNA damage accumulation in triple-negative breast cancer ${ }^{507}$. Moreover, the continue activation of Trx/TrxR system due to the decreased expression of TXNIP plays an important role in the increased metastatic potential of cancer cells ${ }^{188}$. For example, TXNIP can also inhibit cell metastasis by regulating EMT signatures ( e.g., E-cadherin, ZEB1, Slug and Vimentin) in renal cell carcinoma and melanoma ${ }^{508,509}$. In addition, TXNIP has also been observed to decrease metastasis by downregulating glycolysis in lung cancer ${ }^{133}$, emphasising the important role of TXNIP in modulating the proliferative and metastatic capabilities of tumour cells in ROS-dependent or independent pathways.

Additionally, TXNIP is involved in modulating TME by regulating secreted factors. A study with clinical samples identified the close relationship between TXNIP expression and angiogenesis ${ }^{107}$. Knockdown of TXNIP promotes the secretion of VEGF, resulting in increased angiogenesis ${ }^{146,510}$. Furthermore, TXNIP has been reported to regulate the production of inflammatory cytokines, especially NLRP3 inflammasome-associated secreted proteins (such as IL-1 $\beta$ and IL-18). The association of TXNIP with NLRP3 induced by elevated ROS levels leads to inflammasome activation and IL-1 $\beta$ secretion ${ }^{239}$. In Dextran Sodium Sulfate-induced colitis model, inhibition of ROSTXNIP axis alleviates inflammation by deactivating the NLRP3 inflammasome ${ }^{178}$, confirming the role of TXNIP in the regulation of immune responses.

Based on previous publications concerning the biological functions of TXNIP, we investigated the role that TXNIP may exert in this chapter. Especially, we performed assays to explore a possible downstream target of TXNIP.

### 4.2 Aims and objectives

TXNIP has been demonstrated to regulate various physiological and pathological processes. In this chapter, we aimed to investigate the functional roles and the possible downstream targets of chemotherapy-induced TXNIP.

This aim has been addressed with the following specific objectives:

1. To explore the effects of TXNIP on glycolysis by performing glucose uptake, lactate secretion and seahorse metabolic assays;
2. To explore the involvement of TXNIP in chemotherapy-induced cell death and drug resistance using cell viability assay;
3. To explore whether TXNIP regulates metastatic potential of cancer cells by performing wound healing assay;
4. To study whether TXNIP affect angiogenesis using tube formation assay;
5. To explore the effects of TXNIP on the activation of NLRP3 inflammasome by performing western-blot and ELISA assays;
6. To explore the possible secreted factors regulated by TXNIP by mass spectrometry, western blot and ELISA assays.

### 4.3 Results

### 4.3.1 MondoA-TXNIP axis does not regulate glycolysis

Glucose metabolism in cancer cells requires a series of enzymatic reactions ${ }^{487}$. Accordingly, upregulation of glycolytic enzymes and glucose transporters promotes cancer cells to proliferate and metastasise. In one study investigating the role of glycolysis in regulating the immune infiltrates, a panel of glycolysis-related genes were used for analysis ${ }^{487}$. To understand the effects of chemotherapy on glucose metabolism, we treated cells with oxaliplatin and performed the analysis on the same set of
glycolysis-related genes from previous RNA-seq dataset (Figure 3-1, Figure 4-1). The results showed that drug-treated group generally presented decreased expression of these genes, suggesting oxaliplatin can promote reduced glycolysis (Figure 4-1A-B). Multiple testing was also performed, and the data showed that these glycolysis-related genes were still significantly expressed (FDR <0.05) (Appendix Table 9). Increased TXNIP expression has been reported to decrease glycolysis ${ }^{111}$. To find out a possible link between TXNIP and oxaliplatin-induced decreased glycolysis, we then determined the impact of TXNIP activation on oxaliplatin-decreased cellular metabolism by comparing glycolysis gene signatures between control and TXNIP-KO cells with or without oxaliplatin treatment. Changes in the expression of glycolysis genes were not observed between control and TXNIP-KO cells (Figure 4-1C-F). This result was consistent with previous result that ectopically expressing c-Myc, a master protein of glycolysis ${ }^{216,511}$, does not change expression of TXNIP after drug treatment (Figure 314B). Together, these data suggests that TXNIP is not involved in oxaliplatin-mediated metabolic change.


Figure 4-1. TXNIP was not involved in the regulation of oxaliplatin-mediated glycolysis signature.
(A-B) Analysis of the indicated glycolysis-regulated genes in RNA-seq datasets from DLD1 cells (A), HCT15 cells (B) with/ without oxaliplatin treatment; (C-D) Analysis of the indicated glycolysis-regulated genes in RNA-seq datasets comparing TXNIP-KO with control DLD1 cells (C) or HCT15 cells; (E-F) Analysis of the indicated glycolysis-associated genes in RNAseq datasets comparing TXNIP-KO with control DLD1 cells (C) or HCT15 cells that were treated with oxaliplatin for 48 h . Data are mean $\pm \mathrm{SD}$. NS $=$ non-significant, $* \mathrm{p}<0.05$, $* * \mathrm{P}<0.01,{ }^{* * *} \mathrm{P}<0.001, * * * * \mathrm{P}<0.0001$. Abbreviation: NTC: Non-targeting control. TKO: TXNIP knockout. FPKM: Fragments per kilobase of exon model per million reads mapped. PFKP: phosphofructokinase, platelet. PFKL: phosphofructokinase, liver type. PGAM1:
phosphoglycerate mutase 1. ENO3: enolase 3. SLC2A1: solute carrier family 2 member 1. HK2: hexokinase 2. ENO2: enolase 2. ALDOA: aldolase, fructose-bisphosphate A. PGK1: phosphoglycerate kinase 1. SLC16A1: solute carrier family 16 member 1. LDHA: lactate dehydrogenase A. PFKM: phosphofructokinase, muscle. LDHB: lactate dehydrogenase B. ENO1: enolase 1. GAPDH: glyceraldehyde-3-phosphate dehydrogenase. GPI: glucose-6phosphate isomerase.

Glucose transporter 1 (GLUT1) is highly expressed in several cancer types and functionally promotes tumorigenicity ${ }^{512,513}$. TXNIP is reported to mediate the influx of glucose and lactate production by decreasing the expression of GLUT1 via both promotion of internalization and endocytosis of protein levels and deduction at messenger RNA levels ${ }^{219-222}$. We therefore analysed the involvement of TXNIP in GLUT1 protein expression in our system. Consistent with the transcriptomic data in Figure 4-1A-B, oxaliplatin treatment decreased GLUT1 expression at the protein level in DLD1 cells (Figure 4-2A). However, knocking-out TXNIP did not reverse decreased GLUT1 expression induced by oxaliplatin (Figure 4-2A).

As a master of glucose transportation, GLUT1 exerts effects as a cellular membrane protein. Therefore, it is important to understand both the expression and the distribution of GLUT1 in cells. To determine the impact of TXNIP expression on GLUT1 localisation, confocal imaging was used to visualise GLUT1 in TXNIP wild-type and knockout cell lines following oxaliplatin treatment. Under non-treatment condition, GLUT1 was present on the cell membrane of both DLD1-TKO and control cells (Figure 4-2B). GLUT1 internalisation was observed after drug treatment in both TXNIP wildtype and knockout cell lines (Figure 4-2B), indicating TXNIP exerted no impact on GLUT1 internalisation. Together, these results demonstrated that TXNIP had no impact on the expression and localisation of GLUT1 after oxaliplatin treatment.


Figure 4-2. TXNIP was not involved oxaliplatin-induced decreased expression and internalization of GLUT1.
(A) Immunoblot analysis of GLUT1 in control and TXNIP-KO DLD1 cells with/ without oxaliplatin treatment; (B) immunofluorescent detection of GLUT1 in control and TXNIP-KO DLD1 cells with/ without oxaliplatin treatment by confocal microscopy. DAPI (blue), Epcam (green), TXNIP (deep red). Abbreviation: GLUT1: Glucose transporter 1. DAPI: 4',6-diamidino-2-phenylindole.

Further, we measured glucose uptake and lactate production, two primary indicators of the Warburg effect. Expectedly, oxaliplatin decreased glucose uptake, indicating its inhibitory role in glycolysis (Fig 4-3A-B). But lactate secretion was not altered with oxaliplatin treatment (Fig 4-3C-D). Consistently, the results showed no difference between TXNIP-KO and control cells (Figure 4-3A-D). The ECAR is another measurement of glucose metabolism and reflects the lactic acid - induced acidification of the medium surrounding cancer cells ${ }^{217}$. To further verify the effect of TXNIP on the bioenergetic profiling of CRC, we analysed the ECAR of TXNIP-KO DLD1 cells. Correspondingly, the result showed no difference in the absence of TXNIP (Figure 4-3E-F). Altogether, these results suggested TXNIP was not responsible for the oxaliplatin-mediated suppression of the glycolysis phenotype.


Figure 4-3. TXNIP was not involved in metabolic reprogramming colorectal cancer cells. (A-B) The effect of TXNIP knockout on Glucose uptake in the DLD1 cells (A) and HCT15 cells(B) with/without oxaliplatin treatment; (C-D) The effect of TXNIP knockout on lactate secretion in the DLD1 cells (C) and HCT15 cells(D) with/without oxaliplatin treatment; (E) Seahorse metabolic analysis of ECARs in the TXNIP-KO and control cells; (F) Statistic analysis of glycolysis, glycolytic capacity and glycolytic reserve between non-targeting control and TXNIP-KO DLD1 cells. Data are mean $\pm \mathrm{SD}$. NS $=$ non-significant, **P $<0.01$, ***P $<0.001, * * * * \mathrm{P}<0.0001$. Abbreviation: ECAR: Extracellular acidification rate. 2-DG: 2-Deoxy-D-glucose.

### 4.3.2 TXNIP does not affect drug sensitivity, metastasis and angiogenesis

Our previous results showed that oxaliplatin-induced TXNIP expression is dependent on ROS generation. ROS induced by oxaliplatin has been reported to mediate apoptosis and autophagy, promoting cell death ${ }^{68,452}$. Compared to other chemotherapy regimen such as irinotecan, oxaliplatin-mediated cytotoxicity, to a higher extend, relies on ROS production ${ }^{455}$. In line with other studies, we observed that the addition of NAC $(10 \mathrm{mM})$ significantly reduced the cytotoxicity of oxaliplatin and increased the cell viability in both DLD1 and HCT15 cells ${ }^{412,514}$ (Figure 4-4A-B), suggestive of the important role of ROS production in driving oxaliplatin-induced cytotoxicity.

It is reported that oxidative stress facilitates the translocation of TXNIP into mitochondria, which activates downstream death signalling pathways ${ }^{499}$. Moreover, TXNIP overexpression has been shown to render cells more susceptible to oxidative stress and increase chemotherapy sensitivity by regulating ASK1 signalling ${ }^{515,516}$. Therefore, we wondered whether TXNIP is responsible for oxaliplatin-induced cytotoxicity for several reasons: 1) It was previous identified that ROS regulates TXNIP expression (Chapter III). The role of ROS in regulating TXNIP expression suggests TXNIP may be important in mediating oxaliplatin-induced cytotoxicity; 2) ER stress signalling (mainly PERK/eIF2a axis) was also observed to regulate TXNIP expression. The maintenance of ER proteostasis is one of the key determinants for cell fate ${ }^{474}$, which suggested TXNIP may regulated cell fate determined by ER stress; 3) TXNIP has also been known to exert tumour-suppressive effects ${ }^{450}$.

Viability assays showed the deletion of TXNIP had no impact on drug sensitivity to oxaliplatin in both 2D and 3D cell models (Figure 4-4C-D). The volume of spheroids was also assessed after oxaliplatin treatment. In 3D spheroid models derived from DLD1 cell lines, spheroid volume showed a similar level of reduction after oxaliplatin treatment between control and TXNIP-KO spheroids (Figure 4-4E). Moreover, TXNIPKO organoids were generated and showed similar drug sensitivity to control organoids (Figure 4-4F-G). Together, these data indicate that oxaliplatin-induced cytotoxicity is not dependent on TXNIP expression.


Figure 4-4. Induced TXNIP expression was not responsible for oxaliplatin cytotoxicity in colorectal cancer cells.
(A-B) Assessment of cell viability following 48 h of $10 \mu \mathrm{M}$ oxaliplatin $10 \mu \mathrm{M}$ or combined treatment with NAC in DLD1 cells (A) and HCT15 cells (B); (C) Assessment of cell viability in TXNIP-KO and control DLD1 cells following 48 h of $10 \mu \mathrm{M}$ oxaliplatin. (A-C) Cell viability was measured by the Deep Blue Cell Viability ${ }^{\text {TM }}$ Kit. (D) Assessment of cell viability in TXNIP-KO and control DLD1 3D spheroids following 48 h of $10 \mu \mathrm{M}$ oxaliplatin; (E) Calculated spheroid volume of control and TXNIP-KO DLD1 cells 48 hrs post oxaliplatin treatment; (F) Immunoblotting of TXNIP for identification of TXNIP knockout in CRC001
organoids; (G) Assessment of cell viability in TXNIP-KO and control CRC001 PDTO following 48 h of $10 \mu \mathrm{M}$ oxaliplatin. ( $\mathrm{D}, \mathrm{G}$ ) Cell viability was assessed by the Cell Titer-Glo ${ }^{\text {R }}$ Kit. Data are mean $\pm \mathrm{SD}$. NS $=$ non-significant, $* * * * \mathrm{P}<0.0001$.

Next, we assessed the role of TXNIP in migratory capacity and performed a wound healing assay. The result showed that there was no difference in the rate of cell migration between TXNIP wild-type and KO cell lines with or without oxaliplatin treatment (Figure 4-5A-B).


Figure 4-5. Ability of cell migration associated with TXNIP expression in DLD1 cells.
The migration of DLD1 cells was measured with wound-healing assay. After 48h of oxaliplatin treatment, cells were reseeded overnight and then wound closure percentage was analysed at
different timepoint. (A) Phase contrast micrographs showing the representative result of wound healing assay in control and TXNIP-KO cells with/ without oxaliplatin treatment; (B) The statistical analysis of wound closure percentage measured by Image J software. Results are expressed as mean $\pm \mathrm{SD}$ of three experiments.

In order to further assess the impact of TXNIP induction by oxaliplatin on the TME, the angiogenic potential of cells was measured in TXNIP-overexpressing DLD1 cells. Following TXNIP overexpression (Figure 4-6A), the supernatant was collected from both non-targeting control and TXNIPa cell model to treat HUVEC seeded on Matrigel. These results showed no difference in the capacity of HUVEC to align and form meshlike structures (Figure 4-6B-C), indicating that TXNIP has no impact on angiogenesis.


Figure 4-6. TXNIP had no effect on angiogenesis and NLRP3 inflammasome activation. (A) Immunoblot analyses showing TXNIP-overexpression in DLD1 CRISPR-Cas9a cells; (BC) assessment of TXNIP on angiogenesis by tube formation assay. HUVECs were seeded on Matrigel-precoated 96-well plates in conditional media from control and TXNIPoverexpressing DLD1 cells for 48 h . Phase contrast micrographs showing the effects of TXNIP on differentiation of HUVECs (B), Graphical depiction of statistical analysis of the effect of TXNIP on the length of capillary like structures of HUVECs (C). Data are mean $\pm$ SD. NS= non-significant.

### 4.3.3 TXNIP does not affect inflammasome activation

Previous studies provided evidence that TXNIP can regulate both innate and adaptive immune system ${ }^{243,246,252,256}$. According to previous publications, in order to investigate the potential correlation between gene of interest and immune system processes, several immune relevant factors were selected for analysis ${ }^{517}$. For the same purpose, we used TCGA_COADREAD dataset (including RNA sequencing data from 379 patient
samples) to analyse the correlation between TXNIP and the same set of immune related genes (Table 4-1). The result showed that TXNIP expression was potentially associated with the expression of T cell markers, antigen presentation and cytokine transcripts from TCGA analysis (Table 4-1). However, the correlations were low for 10 factors (CD247, CD4, CD8A, B2M, CD86, CXCL9, IL15, CCL2, CCL4 and CCL5), negligible or non-significant for others (CD8B, CD80, BATF3, IFNG, TNF, CXCL10, IL2 and CCL3).

Table 4-1 Pearson correlation coefficient scores of selected genes positively correlated with TXNIP gene expression from the colorectal TCGA dataset, categorized by their functions.

| Gene <br> symbols | Pearson <br> Score | p-value |
| :---: | :---: | :---: |
| T cell |  |  |
| CD247 | 0.2584 | $3.374 \mathrm{e}-07$ |
| CD4 | 0.3585 | $6.210 \mathrm{e}-13$ |
| CD8A | 0.2658 | $1.501 \mathrm{e}-07$ |
| CD8B | 0.4466 | 0.3859 |
| Antigen Presentation |  |  |
| B2M | 0.2381 | $2.766 \mathrm{e}-06$ |
| CD80 | 0.1975 | $1.085 \mathrm{e}-04$ |
| CD86 | 0.3651 | $2.146 \mathrm{e}-13$ |
| BATF3 | 0.1691 | $9.485 \mathrm{e}-04$ |
|  |  |  |
| Cytokine |  |  |
| IFNG | 0.0015 | 0.0484 |
| TNF | 0.1974 | $1.098 \mathrm{e}-04$ |
| CXCL9 | 0.2375 | $2.933 \mathrm{e}-06$ |
| CXCL10 | 0.1492 | $3.605 \mathrm{e}-03$ |
| IL2 | 0.1725 | $7.467 \mathrm{e}-04$ |
| IL15 | 0.2586 | $3.312 \mathrm{e}-07$ |
| CCL2 | 0.2679 | $1.192 \mathrm{e}-07$ |
| CCL3 | 0.1463 | $4.317 \mathrm{e}-03$ |
| CCL4 | 0.2122 | $3.110 \mathrm{e}-05$ |
| CCL5 | 0.2617 | $2.355 \mathrm{e}-07$ |

Pearson correlation coefficient scores between TXNIP mRNA expression and different immune markers, including T cells markers (CD247, CD4, CD8A), antigen presentation markers ( $B 2 M$, CD80, CD86, BATF3) and cytokines (IFNG, TNF, CXCL9, CXCL10, IL2, IL-15, CCL2, CCL3, CCL4, CCL5). The analysis was done using LinkedOmics (http://linkedomics.org/login.php). Pearson score: low correlation (0.2-0.4), negligible correlation (0-0.2).

It is well-known that TXNIP can activate NLRP3 inflammasome ${ }^{231}$. The formation and activation of NLRP3 inflammasome leads to self-cleavage and activation of caspase 1, which in turn promotes the release of the pro-inflammatory cytokines IL-1 $\beta^{518}$. We tested whether oxaliplatin-induced TXNIP causes inflammasome activation by measuring caspase 1 and IL- $1 \beta$ levels. However, knockout of TXNIP did not alter caspase 1 activation or IL-1 $\beta$ production following oxaliplatin treatment (Figure 4-7AD), with no detectable IL-1 $\beta$ in the supernatants (Data not shown). These findings are surprising as NLRP3 inflammasome is the most studied mediator linking TXNIP and immune regulation ${ }^{231,519}$. As our data suggest TXNIP does not promote the activation of NLRP3 inflammasome, we wondered whether TXNIP may be involved in mediating immune activation via a different pathway.


Figure 4-7. TXNIP had no effect on the activation of NLRP3 inflammasome.
(A-D) Immunoblot analysis of IL-1 (A, B) and cleaved caspase 1(P20) (C, D) in control and TXNIP-KO DLD1 cells with/ without oxaliplatin treatment.

### 4.3.4 TXNIP suppressed GDF15 expression after oxaliplatin treatment

From previous data, TXNIP was suggested to be involved in immune activation (Table 4-1), but not associated with inflammasome activation (Figure 4-7). We hypothesised that TXNIP may be capable of regulating the expression and secretion of soluble factors, which may in turn regulate the TME. To thoroughly assess this, we performed massspec analysis of supernatants collected from non-targeting control (NTC) and TXNIPKO (TKO) cell models and identified a total of 832 proteins from the conditional media and 157 differentially expressed soluble proteins ( $\mathrm{p}<0.05$ ). Protein quantification data can be found from Appendix Table 10 (Top 20 targets). Among them, seven proteins were upregulated in conditional media from TXNIP-KO DLD1 cells with median ratio
(fold change) $>2$, including PRSS2 (3.7 FC), GDF15 (2.37 FC), SERPINA1(2.23 FC), LCN2 (2.2 FC), VGF (2.11 FC), SEMA3F (2.08 FC) and MUC5AC (2.02 FC) (Figure 4-7A). PRSS2 (trypsin) was excluded since it was used in the preparation of samples, therefore, Growth Differentiation Factor 15 (GDF15) was the most highly differentiated secreted protein associated with TXNIP loss (Figure 4-7A-B). This result was confirmed using a cytokine array assay, which showed that knocking out TXNIP increased the concentration of GDF15 in the supernatant. Moreover, GDF15 was secreted at lower levels in response to oxaliplatin, in line with the upregulation of TXNIP, with this being rescued by the knockout of TXNIP (Figure 4-7C-D). These results showed that oxaliplatin decreases GDF15 secretion in a TXNIP dependent manner, and that the knockout of TXNIP alone could drive the secretion of GDF15.


Figure 4-8. Proteomic analysis reveals higher GDF15 concentration in the conditional media of TXNIP-KO DLD1 cells.
(A) (Left) Heatmap demonstrating differentially expressed proteins between conditional media from TXNIP-KO and control DLD1 cells, (Right) the table showing 7 upregulated proteins in conditional media from TXNIP-KO DLD1 cells with median ratio (fold change) $>2$. (B) Volcano plot showing GDF15 (Q99988, labelled as red) was significantly upregulated. (C) Cytokine arrays incubated with conditional media from TXNIP-KO and control DLD1 cells
with or without oxaliplatin treatment. The respective GDF15 spot was highlighted (red box). (D) Statistical quantification of GDF15 cytokine from cytokine arrays experiment. Cytokine array assay was done one time $(\mathrm{n}=1)$. Abbreviation: PRSS2: Serine protease 2. GDF15: Growth differentiation factor 15. SERPINA1: Serpin family A member 1. LCN2: Lipocalin 2. VGF: VGF nerve growth factor inducible. SEMA3F: Semaphorin 3F. MUC5AC: Mucin 5AC, oligomeric mucus/gel-forming.

We next assessed the kinetics and dose-responsiveness of GDF15 in DLD1 cells to oxaliplatin. The downregulation of GDF15 was more pronounced at later time points and higher drug dosages, which showed the opposite trend to TXNIP (Figure 4-8A-B).


Figure 4-9. Assessment of GDF15 expression in cell lysate of DLD1 cells with oxaliplatin by western blotting.
(A) Immunoblotting analyses of GDF15 after treatment of different dosages of oxaliplatin in DLD1 cells; (B) Immunoblotting analyses of GDF15 at different time points post oxaliplatin treatment in DLD1 cells.

GDF15 is also named as MIC-1 as it was firstly reported in macrophages with an inhibitory effect ${ }^{270}$. GDF15 is a stress-induced factor with significant overexpression in cancer ${ }^{338}$. We compared the transcript of GDF15 between normal tissue and tumour tissue from the TCGA colorectal cancer dataset (COAD) and observed an increase in GDF15 transcripts in tumour samples (Figure 4-10A). Correspondingly, immunohistochemistry staining showed tumour lesions presenting higher protein expression of GDF15 compared with adjacent normal tissues in our study cohort samples (Figure 4-10B-C).


Figure 4-10. GDF15 expression increased in human CRC samples.
(A) Comparative analysis of substantial expression of GDF15 transcript between adjacent normal tissue and cancer tissues from TCGA colorectal cancer cohorts, $\mathrm{P}<2.2$ e-16; (B) Detection of GDF15 protein levels of both tumour and adjacent normal tissue (ANT) samples from 32 patients with primary colorectal cancer. HE, EnVision, serial sections, original magnification $\times 200$; (C) Statistical analysis of GDF15 IHC score between adjacent normal tissue and tumour tissue specimen. The semi-quantitative scoring of each specimen was calculated by "expression intensity $\times$ expression area", all values are mean $\pm$ SD. ****p $<0.0001$.

To better examine the regulatory effects of TXNIP on GDF15 expression, we treated
TXNIP-KO DLD1 cells with oxaliplatin and collected cell lysate to measure cellular GDF15 by western blotting. In agreement with the previous results, we observed that TXNIP knockout rescued the inhibitory effects of oxaliplatin on GDF15 expression in

DLD1 cells (Figure 4-11A-B). Moreover, the similar pattern was observed in TXNIPKO HCT15 cells (Figure 4-11C-D). In contrast, TXNIP-overexpressing DLD1 cells showed lower GDF15 expression compared to control cells. Expectedly, the decreased GDF15 expression was more pronounced in TXNIP-overexpressing DLD1 cells after oxaliplatin, accompanied with higher expression of TXNIP (Figure 4-11E-F).

Using confocal imaging, we observed GDF15 was enriched in the cytoplasm in both untreated and treated conditions, which indicates it is a secreted protein (Figure 4$11 G)^{281}$. In line with immunoblot analysis, confocal imaging showed TXNIP-KO cells expressed more GDF15, which, unlike the control, was retained after oxaliplatin treatment (Figure 4-11G). We also quantified soluble GDF15 concentrations by ELISA in cell lines, with the highest level measured as $5976 \mathrm{pg} / \mathrm{ml}$ in the supernatant of TXNIPKO cells (Figure 4-11H).

To verify these findings in patient samples, we knock-out TXNIP in two patient-derived organoids (Figure 4-11I). As observed in 2D cell lines, a higher expression of GDF15 was also detected in TXNIP-KO PDTOs (Figure 4-11I).


Figure 4-11. TXNIP negatively regulated GDF15 expression.
(A-B) Immunoblotting analyses of TXNIP and GDF15(A) and the corresponding statistical analysis for the mean of GDF15 expression and standard errors (B) in control and TXNIP-KO DLD1 cells with/ without oxaliplatin treatment. (C-D) Immunoblotting analyses of TXNIP and GDF15 (C) and the corresponding statistical analysis for the mean of GDF15 expression and standard errors (D) in control and TXNIP-KO HCT15 cells with/ without oxaliplatin treatment. (E-F) Immunoblotting analyses of TXNIP and GDF15(E) and the corresponding statistical analysis for the mean of GDF15 expression and standard errors ( F ) in control and TXNIPoverexpressing DLD1 cells with/ without oxaliplatin treatment. (B, D, F) All values were expressed as mean $\pm$ SD. NS $=$ non-significant, $\quad * p<0.05, \quad * * p<0.01, \quad * * * p<0.001$, ${ }^{* * * *} \mathrm{p}<0.0001$, vs. Control. (G) immunofluorescent detection of GDF15 in control and TXNIP-KO DLD1 cells with/ without oxaliplatin treatment by confocal microscopy. DAPI (blue), Phalloidin (green), GDF15 (red). (H) GDF15 concentration in different media were determined by ELISA ( $\mathrm{n}=3$ ). (I) Immunoblot analyses of TXNIP and GDF15 in control and TXNIP-KO PDTOSs (left, CRC001; right, CRC002).

Next, we assessed for the presence of the TXNIP/GDF15 regulatory axis in human samples. We analysed the correlation between TXNIP and GDF15 transcripts and protein, in the TCGA-COAD dataset and patient tissue respectively, finding negative correlations in both (Figure 4-12A-B). Further, we stained the sequential sections of patient samples to characterise the expression of both TXNIP and GDF15 before and
after oxaliplatin-based neo-adjuvant chemotherapy. Encouragingly we also observed an inverse negative correlation in matched cases after oxaliplatin-based neo-adjuvant chemotherapy, compared to pre-treatment (Figure 4-12C).


Figure 4-12. The correlation analysis in human samples.
(A) Correlation analysis between TXNIP and GDF15 based on IHC staining score in our study cohort ( $\mathrm{n}=32$ ). (B) The correlation analysis between TXNIP and GDF15 expression across colorectal cancer epithelial enriched samples from TCGA COAD RNA-seq data. TCGA COAD GDC gene expression data for GDF15, TXNIP, EPCAM and MUC1 were downloaded from xenabrowser.net. Samples were sorted on the product of EPCAM and MUC1, with the highest $50 \%$ being taken forward for analysis as a form of 'epithelial enrichment'. Correlation between expression of GDF15 and TXNIP in the epithelial enriched population was displayed. $\mathrm{n}=255$. (C) Sequential sections from colorectal tumour samples collected pre- and post neo-adjuvant chemotherapy ( $\mathrm{n}=3$ ). Detection of TXNIP and GDF15 protein levels by IHC.

As ROS mediated the activation of the MondoA-TXNIP axis, we aimed to assess the effect of these factors on GDF15 expression. In line with our previous findings, knocking down MondoA decreased the expression of TXNIP, but increased GDF15 expression (Figure 4-13A), indicating the involvement of MondoA in the regulation of GDF15 expression as well. Further, pre-incubation of the target cells with NAC abolished the suppression of GDF15 by oxaliplatin, which was partially rescued by
overexpressing TXNIP (Figure 4-13B), suggestive of the important role of ROS in GDF15 regulation. Collectively, these data demonstrated the activation of MondoA induced by ROS modulated TXNIP and GDF15 expression.


Figure 4-13. GDF15 was regulated by ROS/ MondoA axis.
(A) Immunoblotting analyses of MondoA, TXNIP and GDF15 in MondoA-knockdown and control DLD1 cells. (B) Immunoblotting analyses of TXNIP and GDF15 in TXNIPoverexpressing DLD1 cells treated with oxaliplatin or combined treatment with oxaliplatin and NAC.

### 4.3.5 High GDF15 expression was associated with poor prognosis

Then we sought to understand the clinical relevance of GDF15. We investigated whether TXNIP and GDF15 expression levels had prognostic value by using tumour tissues from tumour microarray and public datasets (Figure 4-14). The data indicated that CRC patients with high levels of TXNIP in tumour tissues has improved clinical outcomes, with hazard ratio (high/low expression) 0.2763 ( $95 \%$ CI: $0.1374-0.5559$ ) (Figure 4-14A). We also found associations between low GDF15 and favourable outcome (Figure 4-14B), with hazard ratio (high/low expression) 3.0685 ( $95 \% \mathrm{CI}$ : 1.5545-6.0570). Consistently, analysis from public datasets showed the similar trend (Figure 4-14C-D). Multivariable analyses were further performed with other known clinical prognostic factors. However, the result showed neither TXNIP or GDF15 was independent prognostic factor, even though there was a trend for TXNIP (Appendix Table 11).


Figure 4-14. The impact of differential TXNIP/GDF15 expression on survival.
(A-B) Kaplan-Meier analysis of OS in CRC patients with different TXNIP expression levels. Median values as cut-offs. (A) or GDF15 expression levels (B) based on IHC staining score from tumour microarray. (C-D) Gene Expression Omnibus (GEO) databases analysis. KaplanMeier analysis of the OS (Upper panel) and DFS (bottom panel) in CRC patients with different TXNIP mRNA expression levels (C) or GDF15 mRNA expression levels (D).

### 4.4 Discussion

In chapter 4, the aims were to explore the possible function and the downstream targets of TXNIP. Since TXNIP has already been well studied and shown to be involved in different aspects of cancer biology, we explored the possible function of TXNIP in oxaliplatin-treated condition using TXNIP-KO cell models. Firstly, as MondoATXNIP axis has been mainly reported to affect cellular metabolism, we analysed the glycolytic signature of TXNIP-KO cells. The result showed that the expression of glycolysis-associated genes was unaltered in the absence and presence of oxaliplatin compared to control cells, even though oxaliplatin was able to decrease glycolytic phenotype. Secondly, we measured a well-studied TXNIP target, GLUT1. However, the depletion of TXNIP didn't change GLUT1 expression, even though oxaliplatin induced endocytosis and downregulation of GLUT1. Further, the functional assays confirmed the loss of TXNIP didn't affect the state of glycolysis.

ROS is reported to be responsible for chemotherapy-induced cytotoxicity ${ }^{417}$. Moreover, TXNIP has shown tumour suppressive effects, leading to cell death ${ }^{450}$. We then tested whether ROS-induced TXNIP contributed to oxaliplatin-mediated cell damage. Even though the addition of NAC compromised the cytotoxicity of oxaliplatin, no significant change was observed in the drug sensitivity of cells with silencing of TXNIP compared to non-target control cells, suggesting the upregulation of TXNIP was not a contributor for cytotoxicity caused by oxaliplatin. Further, a recent study showed the important role of ROS/TXNIP axis in inhibiting cancer cell migration and invasion ${ }^{520}$. We performed scratch assay and observed no change regarding migratory potential between TXNIPKO and control cells.

As our data demonstrated that TXNIP-KO cells showed no change concerning potentially involved biological properties mentioned above, we then speculated
whether TXNIP was able to modulate tumour microenvironment as it was reported to regulate the expression and secretion of several cytokines (such as VEGF, IL-1 $\beta$ and $\mathrm{IL}-18)^{231,521}$. Cytokines are messengers enabling the crosstalk among different cells ${ }^{522}$. However, we observed TXNIP-KO cells showed similar capacity for tube formation compared with control cells. Further, we analysed the correlation between TXNIP expression and immune-related markers from TCGA-COAD dataset and observed TXNIP expression was positively correlated with immune-associated factors (but weak), indicating the potential role of TXNIP in immune regulation. Based on previous studies, TXNIP plays an important role in regulating NLRP3 inflammasome signalling ${ }^{523-525}$. NLRP3 inflammasome activation leads to the release of IL-1 $\beta$ and IL18 and these cytokines play essential roles in tumour suppression and progression ${ }^{526-}$ ${ }^{529}$. However, our data showed that the expression of $\operatorname{IL}-1 \beta$ and cleaved caspase 1 showed no difference between TXNIP-KO and control cells. Especially, the concentration of IL-1 $\beta$ in the culture media from both control cells and TXNIP-KO cells with or without oxaliplatin treatment was undetectable, which confirmed that oxaliplatin-induced TXNIP didn't regulate the activation of NLRP3 inflammasome in our system.

To investigate whether there are other unreported secreted proteins regulated by TXNIP, we then performed unsupervised proteomic assay (Mass spectrometry analysis) combined with protein array experiment. Both assays showed that, GDF15, a distant TGF $\beta$ family member, was negatively regulated by TXNIP. It was interesting as GDF15 has been reported to promote tumour progression ${ }^{530}$. Consistently, our result showed high GDF15 expression was associated with poor prognosis from TMA and publica datasets analyses. Notably, there were other cytokines tested by either mass spectrometry analysis or cytokine array. But GDF15 was the only proteins identified
by both assays. This finding was further verified by TXNIP-overexpressing cell model and TXNIP-KO patient-derived organoid models. Moreover, GDF15 was observed to be upregulated when knocking down MondoA, highlighting MondoA-TXNIP-GDF15 axis.

Oxidative stress has been reported to induce GDF15 expression ${ }^{531,532}$. However, in our system, ROS generation supressed the expression of GDF15, which can be reversed by the addition of an antioxidant agent (NAC), suggestive of the stimulatory and inhibitory effects of ROS on GDF15 regulation. The overexpression of TXNIP can partially suppress the abolishment of GDF15 by combined treatment of oxaliplatin and NAC, confirming the negative regulation of TXNIP on GDF15 expression, and further indicating other regulators may also mediate oxaliplatin-induced decreased GDF15 expression.

How TXNIP regulates the expression of GDF15 remains to be investigated. The possible explanation could be TXNIP is a transcriptional repressor, which interacts with other corepressors to form a complex and in turn to supress the expression of GDF15 ${ }^{163}$. Moreover, another assumption could be TXNIP mediates GDF15 protein degradation due to its ability to bind other proteins.

Chapter V. The role of the TXNIP/GDF15 axis on the immune compartments

### 5.1 Introduction

We identified GDF15 as a downstream target of TXNIP in chapter IV. Thus, we aimed to understand the role of GDF15 and TXNIP/GDF15 axis in manipulating the TME in this chapter. GDF15, also designated as MIC-1, is a distant member of the TGF- $\beta$ superfamily and can be found on chromosome 19 p13.11. It shows low to absent constitutive expression in most tissue except for reproductive organs under quiescent conditions ${ }^{533}$. However, GDF15 expression is activated under different stress conditions, such as exercise, aging, diabetes, cancer and even drug consumption, in a variety of different cell types (eg. epithelial and immune cells). As such the top transcription factors which are predicted to bind the promoter region of GDF15 are broadly associated with inflammation: AP-1, ATF-2, c-Jun, C/EBPbeta, PPARgamma1, PPAR-gamma2 and STAT3 (Genecards, Qiagen analysis). Hence, cytokines, such as IL-1, TNF $\alpha$, and TGF- $\beta 1{ }^{534}$, can stimulate GDF15 expression. Collectively, these data suggest that GDF15 is an important regulator of inflammation and cancer.

GDF15 has been shown to contribute to multi-faceted biological events, including bone formation, cardiovascular diseases and cancer development in animal models ${ }^{535}$. GDF15 is hypothesised to affect pathology by acting on neighbouring cells (especially immune cells) as an "extracellular" messenger after being secreted ${ }^{536}$. Through this paracrine functionality, GDF15 has been shown to play an important role in remodelling the local, and even systemic, immune compartment. For example, its ubiquitous overexpression drives decreased systemic inflammatory responses ${ }^{369}$. In macrophages, the addition of exogenous GDF15 protein suppresses the LPS- and IFN-$\gamma$-induced production of Il6, Nos2, and Tnf, but enhances IL-4-mediated expression of Arg1, Fizz1, and Ym1 in macrophages ${ }^{279}$, suggesting that it supports M2 differentiation. GDF15 has also been shown to inhibit NK cell function. During systemic inflammation,

GDF15 suppressed phosphorylation of STAT4 and IFN- $\gamma$ production in NK cells, resulting in an exhaustion phenotype (defined by suppressed IFN- $\gamma$ production) ${ }^{280}$. Similarly, GDF15 also contributes to the decreased lytic activity of NK cells in glioma models ${ }^{362}$. Moreover, GDF15 is observed to be negatively associated with DC infiltration, maturation and function (such as IL-12 and TNF- $\alpha$ secretion) in ovarian cancer ${ }^{537}$. Regarding Tregs, GDF15 has been shown to stabilise FOXP3 expression, maintaining regulatory phenotype and function by binding to CD48 ${ }^{294}$. Thus, GDF15 is believed to promote a shift to an immune-suppressive phenotype. However, some studies have also demonstrated GDF15 has pro-inflammation properties. For instance, in an asthma model, GDF15, induced via Notch4/WNT pathway in Tregs, directly activates group 2 innate lymphoid (ILC2) cells to promote tissue inflammation ${ }^{538}$.

As a soluble protein, GDF15 exerts effects by binding to its cognate receptor. So far, there are three types of receptors reported, including TGF- $\beta$ receptor, GDNF-family receptor a-like (GFRAL) and CD48 receptor (SLAMF2). Through TGF- $\beta$ receptors, GDF15 has been reported to activate SMAD family members. In cultured neonatal cardiomyocytes and pancreatic cancer cells, recombinant GDF15 promotes the phosphorylation of SMAD $2 / 3^{539,540}$. However, in NK cells, it is the phosphorylation of SMAD1/5 that plays a role in recombinant GDF15-mediated NK cells suppression ${ }^{280}$. GFRAL, an orphan receptor for GDF15 mainly expressed on neurons in the brain, signals through the coreceptor RET $^{293}$. The binding of GDF15 to GFRAL is critical in body weight regulation and cachexia driven by cancer and chronic disease ${ }^{290,541}$. CD48 is a newly identified receptor for GDF15, mediating the generation of peripherally derived induced Tregs (iTreg), and the maintenance of suppressive function of natural Tregs (nTreg) cells by inhibiting the degradation of FOXP3 protein in hepatocellular carcinoma ${ }^{294}$.

Regulatory T cells (Treg) are commonly considered a subtype of CD4 T cells, expressing high levels of CD25 and FOXP3 and accounting for 5-10\% of CD4 ${ }^{+} \mathrm{T}$ cells in the periphery. Due to their immune suppressive roles, they are closely involved in the development of several diseases, including autoimmune disorders, allergic reactions and cancers ${ }^{542}$. Tregs are mainly divided into two types, namely nTregs and iTregs. nTregs are generated in the thymus, where they undergo the lineage commitment and maturation ${ }^{543,544}$; and iTregs are generated in the periphery in the presence of antigenic stimulation from conventional CD4 ${ }^{+}$T cells ${ }^{544,545}$. Importantly, MHC- II dependent T cell receptor (TCR) interactions are required for the generation of nTregs ${ }^{546}$. Notably, the production of both $n$ Tregs and iTregs are affected by TGF- $\beta 1$ and IL- $2^{547}$. Moreover, both nTregs and iTregs are critical in immunological tolerance, but they have different mechanisms of suppressing T-cell function. nTregs show inhibitory effects on Teffector cell trafficking to the target organ, while iTregs are known to act on antigenpresenting dendritic cells, such as DCs, for further prevention of T-cell priming ${ }^{545}$. In cancers, Tregs function to establish a tumour-promoting microenvironment, primarily by inhibiting adaptive anti-tumour immune responses, leading to tumour survival and ultimately tumour progression, metastasis and poor prognosis ${ }^{548,549}$. The mechanisms by which Tregs contribute to tumour progression include the expression of immune checkpoint molecules (such as PD-L1, CTLA-4) and secretion of immunosuppressive cytokines (such as IL-10, TGF- $\beta 1$ ) ${ }^{549}$. Immune checkpoint molecules are inhibitory immunoreceptors, which function as gatekeepers of immune responses ${ }^{550}$. Immunosuppressive cytokines are secreted factors to inhibit the maturation of DCs and the activation of anti-tumour T cells ${ }^{551}$. Thus, Tregs facilitate tumour progression by building an immune-suppressive microenvironment. Notably, Tregs are capable of proliferating in acidic and nutrient-lacking tumour microenvironments ${ }^{552}$.

Natural killer (NK) cells are a unique population of innate lymphoid cells, who, along with NKT cells, $\gamma \delta$ T cells and ILCs, contribute to tumour immunosurveillance ${ }^{553}$. The main role for NK cells is to discern 'self' from 'non-self' via engagement with the major histocompatibility complex-I ${ }^{554}$. The functions of NK cells are tightly regulated by activating and inhibitory signals ${ }^{84}$. CD244, an immunoregulatory receptor belonging to the SLAM family of receptors, is expressed in many immune cell types, especially NK cells. CD244 mainly binds to a ligand of another SLAM family member, CD2 and CD48 ${ }^{555}$. CD48 is a GPI-linked protein and found on most hematopoietic cells and upregulated under inflammatory conditions ${ }^{295}$. CD244-CD48 interactions have been reported to be essential for cell proliferation and anti-tumour activity in NK cells ${ }^{556}$. For instance, knocking-out CD48 in tumour cells blunts NK-cell-mediated cytotoxicity. Similarly, the anti-CD48 monoclonal antibody also inhibits the lysis of target cells ${ }^{557,558}$.

GDF15 is strongly over-expressed in cancers, including hepatocellular carcinoma, prostate and colorectal cancers ${ }^{559,560}$. Initially, GDF15 was identified as an antitumorigenic protein with pro-apoptotic capability as it was observed to promote proliferation of tumour cells ${ }^{366}$. However, a number of studies have shown that GDF15 expression can also drive tumour development rather than inhibition. This paradigm is supported by the evidence that increased GDF15 serum concentrations are associated with cancer incidence, progression, recurrence and cancer-related death ${ }^{561,376}$. In colorectal cancer tissue samples, high GDF15 expression is associated with poor prognosis ${ }^{562,563}$. GDF15 is also found to be a reliable marker to discriminate between prostate cancer and benign hyperplasia ${ }^{564}$, as well as between pancreatic adenocarcinoma and chronic pancreatitis ${ }^{565}$. Since our previous results showed that oxaliplatin led to TXNIP-mediated decrease of GDF15 expression, we, here, tried to
understand the role of GDF15 in regulating the function of potential target immune cells, including myeloid cells, Tregs and NK cells.

### 5.2 Aims and objectives

GDF15 is a secreted protein with immunomodulatory properties. We aimed to gain understanding in the immune functions of GDF15 on target immune cell types. Further, we aimed to understand the potential clinical application of GDF15 based on these findings. In detail, we aimed:

1) To explore whether myeloid cells, Tregs and NK cells were regulated by TXNIP/ GDF15 axis by performing in vitro co-culture assays;
2) To identify the receptor for GDF15 signalling by using blocking antibodies (anti-CD48 antibody);
3) To identify the association between GDF15 and iCMS classification by performing scRNA analysis;
4) To analyse the clinical outcome of TXNIP/GDF15 axis in publicly available clinical datasets and in-house patient-derived organoids.

### 5.3 Results

### 5.3.1 GDF15 has limited impacts on macrophage differentiation, phenotype and function

In this chapter, we sought to achieve a better understanding of the effects of TXNIPGDF15 signalling pathways on immune cells. Given the discovery of contaminating TGF- $\beta 1$ in recombinant GDF15 preparations ${ }^{566}$, we opted to predominantly use CRISPR knockout and overexpression systems to produce conditioned GDF15enriched supernatant for in vitro immunological assays. Specifically, we established TXNIP $^{-/-}$(hereafter TKO), GDF15 $5^{-/-}$(hereafter GKO), TXNIP ${ }^{-1 /} / \mathrm{GDF}^{-/-}$double KO
(hereafter GTKO) and GDF15 overexpressing (hereafter GDF15a) cell models, and suitable non-targeting controls (NTC) using the DLD1 cell line (Figure 5-1).


Figure 5-1. The establishment of CRISPR-knockout and CRIPSRa-GDF15 DLD1 cell models.
(A) Immunoblot analysis of TXNIP and GDF15 expression in NTC, GKO, TKO, GTKO DLD1 cell lines after oxaliplatin treatment; (B) Immunoblot analysis of GDF15 expression in GDF15CRISPRa cells in the presence of oxaliplatin. Abbreviation: NTC: Non-targeting control. TKO: TXNIP knockout. GKO: GDF15 knockout. TGKO: TXNIP and GDF15 double knockout. NTCa: NTC CRISPR activation. GDF15a: GDF15 CRISPR activation.
GDF15 is important in modulating myeloid cells ${ }^{533}$. For example, GDF15 was observed to suppress anti-tumour activities of macrophages and promote tumour development ${ }^{319,533}$. Thus, we first sought to assess if we could replicate and build on these observations using our methodologies and tools. Aware of the literature concerning the importance of monocyte to macrophage differentiation in the establishment and maintenance of the $\mathrm{TME}^{567}$, we first assessed if GDF15 could act as a differentiating factor by culturing primary monocytes for 7 days in GDF15 rich supernatant (from TXNIP ${ }^{-/}$DLD1 cells) $+/-$MCSF (as a positive control) in serum-free (AIM-V, commonly used for immune cells culture ${ }^{568}$ ) or RPMI media plus serum (R10). We saw no evidence of GDF15 being able to drive differentiation, nor enhance or limit MCSF dependent differentiation when assessing live cell number (Figure 5-2A).

Although there was no difference in cell number, we could not rule out if there was a difference in phenotype. Macrophages are famously 'plastic' cells owing to their ability to be conditioned by their environments to adopt diverse and functionally-appropriate phenotypes ${ }^{569}$. Until recently, these phenotypes were commonly considered to sit on a
gradient between 'M1' and 'M2' subtypes. M1 cells were broadly thought of as inflammatory, supporting Th1/CD8 cytotoxic responses, and M2 cells were broadly thought of as anti-inflammatory/humoral, supporting Th2/B cell humoral responses ${ }^{570}$. This paradigm has recently been challenged by single cell sequencing technology which clearly shows multiple tissue and disease specific subtypes; often $>20^{571}$. We therefore assessed cell surface expression of 7 markers, including HLA-DR, CD14, PD-L1, CD163, MMR, CD86 and PD-1. All these selected markers are associated with macrophage phenotype and function ${ }^{572,573}$. The results showed no significant difference between cells differentiated with MCSF in the presence of the different conditioned supernatants (Figure 5-2B; DLD1 knockouts as defined at the beginning of this chapter). Having assessed the impact of GDF15 on monocyte to macrophage differentiation, reflecting its effects on monocytes recruited to the TME, we next wished to model the impact of GDF15 on tissue resident macrophages. Monocytes differentiated with MCSF are commonly considered to be 'M0', ie naïve mature macrophages, akin to naïve tissue resident macrophages; cells which can be matured towards different functional phenotypes with different factors (e.g. IFN +/- LPS will drive 'M0' cells to an 'M1' phenotype) to reflect specific conditions. Culturing M0 macrophages in the presence of the different conditioned supernatants yielded no difference in phenotype when measuring the cell surface expression of 6 appropriate markers (Figure 5-2 C). In the knowledge that a 'danger signal' (e.g. a pathogen associated molecular pattern [PAMP] such as LPS, a TLR4 agonist) is often required to drive the adoption of M1 and M2 phenotypes ${ }^{574}$, we repeated the above experiments (referring to Figure 5-2 BC) with the addition of LPS (Figure 5-2 D-E). Again, no change in macrophage differentiation and phenotype were observed.


Figure 5-2. GDF15 has limited impacts on macrophage differentiation, phenotype or function.
(A) Primary monocytes were cultured in different media (AIMV or R10; RPMI + $10 \% \mathrm{FBS}$ ) +/- MCSF, with conditioned supernatant from NTC or TKO cell lines at a $1: 1$ ratio as indicated. After 7 days the number of live cells were counted. $n=5$. (B) Primary monocytes were cultured in R10 media + MCSF, with conditioned supernatant from NTC, GKO, TKO, GTKO cell lines at a 1:1 ratio as indicated. After 7 days, surface expression of indicated proteins were measured by flow cytometry. MFIs were corrected against isotype controls and normalized against NTC MFI. n=3-16 (C) Primary monocytes were cultured in R10 media + MCSF for 7 days, before being cultured with conditioned supernatant from NTC, GKO, TKO, GTKO cell lines at a $1: 1$ ratio for a further 2 days. Surface expression of indicated proteins were measured by flow cytometry. MFIs were corrected against isotype controls and normalized against NTC MFI. $n=3-15$. (D) As (B) with the addition of LPS at day 7 and analysis performed on day 9.n=3 (E) As (C) with the addition of LPS on day 9 and analysis performed on day 11. $n=3$.

Having seen no GDF15 dependent difference in differentiation or phenotype, we next investigated whether GDF15 affected the functions of macrophages. Macrophages have diverse functions linked to their critical role in maintaining immune and tissue homeostasis ${ }^{575}$. One of the ways in which macrophages perform this role is by acting as sentinel cells in vulnerable tissues, with their cell surface carrying multiple pattern recognition receptors ( PRRs ) which, when activated by a PAMP, will activate the cell to adopt an inflammatory phenotype, enabling the direct or indirect destruction or inhibition of the pathogen that carries the triggering PAMP ${ }^{576}$. A key protein in these immune responses is $\mathrm{TNF} \alpha$, and $\mathrm{TNF} \alpha$ release has been previously reported to be regulated by GDF $15^{319}$. Thus, we measured TNF $\alpha$ secretion from macrophages after
treatment with conditional media. As can be seen in Figure 5-3A, we were unable to see the reported differences in both monocytes and MCSF macrophages using our systems. In cancer immunology, macrophages are frequently considered as negative prognosticators ${ }^{570}$. One of the reasons for pro-tumour effects of macrophages is their ability to 'shut down' antigen specific cytotoxic adaptive responses directly through the expression of inhibitory molecules such as PD-L1 or the release of inhibitory factors such as IL-10 $0^{577}$. To test GDF15's ability to modify the ability of macrophages to stimulate T cell proliferation, we treated labelled PBMCs with anti-CD3 and anti-CD28 antibodies in the presence of supernatant from either macrophage treated with the indicated cell line supernatant or monocytes differentiated in the presence of the indicated cell line supernatant. As can be seen in Figure 5-3B, there were no significant differences regarding T cell proliferation. Next, macrophages are potent cells with powerful phagocytosis, being able to engulf pathogens and/or apoptotic/necrotic cells amongst others ${ }^{578}$. We therefore wished to assess whether GDF15 affected the ability of macrophages to phagocytose. Using dextran FITC uptake as a readout, we saw no difference in both monocytes and MCSF macrophages when treated with the supernatant from the indicated cell lines (Figure 5-3C). Finally, we wished to understand whether GDF15 may educate macrophages to recruit other cell types that may impact on the TME. To assess this, we used the supernatant from monocytes differentiated in MCSF in the presence of GDF15a supernatant or recombinant human GDF15 or controls +/- LPS (Figure 5-3D is without LPS, Figure 5-3E is with LPS) in the bottom well of a transwell system. In the top well we placed freshly isolated PBMCs, and after several timepoints we measured the number of cells that had migrated (NB. Only 48h is shown). Although a trend for increased migration towards monocytes
differentiated with MCSF and GDF15 could be seen, this change was not significant
(Figure 5-3D-E).


Figure 5-3. GDF15 has limited impacts on macrophage function.
(A) TNFa concentrations in the supernatant from cells in (Figure 5-2D) and (Figure 5-2E). $\mathrm{n}=5$. (B) PBMCs were stimulated with aCD 3 and aCD 28 in the presence of supernatant (3 parts sup to 1 part media) from cells from (Figure 5-2B) ('Monocytes') and (Figure 5-2C) ('MCSF macrophages'). Proliferation (dye MFI) was normalised to cells treated with NTC supernatant generated macrophages. $\mathrm{n}=5$ (C) Cells from (Figure 5-2B) ('Monocytes') and (Figure 5-2C) ('MCSF macrophages') were cultured with dextran-FITC at $37^{\circ} \mathrm{C}$ with MFI corrected against cells cultured with dextran-FITC at $4^{\circ} \mathrm{C}$. Corrected values were then normalized against NTC supernatant treated macrophages. $\mathrm{n}=5$ (D) Primary monocytes were cultured for 7 days in the presence of R10 + MCSF + controls (1:1 ratio of NTC media or R10 media) or GDF15(a) or rhGDF15. Day 7 supernatant was taken and placed in the bottom well of a Thin Cert transwell. Graph shows migration of PBMCs at 18 hrs normalized to controls. $\mathrm{n}=6$. (E) as (D) with monocyte-derived macrophages treated with LPS for 48 hrs from day 7 to day 9 before commencing the trans-well assay. $\mathrm{n}=6$.

### 5.3.2 GDF15 induces Tregs in a CD48 dependent manner

Interestingly, during the course of these functional assays it was observed that PBMC numbers were reduced in GDF15-enriched conditioned media when stimulated with anti-CD3 and anti-CD28 (Figure 5-4A-B). Further analysis showed that supernatant
from GDF15 enriched supernatant (including from GDF15a and TXNIP-KO cells) inhibited the proliferation of both CD8 (Figure 5-4C-D) and CD4 T cells (Figure 5-4EF). Moreover, the similar observation was seen regarding IFN $\gamma$ release as well (Figure

5-4G-H).


Figure 5-4. GDF15 inhibited the proliferation and functions of $T$ cells.
(A-B) PBMCs were stimulated with anti-CD3 and anti-CD28 for 4 days in the presence of fresh supernatant from indicated cell lines (NTC; non-targeted control. GKO; GDF15*-. TKO; TXNIP ${ }^{-/-}$. GTKO; GDF15 ${ }^{-/-}$and TXNIP ${ }^{-/-}$. GDF15(a); GDF15 over-expressing). Live cells were counted using trypan blue and a haemocytometer. $\mathrm{n}=10$ (A) and $\mathrm{n}=5$ (B). (C-F) Labelled PBMCs were stimulated with anti-CD3 and anti-CD28 for 4 days in the presence of fresh supernatant from indicated cell lines, before being stained with anti-CD3 and anti-CD8 (C-D) or anti-CD4 (E-F) antibodies and measured by flow. Normalised proliferation on gated CD3+CD8+ or CD3+CD4+ cells is shown. $\mathrm{n}=6$. (G-H) Normalised IFN $\gamma$ concentrations in the supernatant of cells from C-F. All values were expressed as mean $\pm$ SD. ns= non-significant. $* \mathrm{p}<0.05, * * \mathrm{p}<0.01, * * * \mathrm{p}<0.001, * * * * \mathrm{p}<0.0001$.

A recent paper has shown that GDF15 is able to drive the differentiation of regulatory
T cells (Tregs) from naïve CD4 cells via CD48 ligation ${ }^{294}$. Then we hypothesised that Tregs are the mediators to inhibit T cell proliferation and IFN $\gamma$ release within the mixed

PBMC population in our experiments. To start with, we measured whether GDF15 affect the Tregs generation by treating PBMCs with either recombinant GDF15 protein or GDF15 enriched media. The result showed a GDF15-dependent increase of FOXP3 within the CD4 pool (Figure 5-5A), however to a much lesser extent than when using recombinant TGF $\beta 1$ protein, a potent driver for Tregs generation ${ }^{579}$ (Figure 5-5B). Further, we tested clinical relevance by staining GDF15 and FOXP3 on serial colorectal sections. Correspondingly, we observed enrichment of FOXP3 in the GDF15 high cases (Figure 5-5C-D). Finally, in light of the recent publication previously mentioned ${ }^{294}$, where Tregs were seen to be induced from naïve CD4 cells stimulated in the presence of recombinant GDF15, we sought to see if we could observed the similar phenotype using our tools and methodology. We negatively isolated naïve CD4 T cells from healthy donor PBMCs using magnetic beads before treating them with anti-CD48 antibody or isotype control. These cells were then stimulated with anti-CD3 and antiCD28 in the presence of conditioned media from DLD1 cells over-expressing GDF15 (GDF15a) or control (NTC) for 4 days. On day 4 these 'Tregs' were co-cultured with proliferation-dye-labelled allogeneic PBMCs (responder cells; responders) in the presence of anti-CD3 antibodies for 3 days. Responder cells were stained with antiCD4 and anti-CD8 antibodies and proliferation for each T cell subset was measured (proliferation dye MFI) and displayed in Figure 5-5E-F. Only naïve CD4 T cells treated with isotype control and stimulated in the presence of GDF15 were able to inhibit the proliferation of responders. These data further support the concept that GDF15 can induce Tregs from naïve CD4 T cells through engagement with CD48 ${ }^{294}$.


Figure 5-5. GDF15 induces Tregs in a CD48 dependent manner.
(A-B) PBMCs were stimulated with anti-CD3 and anti-CD28 for 4 days in the presence of fresh supernatant from NTC or GDF15 (a) cell lines or media alone or $200 \mathrm{ng} / \mathrm{ml}$ recombinant human

GDF15 (A) or $5 \mathrm{ng} / \mathrm{ml}$ recombinant human TGF $\beta 1$ (B). Cells were stained with anti-CD3, antiCD4 antibodies extracellularly before intranuclear staining of FOXP3 was performed. \% of $\mathrm{CD} 4{ }^{+} \mathrm{FOXP}^{+}$cells are shown. $\mathrm{n}=10$ (A) and $\mathrm{n}=5$ (B). (C-D) Immunohistochemistry using anti-GDF15 and anti- FOXP3 antibodies on serial sections from colorectal cancer cases. Pooled data showing $\mathrm{FOXP}^{+}$cell counts in GDF15 ${ }^{\text {low }}$ and GDF15 ${ }^{\text {high }}$ populations; median split. $\mathrm{n}=32$. (E-F) Isolated naïve CD4 cells were stimulated with anti-CD3 and anti-CD28 for 4 days in the presence of indicated cell line supernatant + either isotype control $(10 \mu \mathrm{~g} / \mathrm{ml})$ or anti-CD48 $(10 \mu \mathrm{~g} / \mathrm{ml})$ as indicated. These cells were then co-cultured with anti-CD3 stimulated labelled responder PBMCs for 4 days, before being stained with anti-CD3, anti-CD8 and anti-CD4 antibodies. Normalised proliferation dye (MFI) of the indicated responder population is shown. $\mathrm{n}=9$. All values were expressed as mean $\pm \mathrm{SD}$. $\mathrm{NS}=$ non-significant. $* \mathrm{p}<0.05, * * * \mathrm{p}<0.001$.

### 5.3.3 GDF15 blocks the interaction of CD48 and CD244 impairing NK cell

## degranulation

Previous result showed GDF15 was able to affect the generation of Tregs, and further the proliferation and functions of CD8 T cells. Then we were interested in seeing whether other immune cell types correlated with the levels of GDF15 and TXNIP expression. We therefore performed the correlation between TXNIP/GDF15 expression and immune subsets by transcriptomic analysis. The data showed that other cell types correlated more strongly with GDF15 and TXNIP than FOXP3 expressing cells in the opposite direction (Figure 5-6A-B). NK cells, as defined by NCAM1 (CD56), showed the strongest negative correlation with GDF15 (Figure 5-6A) and positive correlation with TXNIP (Figure 5-6B) compared with other immune subsets. In accordance, GDF15 has previously been reported to inhibit NK cell function in glioma ${ }^{362}$. As mentioned, a recent paper has reported the binding of GDF15 to CD48 ${ }^{294}$, we therefore considered whether this binding may inhibit the binding of CD48 to CD244, an important costimulatory molecule for NK cell functionality ${ }^{556}$. We first used a platebased system assay and found the ability of GDF15 to inhibit the binding of recombinant CD48 to recombinant CD244 (Figure 5-6C). Next, we assessed the impact of CD48 blockade on NK cell degranulation when targeting plate bound recombinant CD48, using anti-CD48 (Figure 5-6D), recombinant GDF15 (Figure 5-6E) and GDF15 enriched supernatant (Figure 5-6F). The results showed that both anti-CD48 antibody
and GDF15 enriched media decreased the production of CD107a ${ }^{+}$NK cells (Figure 5-
6D-F). Finally, we assessed NK cell degranulation when targeting NTC and GDF15
KO cell lines and identified the increased generation of CD107a ${ }^{+}$NK cells when cocultured with GDF15 KO cells, suggesting GDF15 suppressed NK cell degranulation (Figure 5-6G). Taken together, these data suggested that GDF15 can both drive Treg generation and inhibit NK cell functionality by binding to CD48.


Figure 5-6. GDF15 blocks the interaction of CD48 and CD244 impairing NK cell degranulation.
(A-B) Linear regression analysis of transcript expression (TCGA COAD dataset) of GDF15 (A) or TXNIP (B) against indicated immune associated transcript expression levels. n=512. TCGA COAD GDC gene expression data for GDF15, TXNIP, ACTA2 (Fibroblasts), CD4 (T cells), CD8A (T cells), CD68 (Macrophages), CD19 (B cells), FOXP3 and NCAM1 (NK cells) were downloaded from xenabrowser.net. Correlations between expression of GDF15 (A)/TXNIP (B) were made against the other markers and are illustrated in A and B. (C) Plate bound recombinant CD48 was treated with indicated factor before recombinant avidin CD244 was added and binding measured, $\mathrm{n}=5$. (D-F) Plate bound anti-CD2, anti-NKp46 and recombinant CD48 were treated with anti-CD48 (D), recombinant GDF15 (E) or supernatant from indicated cell line (F) before isolated primary NK cells were added and cultured for 18h. Cells were harvested and stained for CD107a and analysed by flow cytometry, to measure degranulation. $\mathrm{n}=10$. (G) Target cells (wild type or GDF15KO, as indicated) were plated out and co-cultured with primary NK cells for 18h, cells were harvested and stained for CD107a, with \% of CD107a positivity shown. $\mathrm{n}=10$. All values were expressed as mean $\pm$ SD. ${ }^{* *} \mathrm{p}<0.01$, ${ }^{* * * *} \mathrm{p}<0.0001$.

### 5.3.4 GDF15 expression is associated with iCMS2, and GDF15 high TXNIP ${ }^{\text {low }}$

 phenotype is associated with poor prognosis and chemotherapeutic resistance The Consensus Molecular Subtypes (CMS) of Colorectal Cancer is a genomic classification system determined by an international consortia in $2015^{14}$, which is based on bulk transcriptomics. Recently, in order to better identify the cell types and their expression profile, the intrinsic-consensus molecular subtypes (iCMS) classification system was established by analysing single-cell transcriptomes of epithelial cells ${ }^{19}$, leading to the discovery of two intrinsic subtypes, iCMS2 and iCMS3. When assessing the association between GDF15 expression and iCMS subtype, we observed GDF15 to be significantly enriched in iCMS2 (Figure 5-7A-B). Additionally, low expression of TXNIP was also observed to be enriched in iCMS2 (Figure 5-7C-D). iCMS2 is a subtype that can be associated with low immune cell infiltrate ${ }^{19}$, including low NK cells, CD8 T cells, with a slight increase of Tregs. This finding was consistent with our previous results that GDF15 promoted the generation of Tregs and inhibited NK cells. Therefore, this association broadly supports the GDF15-dependent immunological impacts we have observed in vitro and in situ.

Figure 5-7. GDF15 expression is associated with iCMS2.
(A-D) GDF15 and TXNIP expression levels in tumour cells for each patient and each iCMS subtype, coloured by iCMS classification (iCMS2; purple, iCMS3; orange). (A-B) Boxplots show cellular GDF15 expression levels of tumour cells in patients classified to be enriched in iCMS2 subtype (A) or pooled as expression means per donor (B) or individual cells; (C-D). Boxplots show cellular TXNIP expression levels of tumour cells in patients classified to be enriched in iCMS2 subtype (C) or pooled as expression means per donor (D) or individual cells. Previous results suggested that the TXNIP-GDF15 axis was associated with patient prognosis and regulated the functions of immune cells. With high GDF15, a lack of NK cells, CD8 T cell dysfunction and Treg infiltration all being shown to be associated with poor prognosis in $\operatorname{CRC}^{562,580,581}$, and with the vast majority of patients being treated with oxaliplatin, we next considered whether the TXNIP-GDF15 axis remained functional in metastatic disease. We, firstly, tested the levels of TXNIP and GDF15 expression following oxaliplatin treatment in different CRC cell lines derived from primary and metastatic sites. Interestingly, we observed loss of significant change in TXNIP and GDF15 expression and the maintenance of a high level of GDF15 in cell lines derived from secondary sites ( DiFi and LIM1215) (Figure 5-8A-B).


Figure 5-8. Maintenance of high GDF15 level in colorectal cancer cell lines derived from secondary sites.
(A-B) Immunoblot analysis of TXNIP and GDF15 expression after oxaliplatin treatment in colorectal cancer cell lines, including DLD1, HCT15, HT29, SW48(A, primary site), and DiFi, LIM1215 (B, secondary site).

We further analysed human samples data from publicly available datasets. Data analysis confirmed the higher expression of GDF15 in metastasis tissue (Figure 5-9A). Indeed, high levels of GDF15 were seen in matched primary and secondary tissue using an array and single cell sequencing analysis ${ }^{582}$ (in the single cell sequencing dataset, GDF15 was highly upregulated in liver metastases) (Figure 5-9B). These data
suggested that the cells had become refractory to oxaliplatin and continued to secrete large amounts of GDF15. To support this hypothesis, GDF15 is enriched in patients who do not respond to chemotherapy (Figure 5-9C).
A

B

C


Figure 5-9. High GDF15 levels were associated with metastasis and chemotherapeutic resistance.
(A) The comparison of GDF15 between primary tumour and lymph metastasis in GSE6988. (B) A volcano plot used to visualize single cell analysis of GDF15 in matched primary and secondary tissue (Liver metastasis), data collected from previous publication (Appendix Table 12). (C) Fractions of responder or non-responder cases that express high or low GDF15 in GSE52735.

Furthermore, we developed oxaliplatin resistant cell lines by constantly treating cells with high oxaliplatin concentration for 12 months (Figure 5-10A-C). Then we treated resistant cells with $10 \mu \mathrm{M}$ of oxaliplatin. The results showed that oxaliplatin-mediated TXNIP and GDF15 expression changes were compromised in both DLD1 and HCT15 resistant models (Figure 5-10D-E).

A

B

C


D

E


Figure 5-10. TXNIP-GDF15 axis responsiveness largely lost in oxaliplatin-resistant cell models.
(A) A schematic model presenting the process to acquire oxaliplatin-resistant CRC cells. (B-C) IC50 values of oxaliplatin in oxaliplatin-resistant cells (OXAR) and their parental cells. DLD1 and DLD1-OXAR (B); HCT15 and HCT15-OXAR (C). (D-E) Immunoblot analysis of TXNIP and GDF15 expression after oxaliplatin treatment in oxaliplatin-resistant (OXAR) cells: DLD1OXAR (D) and HCT15-OXAR (E).

Finally, we generated nine patients-derived colorectal cancer organoids (Figure 5-11A,
Table 5-1). Then TXNIP and GDF15 mRNA levels were tested after oxaliplatin treatment. Further, a ratio of GDF15 to TXNIP expression post treatment from each organoids line was measured. The result showed that there was a clear trend between high ratio of GDF15/TXNIP and extramural invasion, although the ratio of GDF15/TXNIP was variable in different organoids (Figure 5-11B). Collectively, these
data suggested that there is an association between GDF15/TXNIP expression and metastatic disease and drug resistance.


Figure 5-11. Loss of oxaliplatin-induced increased TXNIP and decreased GDF15 expression was associated with extramural invasion in patient-derived tumour organoids. (A) Brightfield images of 9 PDTO cultures, shown in 3 magnifications (4X, 10X, 20X). (B) Assessment of expression change of TXNIP and GDF15 of organoids post oxaliplatin. All values were expressed as mean $\pm$ SD. ${ }^{* * *} \mathrm{p}<0.001$.

Table 5-1 The clinical characteristics of tumour tissue for organoids establishment

| Organoi ds name | Sex | Collect procedure | Origin of tissue | Age at diagnosis | TNM <br> stage | Presence of invasive disease |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| CRC001 | M | Resection | Rectum | 69 | pT3 N1a | 1/17 nodes contain metastatic ADC <br> Intramural lymphovascular invasion present. <br> No venour or perineural invasion |
| CRC002 | M | Resection | Proximal transverse colon | 72 | pT3 N0 | No |
| CRC003 | M | Resection | Rectum | 72 | pT3 N0 | No |
| CRC004 | M | Resection | Right colon | 64 | T4a N1b $\mathrm{Mx}, \mathrm{R} 0$ | Invades into the subserosa and 12 mm beyond the muscularis propria |
| CRC005 | M | Residual tumour | Rectosigm oid colon | 57 | $\begin{gathered} \text { ypT3 } \\ \text { N2b Mx } \end{gathered}$ | Extramural venous invasion Liver metastasis detected on MRI |
| CRC006 | M | Resection | Rectum | 69 | $\begin{gathered} \text { pT2N0M } \\ 0 \\ \hline \end{gathered}$ | Local invasion: muscularis propria |
| CRC007 | M | Resection | Upper rectum | 81 | $\begin{gathered} \text { pT3 N0 } \\ \text { Mx } \\ \hline \end{gathered}$ | Extramural venous invasion |
| CRC008 | F | Resection | Rectum | 42 | pT3 N0 | Local invasion: Beyond muscularis propria. No large vessel invasion |
| CRC009 | F | Resection | Hepatic flexure | 71 | $\mathrm{pT3} \mathrm{pN0}$ | Extramural venous invasion present |

### 5.4 Discussion

In chapter V, we identified high GDF15 expression was associated with poor prognosis in CRC, which is consistent with other studies ${ }^{562}$. Similar to TGF- $\beta$, GDF15 can be released by several cellular sources ${ }^{275}$. GDF15 secreted from different cell types, including macrophages, has been reported to create a tumour-promoting microenvironment, directly or indirectly facilitating the proliferation and metastasis of tumour cells ${ }^{344,583}$. However, we observed GDF15 is mainly expressed in malignant cells from single cell analysis in colorectal cancer ${ }^{584}$, which further suggests that the immune-tumour cells crosstalk.

According to various studies, GDF15 has been reported to act as either a protumorigenic or anti-tumorigenic protein in different models. This could be possibly explained by several reasons: 1) it could exert the effects as a cellular protein or autocrine factor, which in turn can activate SMAD signalling ${ }^{281}$. This would result in the promotion or inhibition of cancer progression and metastasis ${ }^{277,370}, 2$ ) it is an antiinflammatory factor and shows impacts on other immune cells as a secreted cytokine, and be closely associated with tumorigenesis through inflammation ${ }^{585,586}$. At the early stage of oncogenesis, anti-inflammatory role of GDF15 abrogates the initiation and development of tumours. However, for the late-stage established tumours, effective anti-tumour inflammation is required to eliminate cancer cells, including the activation of DCs, M1 macrophages, NK cells and T cells. The switch of cold tumours (noninflamed) into hot tumours (inflamed) is indispensable for cancer immunology due to the recruitment and activation of immune cells in tumours ${ }^{533,587}$. Therefore, the inhibition of the activation of anti-tumour immune cells restricts the efficiency.

As GDF15 is an important cytokine and involved in immune regulation, including the modulation of both innate and adaptive immune cells. Thus, we explored the function
of TXNIP/ GDF15 axis in the remodelling of tumour immune microenvironment in this chapter. To establish whether TXNIP-dependent GDF15 modulates immune cell responses in the TME, several cell line models with genetic perturbations in TXNIP and GDF15 were established. These models included GDF15-KO, GDF15-activation and $\mathrm{TXNIP}^{-1 /} / \mathrm{GDF}^{-/-}$double knockout cell models. The establishment of these models were used to avoid TGF- $\beta 1$ contamination in GDF15 preparation.

GDF15 was firstly reported in macrophages with inhibitory effects, promoting their differentiation towards M2 phenotype, followed by cumulative studies emphasising the importance of GDF15 in the regulation of macrophages ${ }^{270}$. Thus, we initially tested the potential function of TXNIP/GDF15 axis in myeloid cells/macrophages. However, we observed no involvement of GDF15 in the differentiation of monocytes by analysing expression of specific markers and TNF $\alpha$ production for macrophage phenotype and function. Moreover, further analysis revealed GDF15-educated monocytes didn't effectively affect the recruitment of immune cells.

Tregs are a subset of $\mathrm{CD} 4^{+} \mathrm{T}$ cells with immunosuppressive functions. In cancer, Tregs help to promote tumour development and progression by inhibiting effective antitumour immune responses ${ }^{588}$. A recent publication showed that GDF15 was capable of inducing the generation of iTregs (induced Tregs) in HCC ${ }^{294}$. Then we speculated whether Tregs generation and function is modulated by TXNIP-induced GDF15 in our system. Firstly, we tested the impact of TXNIP/GDF15 axis on the proliferation and function of CD8 and CD4 T cells. The results demonstrated that GDF15-enriched conditioned media, collected from both GDF15a and TXNIP-KO cells, had suppressive effects on both cell types. Based on this observation, we speculated that the inhibitory effects of GDF15 on CD8 and CD4 T cells were dependent on its role on Tregs. Indeed, GDF15 was observed to promote the induction of $\mathrm{FOXP}^{+}$CD4 T cells, which showed
potent suppressive effects on responder cells (allogeneic PBMCs). This finding was further verified in patient samples, with more FOXP3 staining in patient tumour samples of high GDF15 expression. Moreover, previous study demonstrated that CD48 is required to transmit signals induced by GDF15 ${ }^{294}$. Accordingly, we observed a similar phenotype using CD48 antibody. The immune-suppressive effects of GDF15induced Tregs were compromised by treating cells with CD48 antibody.

CD48-CD244 binding has been well studied and is critical for NK functionality ${ }^{556}$. Therefore, we speculated whether GDF15 affected the interaction between CD48 and CD244. After analysing TCGA-COAD dataset, we found NCAM1 expression (a marker for NK cells) negatively correlated with GDF15 expression, but positively correlated with TXNIP expression, indicating that TXNIP and GDF15 expression was associated with the levels of NK cell in the TME. Consistently, further analyses showed that GDF15 inhibited NK cell degranulation by binding to CD48, confirming the suppressive effects of GDF15-CD48 interaction on the function of NK cells. Collectively, the immune modulation mediated by GDF15 was shown to be dependent on both Treg and NK cells via the binding to CD48 in this study.

Previous publications suggest increased NK cells and decreased Tregs are associated with favourable prognosis in colorectal cancer ${ }^{588,589}$. We analysed public datasets, as well as tested patient-derived organoids and oxaliplatin-resistant cell models, to identify whether the levels of GDF15 are indicative of clinical outcomes. The results showed that high GDF15 expression was associated with metastatic potential, chemotherapy responses and drug resistance.

Taken together, our data have revealed a previously unreported broad epithelialimmune axis - (ROS/MondoA)/TXNIP/GDF15 induced by chemotherapy in CRC that
is associated with NK cell and Treg regulation (Figure 5-12), and GDF15 expression levels are associated with extramural invasion.


Figure 5-12. Schematic diagram
Diagram of the underlying mechanism of oxaliplatin-induced immunogenicity by regulating MondoA/TXNIP/GDF15 signalling pathway in CRC.

Chapter VI. Summary \& Future Directions

### 6.1 Overview

Cancer has been widely considered the results of the accumulated genetic mutations. Even though the gain-of-function of oncogenes and loss-of-function of tumour suppressor genes are the key driving force for tumorigenesis ${ }^{590}$, the involvement of the immune system in cancer development cannot be ignored due to the cancerimmunoediting theory, which consists of three major phases: elimination (protection), equilibrium (persistence) and escape (progression) ${ }^{591,592}$. The progression or suppression of tumours relies on a threshold balanced by tumour cells, immune cells and other relevant factors in the TME, named as "cancer-immune set point" ${ }^{593}$. The immune-oncology field has started to attract more attention since the first clear indication that the administration of interleukin-2 (IL-2) mediates the regression of unresectable metastatic cancers by boosting the expansion of anti-tumour lymphocytes ${ }^{594,595}$. The success of immunotherapies, such as IL-2 and interferon- $\alpha$ (IFN $\alpha$ ), have suggested that manipulating immune system to kill tumour cells is an effective strategy for cancer therapy ${ }^{596}$. Accordingly, immune cell infiltration and immune contexture have been observed to exert tremendous effects on clinical outcome ${ }^{597,598}$. Further, the discovery and success of immune checkpoint blockades (ICB), such as PD-1 and CTLA4, have established immunotherapies as a new pillar of cancer treatment ${ }^{599}$. Since ipilimumab (anti-CTLA4 antibody) was first approved in 2011 by the FDA, more ICB drugs have been developed and approved ${ }^{600}$. In addition, CAR-T therapy has also been shown to be effective in treating hematologic malignancies and shown promise in some solid tumours ${ }^{601-603}$.

Despite the success of immunotherapies in certain settings, it remains unclear which patient population will benefit the most from these drugs. Chemotherapies, which have been used for several decades, therefore remains the most effective means of treating
different types of cancers. Interestingly, over the past decade, chemotherapy has shown to trigger anti-tumour immune activation in addition to its cytotoxic effect on tumour cells ${ }^{604}$. These studies provided the potential of chemotherapies to switch cold tumours into hot tumours and promote the infiltration and activation of cytotoxic immune cells in the TME ${ }^{605-607}$. These findings lay the foundations for the combined chemotherapy treatment with other immunotherapies including ICB and CAR-T therapies ${ }^{608,609}$. The underlying molecular mechanisms of chemotherapy to induce the immunogenicity have been widely studied. The discovered mechanisms comprise of the promotion of cytokine production, the triggering of ICD and the increase of MHC-I molecules on cancer cells ${ }^{386}$. It has been well studied that chemotherapies are able to induce the expression of tumour suppressors ${ }^{610,611}$. Importantly, tumour suppressors have been identified to be involved in the regulation of immune responses in cancer ${ }^{612,613}$. However, the role of tumour suppressors invoked by chemotherapy to facilitate immune activation remains poorly understood.

CRC is one of the most advanced tumours worldwide, with oxaliplatin as one of the first-line drugs for CRC treatment. Previous studies have identified that oxaliplatin is an inducer of immunogenic cell death, which facilitates HMGB1 release, CRT exposure and ATP secretion ${ }^{56,614-616}$. Furthermore, oxaliplatin can also create a pro-inflammatory tumour microenvironment and trigger macrophages to secret T-cell-recruiting chemokines, like CXCL9, CXCL10 and CXCL16 ${ }^{609}$. In this study, we aimed to explore the activation of yet unreported tumour suppressor molecules after chemotherapy treatment and identify their roles in the tumour-immune interplay of colorectal cancer. Specifically, we were interested in altered genes induced by oxaliplatin in CRC that promote immune cells activation to the TME. In doing so, we hope to potentially illuminate, based on the scientifically explored evidence provided here, biomarkers for
prognosis prediction and the proof-of concept that chemotherapy could utilise the activation of tumour suppressors to reshape the tumour immune microenvironment.

To start with, as we aimed to perform immune-relevant studies, two colorectal cancer cell lines categorised as an "immune" subtype (CMS1 subtype) from previous publication were selected ${ }^{428}$. RNA sequencing analysis identified the upregulation of TXNIP, a tumour suppressive molecule, following oxaliplatin treatment in both cell lines. TXNIP was also characterised in a CRC study cohort as well as the TCGA COAD dataset and showed that TXNIP expression was decreased in tumour samples compared to normal samples. Consistently, the upregulation of TXNIP after oxaliplatin treatment was also observed in different 3D structure cell models and our own study patient samples, confirming oxaliplatin-mediated TXNIP upregulation in a clinical setting. It is of interest to observe that TXNIP is induced by other treatments (including 5-GU from our own result) and potentiates the effectiveness of radio-chemotherapies ${ }^{617}$, suggesting that the upregulation of TXNIP expression may be due to cytotoxic stress or DNA damage. Moreover, TXNIP has been identified to modulate the immune system. Therefore, we hypothesised that oxaliplatin-induced TXNIP may mediate the crosstalk between tumour and immune cells and decided to focus on the mechanistic study for the rest of the thesis.

The distribution of TXNIP is associated with its function. In the cytoplasm, TXNIP accumulation interferes with Trx-ASK1 ( mitogen-activated protein kinase kinase kinase) binding, activates ASK1 and causes cell apoptosis ${ }^{618}$. Similarly, in beta cells, the shuttling of TXNIP from nucleus to mitochondria upon oxidative stress leads to ASK1-dependent apoptosis ${ }^{449}$. Moreover, the translocation of TXNIP to mitochondria leads to NLRP3 inflammasome activation ${ }^{619}$. Importantly, cytoplasmic TXNIP is a powerful inducer of ROS as it binds and inhibits Trx, an antioxidant enzyme ${ }^{620}$. Thus,
we performed experiments to identify the distribution of TXNIP and observed its enrichment in the cytosol, especially in endoplasmic reticulum and mitochondria, suggestive of the potential involvement of ROS generation in this process ${ }^{621,622}$. Since we did not isolate other organelles, whether TXNIP was enriched in other places is unknown and could possibly provide further links to expanded mechanistic insight. Furthermore, previous studies reported that oxaliplatin treatment promotes the production of ROS, possibly due to DNA damage response ${ }^{68,623,624}$. Consistently, we also observed an increase of ROS upon oxaliplatin treatment. Further analysis revealed that oxaliplatin-induced TXNIP levels were reduced when administrating NAC (a ROS inhibitor). Collectively, these observations suggested that ROS generation contributes to the increased TXNIP expression.

Next, we explored the possible mechanisms of TXNIP induction by chemotherapy agents. Among all the transcriptional factors that have been reported to modulate TXNIP expression, MondoA is the most studied one and has been shown to be involved in ROS-mediated TXNIP regulation ${ }^{114}$. It is reported that ROS interferes with the formation of MondoA-Mlx complexes and the subsequent transcription of TXNIP expression ${ }^{114}$. In addition, from RNA-seq analysis, we identified that both TXNIP and ARRDC4 were upregulated with oxaliplatin treatment. Both these genes have MondoA binding domains in their promoters and are the most highly MondoA-dependent genes ${ }^{458}$, suggesting that MondoA is required for induced TXNIP following oxaliplatin treatment. This hypothesis was verified by MondoA knocking-out models. Loss of MondoA blunted oxaliplatin-induced TXNIP expression. Further, ChIP-qPCR analysis confirmed the enriched MondoA on the promoter of TXNIP gene after oxaliplatin treatment. Importantly, the addition of NAC reversed this phenotype, demonstrating the key role of MondoA activation in ROS-mediated TXNIP upregulation (Figure 3-14C).

To be noted, our finding is opposite to previous studies. ROS was shown to promote the binding between MondoA and mTOR, thus inhibiting the interaction between MondoA and Mlx and the expression of TXNIP ${ }^{109,114}$. However, in our study, we found that oxidative stress (ROS generation) promotes TXNIP expression by facilitating the enrichment of MondoA on the promoter of TXNIP.

We then aimed to explore the function of TXNIP in oxaliplatin-treatment setting. Metabolic remodelling is one of the cancer hallmarks, with contributing to tumour initiation and progression, immune suppression and drug resistance ${ }^{625}$. MondoA is a glucose sensor and mediates glucose-induced transcriptional regulation ${ }^{458,626}$. The activation of MondoA/TXNIP signalling has been shown to reduce glycolysis ${ }^{113}$. Thus, we wondered whether TXNIP affected cellular glycolysis in our model. However, the results showed that TXNIP upregulation upon oxaliplatin treatment showed no impact on the regulation of glycolysis, even though oxaliplatin itself could decrease glycolysis in our system. Tumour cells are sensitive to oxidative stress ${ }^{419}$. ROS generation was shown to mediate oxaliplatin-induced cytotoxicity (Figure 4-4A-B). However, this process was, yet, in a TXNIP-independent manner. Intriguingly, we observed that ROS generation was involved in oxaliplatin-induced cytotoxicity, yet, in a TXNIPindependent manner. Collectively, these data suggested that showed no contribution to metabolic remodelling and drug cytotoxicity.

Further analysis on TCGA dataset indicated that there is a relationship between TXNIP and immune activation. Cytokines are important in immune regulation, stimulating immune effector cells and enhancing cell recognition ${ }^{627}$. As TXNIP is a cytoplasmic protein, we speculated that cytokines may mediate TXNIP-induced immune activation in our system. Thus, we performed mass spectrometric and proteomic array analyses and revealed that GDF15, a family member of TGF- $\beta$, was a downstream target of

TXNIP. ROS/MondoA/TXNIP/GDF15 axis was further confirmed by using genetic modification models (CRISPR-KO and CRISPR-activation).

Next, we aimed to understand the role of GDF15 in oxaliplatin-mediated immune regulation. To date, the mechanisms of GDF15-mediating anti-inflammatory effects are not fully understood. GDF15 has been shown to promote 'M2' macrophage differentiation, inhibit NK cell function and dendritic cell maturation ${ }^{280,361}$. Moreover, GDF15 was observed to induce and maintain Tregs ${ }^{294}$. However, as discussed, recombinant tools have previously been shown to be contaminated with TGF- $\beta 1$, raising concerns within the scientific community ${ }^{291,566}$. TGF- $\beta 1$ is a potent pleotropic cytokine which can also promote M2 macrophage differentiation, inhibit NK activation and DC maturation and induce Tregs. In this study, to avoid this issue, we prioritised the use of endogenously-overexpressing cell systems and knockouts for our immunological assays, before using commercially available recombinant proteins as additional controls.

Monocytes and macrophages are known to be key in establishing and maintaining the TME is many tumour types, including $\mathrm{CRC}^{628}$. We therefore wished to explore whether GDF15 was able to modulate viability, differentiation, phenotype and function of monocytes and macrophages. However, the results showed no significant changes in these experiments (Figure 5-2, 5-3). When assessing the impact of the supernatant from 'GDF15 educated' macrophages on PBMC proliferation, we observed significant changes in the number of cells as compared to the controls ('GDF15 enriched' supernatant from our cell line models). With T cells being inhibited and the report of Tregs being induced by CD48-GDF15 ligation in the literature, we observed evidence of these functions in our systems, and furthermore we were able to block the functional impact of GDF15 using an antibody to CD48.

To support the idea that GDF15 may drive Treg induction, we assessed for correlations between relevant immunological transcripts and GDF15 in the TCGA COAD dataset. Here we observed that NCAM1 was the most negatively correlated transcript, but the most positively correlated transcript when assessed against GDF15 and TXNIP expression, respectively. Given the importance of the CD48-CD244 axis (cis or trans) in NK cell biology, we assessed the impact of GDF15 on the function of this axis. Using a recombinant protein plate-based system, NK stimulation assay and targeting assay, we showed that GDF15 can inhibit CD48-CD244 axis, resulting in defective NK cell degranulation.

These data have shown that GDF15 can inhibit multiple arms of the immune system, through Treg induction and NK dysregulation, by binding to CD48. Although we were unable to demonstrate the direct impact of GDF15 on the CD48-CD244 axis in T cells in our systems (data not shown), we believe this is still a possibility, however our current data suggests that CD4 and CD8 T cells are primarily inhibited indirectly by GDF15-induced Tregs. Data from colorectal cancer patient tissues suggest that the GDF15 (high) samples are associated with an increase in Treg infiltration making GDF15 a potential immunomodulatory target. Oxaliplatin-induced immune recruitment in the TME has been proved to improve anti-tumour efficacy and patient prognosis ${ }^{609,629}$. Therefore, the understanding of the role of GDF15-mediating oxaliplatin-induced immune modulation facilitates the development of anti-cancer treatment.

The high mortality of CRC is associated with chemoresistance and subsequent treatment failure ${ }^{630}$. The molecular mechanisms of platinum-based chemotherapy resistance include molecules determining cellular influx/ efflux of drugs, DNA repair machinery and cell death-related genes ${ }^{631}$. Solute carrier superfamily of membrane
transporters, Copper transporters and ATP-binding cassette (ABC) transporters mediate the absorption and/or excretion of drugs in the intestine, the accumulation of drugs in cancer cells and the pumping-out of drugs, respectively. DNA repair pathways, such as the mismatch repair, nucleotide excision repair (NER) and base excision repair (BER) systems, help to remove corrupt DNA bases and repair DNA breaks, affecting drug efficacy. Moreover, the alterations in regulating cell death signalling enhance the capacity of cancer cells to survive and proliferate, including apoptosis, necrosis, autophagy and senescence ${ }^{631}$. Importantly, recent studies have also identified the important role of tumour microenvironment in establishment of oxaliplatin-resistant phenotypes ${ }^{632,633}$. However, the understanding of TME in drug resistance is still elusive. In this study, we analysed resistant cell models and public datasets, and observed high GDF15 was associated with poor drug responses (Figure 5-9C, Figure 5-10D-E), suggesting that GDF15 could be a predictive biomarker of drug sensitivity.

When assessing for evidence of TXNIP/GDF15 pathway, and its impact in patient datasets, we were confounded by the lack of matched pre- and post-treatment resources, however there is evidence to support the impact of both the post-chemotherapeutic change (TXNIP ${ }^{\text {low }}$ GDF15 $5^{\text {high }}$ to TXNIP ${ }^{\text {high }} \mathrm{GDF} 15^{\text {low }}$ ) and the lack of change on outcome. Firstly, TXNIP is a known tumour suppressive gene and is downregulated in cancerous epithelial cells whilst GDF15 is increased in cancerous epithelial cells, with greater increases in metastatic disease leading to the development of targeting drugs ${ }^{562}$. Second, high expression of TXNIP is associated with positive prognosis with the inverse being true for GDF15. Third, a GDF15 high phenotype is associated with resistance to chemotherapy. Fourthly, the unchanged expression of TXNIP and GDF15 upon oxaliplatin treatment seen in cell lines derived from secondary sites and resistant models suggests that advanced and refractory disease cannot benefit from drug
treatment due to the lack of the activation of TXNIP/GDF15 expression post-treatment. Fifthly, PDTOs showed variability in oxaliplatin-induced gene expression changes. However, those with advanced disease showed minor change in the expression of TXNIP and GDF15 upon treatment, suggesting there may be a subgroup of patients who display an intrinsic lack of responsiveness to drug. This last point raises the possibility of using organoids as a stratification tool for the use of anti-GDF15 therapeutics in early disease. By assessing an organoid's TXNIP/GDF15 ratio pre and post treatment, we may be able to administer the appropriate medication to modulate the TME in an informed and patient-specific manner.

### 6.2 Future direction

### 6.2.1 Establishing CRISPR-KO clones by other guide RNAs

In this study, we just used one guide RNA to build knock-out cell models for TXNIPKO/ GDF15-KO/ MondoA-KO models (see 'CRISPR-CAS9 genome engineering' in method section). However, this process may raise the concern of off-target effects. To reduce this concern, we plan to establish other knock-out cell models by using different guide RNAs to repeat the performed functional assays in the future work.

In addition, in our study, we used SMARTpools to overexpress target genes (see ‘Generation of CRISPRa Constructs’ in method section). Multiple CRISPRa guide RNA designs are pooled together in SMARTpools to increase CRIPSRa efficiency. However, the limitations include that we have no idea which design is the successful one. Thus, in the future, every single gRNA design should be tested to understand the successful one.

### 6.2.2 Clinical validation in large cohorts

In this study, clinical patient samples were used to validate our findings. Patient data (for IHC staining) included 32 patient samples from our own cohort and 96 patient sample from tumour microarray. However, the sample sizes of these cohorts were relatively small, and this could be a possible reason that neither TXNIP or GDF15 was shown to be an independent prognostic factor. Thus, a larger patient cohort could be used in the future to for better validation.

### 6.2.3 Expanding patients-derived organoids (PDTOs) for validation

In our study, we established PDTOs and performed in-vitro experiments (westernblotting and qPCR) to link the altered expression of TXNIP/GDF15 after chemotherapy with clinical outcome. However, there is a limit regarding the number of organoids as we had only 9 PDTOs available during the study. More organoid lines with clinical information could be established to verify our hypothesis.

### 6.2.4 Exploring whether oxaliplatin promotes the formation of MondoA-MIx complexes

In our study, we identified that oxaliplatin-induced ROS production drives TXNIP expression by enriching MondoA on the TXNIP promoter. The expression of TXNIP is mainly dependent on MondoA-Mlx complexes and this complex was reported to be negatively regulated by $\operatorname{ROS}^{114}$. Further analysis (Co-IP experiment) could be done regarding whether ROS promotes the formation of MondoA-Mlx complexes.

### 6.2.5 Exploring whether c-Myc mediated oxaliplatin-induced decreased

 glycolysisOur result demonstrated that oxaliplatin decreased the expression of c-Myc and cellular glycolysis (Figure 3-14A, Figure 4-1A and Figure 4-3A-B). Whether c-Myc mediated
oxaliplatin-induced decreased glycolysis needs to be further studied (using c-Myc KO cell models).
6.2.6 Further molecular investigation in the molecular mechanism of GDF15induced Tregs

In chapter V, consistent with previous study, we observed GDF15 was able to induce Tregs. Previous study reported GDF15-CD48 binding downregulated the expression of STUB1, an E3 ligase mediating the degradation of FOXP3. Consequently, GDF15 increased FOXP3 expression ${ }^{294}$. However, in our study, the underlying mechanism of GDF15-induced FOXP3 ${ }^{+}$Tregs is still unknown. More assays (such as Co-IP, qPCR and western-blot experiments) need to be performed to study whether STUB1 is involved in our work.

### 6.2.7 Exploring the role of the TXNIP-Trx system in the regulation of GDF15 expression

In our study, we found out that TXNIP was a regulator of GDF15 expression and secretion. The observation the combined treatment with NAC abolished the decreased GDF15 induced by oxaliplatin suggested the important role of ROS in the regulation of GDF15 (Figure 4-13B). However, overexpression of TXNIP didn't completely reverse the effect of NAC, yet partially, indicating other factors, especially in TXNIP-Trx system, may also contribute to ROS-mediated GDF15 alteration. Therefore, TXNIPTrx system components need to be tested as well for future work.

### 6.2.8 Improving the cell model for MondoA/PERK experiment

In Figure 3-17H, we tried to identify the essential role of MondoA in regulating TXNIP expression compared to PERK/ATF4 signalling. In this assay, we knocked down PERK expression in Mondo-KO cells, and tested TXNIP expression after oxaliplatin treatment.

However, even though the efficiency of knockdown was acceptable, this assay can still be improved by building double Mondo $\mathrm{A}^{-/} / \mathrm{PERK}^{-/-}$cell model for further verification.

### 6.2.9 Verifying other interesting targets from proteomic assays

In the proteomic assays, there are still other interesting factors, in addition to GDF15, differentially expressed between control cells and TXNIP-KO cells. It is worthy to mention that most of them are associated with wound-healing signature. Whether these factors are actually regulated by TXNIP and involved in TXNIP-mediated functions is still unknown. Therefore, more genetically-manipulated cell models could be established for further analysis.

### 6.2.10 Understanding the molecular mechanism of TXNIP regulating GDF15

A limitation of this study is that we did not elucidate how TXNIP regulates GDF15 expression. We speculate that this could be explained by several possible mechanisms, including: 1) TXNIP might interact with GDF15 and regulate its degradation based on the evidence that another arrestin protein ( $\beta$-Arrestin1, ARRB1) was reported to directly interact with GDF15 ${ }^{634}$ (possible assays include ubiquitylation assay, half-time measurement and protein stabilisation assay); 2) TXNIP is a transcriptional repressor, which interacts with other corepressors to form a complex and in turn to supress the expression of GDF15 ${ }^{163}$ (Co-IP and ChIP assays could be performed).

### 6.2.11 Exploring the possible alternative regulator for GDF15

Given that organoids showed heterogeneous responses upon oxaliplatin treatment regarding TXNIP/ GDF15 regulatory axis, it is reasonable to hypothesise that there are other upstream regulators for GDF15 expression. It has been reported that oncogenes and tumour suppressors, ATF4-CHOP and transcriptional factors like PPAR $\gamma$ can modulate GDF15 expression in certain conditions. Therefore, one of future directions is the exploration of other regulators for GDF15 under oxaliplatin treatment.

### 6.2.12 Exploring the direct impact of GDF15 on cytotoxic T cells via CD48-CD244 blockade

The observation that the downregulation of GDF15 leads to increased infiltration of T cells indicates the negative impacts of GDF15 on T cells ${ }^{362}$. Given signals secreted by innate immune cells can modulate the functions and differentiation of adaptive immune cells ${ }^{635}$, a potential explanation is due to the indirect effects of myeloid cells driven by GDF15 ${ }^{279,319}$. However, whether GDF15 could have direct impact on cytotoxic T cells, especially via CD48-CD244 blockade ${ }^{556}$, is still elusive and needs to be explored further. To answer this question, adoptive syngeneic GDF15-KO MC38 mouse model can be used and immune cells (T cells, NK cells and Tregs) can be measured.
6.2.13 Exploring the feasibility of circulating GDF15 concentration as a biomarker for predicting treatment response

GDF15 is a secreted protein and can be evaluated in the circulation ${ }^{362}$. Our results demonstrate that high GDF15 expression is positively associated with poor chemotherapy responses and clinical outcomes, indicating GDF15 is a potential biomarker for clinical application. Thus, patient liquid samples (such as serum or plasma) could be collected for analysis regarding drug responses in the future.

### 6.3 Key Findings: A Summary

1. The induction of the tumour suppressive protein TXNIP is induced after chemotherapy treatment in colorectal cancer cell lines. This response showed heterogeneity across different colorectal cancer cell lines.
2. The upregulation of TXNIP is mainly due to the enrichment of MondoA on the promoter of TXNIP gene sequence. ER stress (especially PERK-eIF2a pathway) could partially contribute to the alteration of TXNIP expression post chemotherapy, but its underlying mechanism is still unclear.
3. The important role of ROS for TXNIP upregulation is verified. Specifically, the generation of ROS is responsible for both MondoA nuclear translocation and decreased UPR.
4. GDF15 has been shown to inhibit multiple arms of the immune system, through Treg induction and NK dysregulation, by binding to CD48 (using CRISPR-knockout and CRIPSR-overexpressing cell models).
5. Patient-derived organoids have been demonstrated to be useful tools to guide the clinical application of the appropriate medication.

### 6.4 Conclusion

In this study, we demonstrated that oxaliplatin-induced ROS can modulate the TXNIP/GDF15 axis via activation of MondoA. High GDF15 expression (Low TXNIP expression) was associated with poor prognosis. Mechanistically, GDF15 led to Treg induction and defective NK functions by binding to CD48. Finally, PDTOs with advanced disease were less responsive to oxaliplatin regarding TXNIP/GDF15 axis, indicating its potential to predict the clinical prognosis.

## Chapter VII. References

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Chapter VIII. Appendix
Figure 1. Melt curves for each primer


Figure 2. STR profiling of colorectal cancer cell lines

DLD1

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Method:
ONA isolation was carried out from cell pellet (cell layer)
Genetic charactersisics were determined by PCR-single-locus-technology.
16 independent PCR-sytems D8S1179, D211511, D7S822, CSF1PO, D3S1358, TH01, D13S317, D165539, D2S1338, AMEL, D5S818, FGA, D195433, wWA, TPOX and D185551 were investigated (ASN-OOO2 core markers are colcred grey, Thermo Fisher, AmpFISTRe Identitiliere Plus PCR Amplification Kit)
in parallel, positive and negative controls were carried out yielding correct results.
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Result


The table shows the result of the cell line analysis and the comparison with the online database of the DSMZ (hthp:I/www.dsmz.delddefserice/services-human-and-animal-cell) and the Cellosaurus database (https//web..expasy. org/cellosaurus). Please note
hat only the PCR-systems according to ANSVATCC standard ASN-0002 were aligned (CSS818, D13S317, DTSS20, D16S539, WWA, THO1, TPOX, CSF1PO, AMEL - -ollored grey).

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Method:
ONA isolation was carried out from cell pellet (cell layer)
Genetic characteristics were determined by PCR-single-locus-technology.
16 independent PCR-systems D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1333, AMEL, D5S818, FGA, D19S433, wWA, TPOX and D18S51 were investigated.
(ASN-OOO2 core markers are coloced grey. Thermo Fisher, AmpFISTR® Identifilere Pus PCR Amplifation Kit)

Result:

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Table 1. The clinical characteristics of Tumour Microarray samples.

| Patient No. | Sex | Collect procedure | origin of tissue | Sample pathology diagnosis | Age at diagnosis | T stage | N stage | $\begin{gathered} \text { M } \\ \text { stage } \end{gathered}$ | clinical stage |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| D15A3053 | Male | Resection | sigmoid colon | mucinous adenocarcinoma | 40 | T4a | N2b | M0 | 3C |
| D15A3054 | Female | Resection | colon | mucinous adenocarcinoma | 59 | T4a | N0 | M0 | 2B |
| D15A3055 | Male | Resection | right hemicolon | adenocarcinoma | 71 | T4a | N0 | M0 | 2B |
| D15A3003 | Male | Resection | right hemicolon | adenocarcinoma | 82 | T4b | N2b | M0 | 3C |
| D15A3030 | Male | Resection | sigmoid colon | adenocarcinoma | 59 | T4a | N1 | M0 | 3B |
| D15A3066 | Male | Resection | colon | adenocarcinoma | 62 | T3 | N0 | M0 | 2 A |
| D15A3067 | Male | Resection | right hemicolon | adenocarcinoma | 61 | T4a | N2b | M0 | 3C |
| D15A3068 | Male | Resection | sigmoid colon | adenocarcinoma | 75 | T4a | N1 | M0 | 3B |
| D15A3069 | Female | Resection | left hemicolon | adenocarcinoma | 41 | T3 | N0 | M0 | 2 A |
| D15A3070 | Male | Resection | colon | adenocarcinoma | 77 | T4a | N1 | M0 | 3B |
| D15A3072 | Female | Resection | sigmoid colon | adenocarcinoma | 82 | T4a | N0 | M0 | 2B |
| D15A3083 | Female | Resection | ileocecum | adenocarcinoma | 80 | T3 | N1 | M0 | 3B |
| D15A3086 | Male | Resection | right hemicolon | adenocarcinoma | 78 | T4a | N0 | M0 | 2B |
| D15A3092 | Female | Resection | transverse colon | adenocarcinoma | 66 | T3 | N0 | M0 | 2 A |
| D15A3015 | Female | Resection | left hemicolon | mucinous adenocarcinoma | 76 | T3 | N1 | M0 | 3B |
| D15A3096 | Male | Resection | sigmoid colon | adenocarcinoma | 79 | T4a | N1c | M0 | 3B |
| D15A3097 | Female | Resection | right hemicolon | adenocarcinoma | 59 | T4a | N1 | M1 | 4 |
| D15A3098 | Male | Resection | ascending colon | adenocarcinoma | 52 | T4a | N1 | M0 | 3B |
| D15A3104 | Female | Resection | right hemicolon | adenocarcinoma | 64 | T4a | N1 | M0 | 3B |
| D15A3122 | Female | Resection | right hemicolon | adenocarcinoma | 43 | T2 | N0 | M0 | 1 |
| D15A3129 | Female | Resection | right hemicolon | adenocarcinoma | 78 | T4a | N0 | M0 | 2B |
| D15A3169 | Male | Resection | sigmoid colon | mucinous adenocarcinoma | 75 | T3 | N2b | M0 | 3C |
| D15A3170 | Female | Resection | ascending colon | adenocarcinoma | 63 | T3 | N0 | M0 | 2 A |
| D15A3171 | Male | Resection | rectosigmoid | adenocarcinoma | 54 | T3 | N1 | M0 | 3B |
| D15A3172 | Female | Resection | colon | adenocarcinoma | 61 | T4a | N0 | M0 | 2B |
| D15A3173 | Male | Resection | sigmoid colon | adenocarcinoma | 57 | T4a | N0 | M0 | 2B |
| D15A3167 | Male | Resection | rectosigmoid | adenocarcinoma | 64 | T3 | N0 | M0 | 2 A |
| D15A3168 | Male | Resection | ascending colon | adenocarcinoma | 84 | T3 | N0 | M0 | 2 A |
| D15A3177 | Male | Resection | sigmoid colon | adenocarcinoma | 49 | T4a | N1 | M0 | 3B |
| D15A3179 | Male | Resection | sigmoid colon | adenocarcinoma | 45 | T3 | N0 | M0 | 2 A |
| D15A3181 | Male | Resection | sigmoid colon | adenocarcinoma | 57 | T3 | N0 | M0 | 2A |
| D15A3182 | Male | Resection | splenic region of the colon | adenocarcinoma | 77 | T3 | N1 | M0 | 3B |
| D15A3191 | Female | Resection | Hepatic region of colon | adenocarcinoma | 80 | T3 | N1 | M0 | 3B |
| D15A3193 | Male | Resection | sigmoid colon | adenocarcinoma | 76 | T4a | N0 | M0 | 2B |
| D15A3132 | Male | Resection | colon | adenocarcinoma | 54 |  | N0 | M0 |  |
| D15A3195 | Male | Resection | right hemicolon | adenocarcinoma | 79 | T3 | N1 | M0 | 3B |
| D15A3196 | Female | Resection | sigmoid colon | adenocarcinoma | 87 | T4a | N1 | M0 | 3B |


| D15A3197 | Male | Resection | Hepatic region of colon | mucinous adenocarcinoma | 34 | T3 | N1 | M0 | 3B |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| D15A3198 | Female | Resection | transverse colon | adenocarcinoma | 68 | T3 | N0 | M0 | 2A |
| D15A3200 | Female | Resection | rectosigmoid | adenocarcinoma | 57 | T3 | N0 | M0 | 2A |
| D15A3203 | Female | Resection | sigmoid colon | adenocarcinoma | 73 | T3 | N0 | M0 | 2A |
| D15A3209 | Female | Resection | descending colon | adenocarcinoma | 83 | T4a |  | M0 |  |
| D15A3210 | Male | Resection | sigmoid colon | adenocarcinoma | 84 | T3 | N0 | M0 | 2A |
| D15A3212 | Female | Resection | right hemicolon | adenocarcinoma | 75 | T4a | N2b | M1 | 4 |
| D15A3223 | Male | Resection | sigmoid colon | adenocarcinoma | 76 | T3 | N1 | M0 | 3B |
| D15A3134 | Female | Resection | right hemicolon | mucinous adenocarcinoma | 80 | T3 | N0 | M0 | 2A |
| D15A3225 | Female | Resection | splenic region of the colon | adenocarcinoma | 81 | T3 | N1 | M0 | 3B |
| D15A3227 | Female | Resection | sigmoid colon | adenocarcinoma | 74 | T4b | N0 | M0 | 2C |
| D15A3228 | Male | Resection | Hepatic region of colon | adenocarcinoma | 78 | T3 | N0 | M0 | 2A |
| D15A3135 | Male | Resection | splenic region of the colon | adenocarcinoma | 71 | T4a | N0 | M0 | 2B |
| D15A3230 | Male | Resection | sigmoid colon | adenocarcinoma | 55 | T3 | N0 | M0 | 2A |
| D15A3231 | Male | Resection | transverse colon | adenocarcinoma | 54 |  | N1 | M0 | 3 |
| D15A3138 | Male | Resection | right hemicolon | adenocarcinoma | 57 | T4a | N1 | M0 | 3B |
| D15A3139 | Female | Resection | right hemicolon | adenocarcinoma | 76 | T4a | N2b | M0 | 3C |
| D15A3221 | Female | Resection | ascending colon | adenocarcinoma | 71 | T3 | N1 | M0 | 3B |
| D15A3222 | Male | Resection | sigmoid colon | adenocarcinoma | 80 | T3 | N0 | M0 | 2A |
| D15A3233 | Female | Resection | transverse colon | adenocarcinoma | 53 | T3 | N2a | M0 | 3B |
| D15A3141 | Male | Resection | sigmoid colon | adenocarcinoma | 70 |  | N1 | M0 | 3 |
| D15A3234 | Female | Resection | right hemicolon | adenocarcinoma | 84 | T3 | N0 | M0 | 2A |
| D15A3236 | Female | Resection | ascending colon | adenocarcinoma | 67 | T2 | N0 | M0 | 1 |
| D15A3237 | Female | Resection | descending colon | adenocarcinoma | 87 | T3 | N1 | M0 | 3B |
| D15A3238 | Female | Resection | sigmoid colon | adenocarcinoma | 67 | T3 | N0 | M0 | 2A |
| D15A3283 | Male | Resection | sigmoid colon | adenocarcinoma | 56 | T4a | N0 | M0 | 2B |
| D15A3284 | Male | Resection | ascending colon | adenocarcinoma | 54 | T3 | N0 | M0 | 2A |
| D15A3285 | Female | Resection | ascending colon | mucinous adenocarcinoma | 56 | T4b | N1 | M0 | 3C |
| D15A3286 | Male | Resection | sigmoid colon | adenocarcinoma | 74 | T3 | N1 | M0 | 3B |
| D15A3287 | Female | Resection | Hepatic region of colon | adenocarcinoma | 76 | T4a | N1 | M0 | 3B |
| D15A3289 | Female | Resection | descending colon | adenocarcinoma | 54 | T4a | N2a | M0 | 3C |
| D15A3290 | Male | Resection | rectosigmoid | adenocarcinoma | 67 | T3 | N0 | M0 | 2 A |
| D15A3291 | Male | Resection | sigmoid colon | adenocarcinoma | 62 | T3 | N0 | M0 | 2 A |
| D15A3292 | Female | Resection | sigmoid colon | adenocarcinoma | 61 | T3 | N1 | M0 | 3B |
| D15A3293 | Female | Resection | sigmoid colon | adenocarcinoma | 55 | T3 | N1 | M0 | 3B |
| D15A3296 | Male | Resection | descending colon | adenocarcinoma | 73 | T3 | N0 | M0 | 2A |
| D15A3281 | Male | Resection | ascending colon | adenocarcinoma | 63 | T3 | N0 | M0 | 2A |
| D15A3297 | Female | Resection | splenic region of the colon | adenocarcinoma | 72 | T2 | N0 | M0 | 1 |


| D15A3298 | Male | Resection | ascending colon | adenocarcinoma | 70 | T3 | N0 | M0 | 2 A |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| D15A3299 | Male | Resection | sigmoid colon | adenocarcinoma | 58 | T3 | N0 | M0 | 2 A |
| D15A3312 | Male | Resection | ascending colon | adenocarcinoma | 70 | T3 | N0 | M0 | 2 A |
| D15A3313 | Female | Resection | ascending colon | adenocarcinoma | 72 | T3 | N0 | M0 | 2 A |
| D15A3319 | Female | Resection | sigmoid colon | adenocarcinoma | 77 | T3 | N0 | M0 | 2 A |
| D15A3320 | Male | Resection | Hepatic region of colon | adenocarcinoma | 67 | T3 | N0 | M0 | 2 A |
| D15A3321 | Male | Resection | Hepatic region of colon | adenocarcinoma | 49 | T3 | N0 | M0 | 2 A |
| D15A3322 | Male | Resection | ascending colon | adenocarcinoma | 61 | T4b | N0 | M0 | 2C |
| D15A3323 | Male | Resection | left hemicolon | adenocarcinoma | 81 | T4a | N0 | M0 | 2B |
| D15A3059 | Male | Resection | colon | mucinous adenocarcinoma | 60 | T4a | N0 | M0 | 2B |
| D15A3075 | Female | Resection | sigmoid colon | adenocarcinoma | 37 | T4a | N2b | M1 | 4 |
| D15A3077 | Male | Resection | sigmoid colon | adenocarcinoma | 65 | T3 | N0 | M0 | 2 A |
| D15A3091 | Female | Resection | sigmoid colon | adenocarcinoma | 75 | T3 | N2a | M0 | 3B |
| D15A3095 | Female | Resection | right hemicolon | adenocarcinoma | 55 | T4a | N0 | M0 | 2B |
| D15A3131 | Male | Resection | right hemicolon | adenocarcinoma | 19 | T4b | N0 | M0 | 2 C |
| D15A3192 | Female | Resection | right hemicolon | adenocarcinoma | 49 | T4b | N2a | M0 | 3C |
| D15A3194 | Male | Resection | right hemicolon | adenocarcinoma | 47 | T3 | N0 | M0 | 2 A |
| D15A3205 | Male | Resection | right hemicolon | adenocarcinoma | 69 | T4a | N0 | M0 | 2B |
| D15A3136 | Female | Resection | transverse colon | adenocarcinoma | 53 | T4a | N1 | M0 | 3B |
| D15A3140 | Female | Resection | right hemicolon | adenocarcinoma | 61 | T3 | N0 | M0 | 2 A |
| D15A3314 | Female | Resection | Hepatic region of colon | adenocarcinoma | 82 | T4a | N0 | M0 | 2B |



Figure 3. Validation of antibodies for immunohistochemistry staining. (A, B, E) Representative photomicrographs of TXNIP (A), GDF15 (B) and FOXP3 (E) expression in paraffin-embedded human liver tissue, paraffin-embedded human placenta tissue and paraffin-embedded human tonsil tissue slides, respectively. The staining included representative positive control of TXNIP (A)/GDF15 (B)/FOXP3 (E) (left panel) and representative negative control with omission of the primary antibodies (right panel). (C, D) Western blotting of both TXNIP (C) and GDF15 (D) expression in HCT15 with/ without gene editing (TXNIP-KO or GDF15-KO).


Figure 4. This image is for coordinate reference of cytokine array assay.
Table 2. Refer to the table below for the Human XL Cytokine Array coordinates.

| Coordinate | Analyte/Control | Entrez Gene ID | Alternate Nomenclature |
| :---: | :---: | :---: | :---: |
| A1, A2 | Reference Spots | N/A | RS |
| A3, A4 | Adiponectin | 9370 | Acrp30 |
| A5, A6 | Apolipoprotein A-I | 335 | ApoA1 |
| A7, A8 | Angiogenin | 283 | - |
| A9, A10 | Angiopoietin-1 | 284 | Ang-1, ANGPT1 |
| A11, A12 | Angiopoietin-2 | 285 | Ang-2, ANGPT2 |
| A13, A14 | BAFF | 10673 | BlyS, TNFSF13B |
| A15, A16 | BDNF | 627 | Brain-derived Neurotrophic Factor |
| A17, A18 | Complement Component C5/C5a | 727 | C5/C5a |
| A19, A20 | CD14 | 929 | - |
| A21, A22 | CD30 | 943 | TNFRSF8 |
| A23, A24 | Reference Spots | N/A | RS |
| B3, B4 | CD40 ligand | 959 | CD40L, TNFSF5, CD154, TRAP |
| B5, B6 | Chitinase 3-like 1 | 1116 | CHI3L1, YKL-40 |
| B7, B8 | Complement Factor D | 1675 | Adipsin, CFD |
| B9, B10 | C-Reactive Protein | 1401 | CRP |
| B11, B12 | Cripto-1 | 6997 | Teratocarcinoma-derived Growth Factor |
| B13, B14 | Cystatin C | 1471 | CST3, ARMD11 |
| B15, B16 | Dkk-1 | 22943 | Dickkopf-1 |
| B17, B18 | DPPIV | 1803 | CD26, DPP4, Dipeptidyl-peptidase IV |
| B19, B20 | EGF | 1950 | Epidermal Growth Factor |
| B21, B22 | EMMPRIN | 682 | CD147, Basigin |
| C3, ${ }^{\text {c }}$ | ENA-78 | 6374 | CXCL5 |
| C5, 6 | Endoglin | 2022 | CD105, ENG |
| C7, 88 | Fas Ligand | 356 | TNFSF6, CD178, CD95L |
| C9, 10 | FGF basic | 2247 | FGF-2 |
| C11, 112 | FGF-7 | 2252 | KGF |
| C13, 14 | FGF-19 | 9965 | - |
| C15, 116 | Flt-3 Ligand | 2323 | FLT3LG |
| C17, 18 | G-CSF | 1440 | CSF3 |
| C19, ${ }^{\text {c }}$ (20 | GDF-15 | 9518 | MIC-1 |
| C21, 22 | GM-CSF | 1437 | CSF2 |
| D1, D2 | GROa | 2919 | CXCL1, MSGA-a |
| D3, D4 | Growth Hormone | 2688 | GH, Somatotropin |
| D5, D6 | HGF | 3082 | Scatter Factor, SF |
| D7, 88 | ICAM-1 | 3383 | CD54 |
| D9, D10 | IFN- $\gamma$ | 3458 | IFNG |
| D11, D12 | IGFBP-2 | 3485 | - |


| Coordinate | Analyte/Control | Entrez Gene ID | Alternate Nomenclature |
| :---: | :---: | :---: | :---: |
| D13, D14 | IGFBP-3 | 3486 | - |
| D15, D16 | IL-1a | 3552 | IL-1F1 |
| D17, D18 | IL-13 | 3553 | IL-1F2 |
| D19, D20 | Il-1ra | 3557 | IL-1F3 |
| D21, D22 | $\mathrm{ll}-2$ | 3558 | - |
| D23, 224 | $\mathrm{ll}-3$ | 3562 | - |
| E1, E2 | IL-4 | 3565 | - |
| E3, E4 | IL-5 | 3567 | - |
| E5, E6 | IL-6 | 3569 | - |
| E7, 88 | IL-8 | 3576 | CXCl8 |
| E9, E10 | IL-10 | 3586 | - |
| E11, E12 | ll-11 | 3589 | $\square$ |
| E13, E14 | IL-12 p70 | 3593 | $\square$ |
| E15, E16 | ll-13 | 3596 | $\square$ |
| E17, E18 | IL-15 | 3600 | - |
| E19, E20 | IL-16 | 3603 | - |
| E21, E22 | IL-17A | 3605 | IL-17, CTLA8 |
| E23, E24 | $\mathrm{ll}-18 \mathrm{Bpa}$ | 10068 | - |
| F1, F2 | IL-19 | 29949 | - |
| F3, F4 | 1L-22 | 50616 | IL-TIF |
| F5,F6 | 1l-23 | 51561 | IL-23A, SGRF |
| F7, F8 | IL-24 | 11009 | C49A, FISP, MDA-7, MOB-5, ST16 |
| F9, F10 | 1L-27 | 246778 | - |
| F11, F12 | IL-31 | 386653 | $\square$ |
| F13, F14 | IL-32 | 9235 | - |
| F15, F16 | 1L-33 | 90865 | C9orf26, DVS27,NF-HEV |
| F17, F18 | IL-34 | 146433 | C16orf77 |
| F19, F20 | \|P-10 | 3627 | CXCL10 |
| F21, F22 | I-TAC | 6373 | CXCL11, SCYB9B |
| F23, F24 | Kallikrein 3 | 354 | PSA, KLK3 |
| 61, 62 | Leptin | 3952 | OB |
| 63,64 | LIF | 3976 | - |
| 65, 66 | Lipocalin-2 | 3934 | NGAL, LCN2, Siderocalin |
| 67,68 | MCP-1 | 6347 | CCL2, MCAF |
| G9, G10 | MCP-3 | 6354 | CCL7, MARC |
| 611, G12 | M-CSF | 1435 | CSF1 |
| 613,614 | MIF | 4282 | - |
| 615,G16 | MIG | 4283 | CXC19 |


| Coordinate | Analyte/Control | Entrez Gene ID | Alternate Nomenclature |
| :---: | :---: | :---: | :---: |
| G17, G18 | MIP-1a/MIP-1 $\beta$ | 6348/6351 | CCl3/CCl4 |
| G19, G20 | MIP-3a | 6364 | CCL20, Exodus-1, LARC |
| G21,G22 | MPP-38 | 6363 | CLL19, ELC |
| G23, G24 | MMP-9 | 4318 | CL64B, Gelatinase B |
| H1, H2 | Myeloperoxidase | 4353 | MPO, Lactoperoxidase |
| H3, H4 | Osteopontin | 6696 | OPN |
| H5, H6 | PDGF-AA | 5154 | - |
| H7, H8 | PDGF-AB/BB | 5154/5155 | - |
| H9, H10 | Pentraxin 3 | 5806 | PTX3, TSG-14 |
| H11, H12 | PF4 | 5196 | CXCL4 |
| H13, H14 | RAGE | 177 | - |
| H15, H16 | RANTES | 6352 | CCL5 |
| H17, H18 | RBP-4 | 5950 | - |
| H19, H20 | Relaxin-2 | 6019 | RLN2, RLXH2 |
| H21, H22 | Resistin | 56729 | ADSF, FIZZ3, RETN |
| H23, H24 | SDF-1a | 6387 | CXCL12, PBSF |
| 11,12 | Serpin E1 | 5054 | PAI-I, PAI-1, Nexin |
| 13,14 | SHBG | 6462 | ABP |
| 15,16 | ST2 | 9173 | IL-1 R4, IL1RL1, ST2L |
| 17,18 | TARC | 6361 | CCL17 |
| 19,110 | TFF3 | 7033 | ITF, TFI |
| 111, 112 | TfR | 7037 | CD71, TFR1, TFRC, TRFR |
| 113,114 | TGF-a | 7039 | TGFA |
| I15, 116 | Thrombospondin-1 | 7057 | THBS1, TSP-1 |
| 117, 118 | TNF-a | 7124 | TNFSF1A |
| 119, 120 | uPAR | 5329 | PLAUR |
| 121,122 | VEGF | 7422 | BEGFA |
| J1, 12 | Reference Spots | N/A | RS |
| J5, J6 | Vitamin DBP | 2638 | VDB, DBP, VDBP |
| J7, 18 | CD31 | 5175 | PECAM-1 |
| J9, 110 | TIM-3 | 84868 | HAVCR2 |
| J11, J12 | VCAM-1 | 7412 | CD106 |
| J23,124 | Negative Controls | N/A | Control (-) |

Figure 5. The results of quality control for RNA sequencing experiments
A.





 $\forall X O+3 \perp N$


OX-dINXI

$O X-d I N X \perp$
B.


Figure 6. Work flow of library construction for RNA sequencing analysis



Figure 7. Optimization of Chromatin immunoprecipitation assay. A. $10 \mu \mathrm{l}$ of purified DLD1 DNA following sonication and Proteinase K digestion: lane 1. 30 cycles $/ 30 \mathrm{sec}$; lane 2. 40cycles $/ 30 \mathrm{sec}$. B. lane $1.10 \mu \mathrm{l}$ of purified DLD1 DNA following sonication and Proteinase K digestion two rounds of 40 cycles $/ 30$ sec; lane 2. $10 \mu \mathrm{l}$ of purified DLD1 DNA following sonication and Proteinase K digestion two rounds of 40 cycles $/ 30 \mathrm{sec}$; lane $2 . \mathrm{L}=$ Gene ruler mix DNA ladder. C. ChIP-PCR showing TXNIP promoter amplicon on Oxaliplatin treated DLD-1 cells (40cycles PCR). Anti H3K4me3 antibody was used as ChIP positive control for open chromatin.

Figure 8. Mass Spectrometry gel


Figure 9. Proteome discoverer nodal workflow for raw data processing. Spectrum Selector: Min. Precursor mass ( 350 Da ), Max. Precursor mass ( 10000 Da ), S/N Threshold (FT-only) (1.5); Mascot/Sequest: Database (Uniprot), Enzyme (Trypsin), Missed cleavage (2), Precursor mass tol (10 ppm), Fragment mass tol (0.6 Da), Dynamic modifications (TMT6plex K), TMT6plex (N-Term), Carbamidomethyl (C), Oxidation (M); Peptide validator: Target FDR (strict) (0.01), Target FDR (relaxed) (0.05); Reporter ion quantifier: Integration window tol. ( 20 ppm ), Integration method (Most confident centroid); Reporter Quantification: Co-Isolation Threshold. (50), SPS Mass Matches [\%] Threshold (65), Average Reporter S/N Threshold (10).

Table 3. Information of patient samples from GSE29621

| ID | OS | OS.time | RFS | RFS.time | Gender | T | N | M | Stage | TXNIP | GDF15 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM734111 | 0 | 4.405 | 0 | 4.405 | Male | T3 | N 1 | M 0 | III | 0.312783 | -0.14056 |
| GSM734112 | 1 | 4.575 | 0 | 4.575 | Female | T3 | N 1 | M0 | III | 0.151283 | 1.099897 |
| GSM734113 | 0 | 6.1725 | 1 | 2.070833 | Male | T3 | N 1 | M0 | III | 1.093902 | -1.21064 |


| GSM734114 | 0 | 4.945 | 0 | 4.945 | Male | T3 | N1 | M0 | III | 0.32225 | -0.66181 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM734115 | 0 | 2.7225 | 1 | 1.443333 | Female | T3 | N2 | M1 | IV | 0.824354 | -0.99008 |
| GSM734116 | 1 | 3.226667 | 0 | 3.226667 | Female | T3 | N1 | M0 | III | 0.210682 | 0.432979 |
| GSM734117 | 0 | 3.5225 | 1 | 1.09 | Male | T4 | N0 | M1 | IV | 0.463912 | -0.99439 |
| GSM734118 | 1 | 0.745 | 0 | 0.745 | Male | T3 | N1 | M1 | IV | -0.75031 | -0.02026 |
| GSM734119 | 1 | 0.426667 | NA | NA | Female | T3 | N2 | M1 | IV | -1.11088 | -0.19856 |
| GSM734120 | 0 | 3.988333 | 0 | 3.988333 | Male | T3 | N0 | M0 | II | 0.789498 | 1.509899 |
| GSM734121 | 0 | 6.5725 | 0 | 5.360833 | Male | T3 | N1 | M0 | III | -0.45228 | -0.06515 |
| GSM734122 | 0 | 8.764167 | 0 | 8.764167 | Male | T3 | N1 | M0 | III | 0.051037 | -1.01894 |
| GSM734123 | 1 | 3.983333 | 0 | 3.983333 | Male | T3 | N1 | M0 | III | -1.79796 | 0.107784 |
| GSM734124 | 1 | 0.509167 | 1 | 0.445833 | Male | T3 | N1 | M0 | III | 0.344915 | -0.10296 |
| GSM734125 | 1 | 1.703333 | 0 | 1.703333 | Male | T2 | N2 | M0 | III | 0.489811 | -1.91032 |
| GSM734126 | 0 | 7.134167 | 0 | 7.134167 | Female | T3 | N1 | M0 | III | -0.50446 | 0.687436 |
| GSM734127 | 1 | 4.9225 | 0 | 4.9225 | Male | T3 | N2 | M0 | III | 0.921205 | 1.70005 |
| GSM734128 | 1 | 7.160833 | 1 | 6.621667 | Male | T3 | N1 | M0 | III | 0.807814 | 0.961305 |
| GSM734129 | 1 | 1.585833 | 1 | 0.715 | Female | T3 | N1 | M0 | III | 0.027118 | -0.05489 |
| GSM734130 | 1 | 0.413333 | NA | NA | Male | T3 | N1 | M1 | IV | 0.853788 | -0.38418 |
| GSM734131 | 1 | 0.476667 | NA | NA | Male | T3 | N1 | M1 | IV | -1.05661 | 0.004581 |
| GSM734132 | 0 | 7.9225 | 0 | 6.884167 | Male | T3 | N1 | M1 | IV | -0.43585 | -1.53053 |
| GSM734133 | 1 | 2.4075 | NA | NA | Male | T3 | N2 | M1 | IV | -1.38847 | -0.87828 |
| GSM734134 | 1 | 1.545 | NA | NA | Male | T3 | N1 | M1 | IV | 0.851479 | 1.174237 |
| GSM734135 | 1 | 2.835 | NA | NA | Female | T3 | N2 | M1 | IV | 1.069809 | -1.9893 |
| GSM734136 | 1 | 0.12 | NA | NA | Male | T3 | N1 | M1 | IV | -0.74531 | 0.141854 |
| GSM734137 | 0 | 2.654167 | NA | NA | Male | T3 | N1 | M1 | IV | -0.35317 | 0.435311 |
| GSM734138 | 0 | 5.0625 | 0 | 4.599167 | Female | T3 | N1 | M1 | IV | 1.316195 | -1.23847 |
| GSM734139 | 1 | 1.270833 | NA | NA | Male | T3 | N1 | M1 | IV | -0.05212 | 0.471317 |
| GSM734140 | 1 | 1.213333 | NA | NA | Male | T3 | N1 | M1 | IV | 0.82092 | 1.865304 |
| GSM734141 | 1 | 0.83 | 0 | 0.83 | Female | T4 | N0 | M1 | IV | -0.22422 | 1.516205 |
| GSM734142 | 0 | 1.8625 | NA | NA | Male | T3 | N0 | M1 | IV | 0.54646 | 0.787041 |
| GSM734143 | 1 | 4.375 | 0 | 4.375 | Female | T3 | N0 | M0 | II | -1.61394 | -0.33853 |
| GSM734144 | 0 | 7.415833 | 0 | 7.415833 | Male | T3 | N0 | M0 | II | 0.034791 | 0.553182 |
| GSM734145 | 0 | 4.610833 | 0 | 4.610833 | Female | T3 | N0 | M0 | II | -0.56455 | -0.74766 |
| GSM734146 | 1 | 3.109167 | 0 | 3.109167 | Male | T3 | N0 | M0 | II | 0.054999 | -0.79995 |
| GSM734147 | 0 | 5.270833 | 0 | 5.270833 | Male | T3 | N0 | M0 | II | -0.60611 | -1.46353 |
| GSM734148 | 0 | 5.130833 | 0 | 5.130833 | Female | T4 | NA | NA | II | -1.00533 | 0.817282 |
| GSM734149 | 0 | 2.840833 | 0 | 2.015833 | Female | T3 | N0 | M0 | II | -1.84176 | 1.096917 |
| GSM734150 | 0 | 4.996667 | 0 | 4.996667 | Male | T3 | N0 | M0 | II | -0.54442 | 0.545595 |
| GSM734151 | 0 | 4.870833 | 0 | 3.8925 | Female | T3 | N0 | M0 | II | -0.12856 | -2.81641 |
| GSM734152 | 0 | 3.139167 | 0 | 1.495833 | Female | T3 | N0 | M0 | II | 0.450252 | -1.09909 |
| GSM734153 | 0 | 10.05167 | 1 | 2.303333 | Female | T4 | N0 | M0 | II | -0.31588 | 0.359226 |
| GSM734154 | 0 | 2.103333 | 0 | 2.103333 | Male | T3 | N0 | M0 | II | 0.737175 | 0.603849 |
| GSM734155 | 0 | 3.7475 | 0 | 3.7475 | Male | T3 | N0 | M0 | II | -2.67039 | 0.493944 |
| GSM734156 | 0 | 2.991667 | 0 | 2.991667 | Male | T3 | N0 | M0 | II | 0.720277 | -0.12855 |
| GSM734157 | 0 | 2.221667 | 0 | 2.221667 | Male | T3 | N0 | M0 | II | 0.707411 | 0.54882 |
| GSM734158 | 0 | 6.999167 | 1 | 1.865 | Female | T3 | N0 | M0 | II | 1.421195 | 0.530929 |
| GSM734159 | 0 | 1.254167 | 0 | 1.254167 | Male | T3 | N0 | M0 | II | -0.1422 | 0.694252 |
| GSM734160 | 1 | 2.2625 | 0 | 2.2625 | Female | T3 | N0 | M0 | 11 | 0.486333 | -0.8906 |
| GSM734161 | 0 | 4.353333 | 0 | 4.353333 | Male | T2 | N0 | M0 | I | 0.584612 | -0.92646 |
| GSM734162 | 0 | 5.651667 | 0 | 5.651667 | Female | T2 | N0 | M0 | I | -0.62029 | -1.38728 |
| GSM734163 | 0 | 4.594167 | 0 | 4.594167 | Female | T2 | N0 | M0 | 1 | 1.44503 | -1.02212 |
| GSM734164 | 0 | 3.049167 | 0 | 1.996667 | Male | T2 | N0 | M0 | 1 | 0.584612 | 0.389153 |
| GSM734165 | 1 | 5.49 | 0 | 5.49 | Male | T2 | N0 | M0 | I | -2.54118 | 1.002166 |
| GSM734166 | 0 | 4.960833 | 0 | 4.960833 | Male | T2 | N0 | M0 | I | 0.730398 | 1.146522 |
| GSM734167 | 0 | 0.303333 | 0 | 0.303333 | Male | T2 | N0 | M0 | 1 | -1.23541 | 0.909908 |
| GSM734168 | 0 | 8.2925 | 0 | 8.2925 | Female | T3 | N1 | M0 | III | 0.879437 | -0.25072 |
| GSM734169 | 0 | 4.870833 | 0 | 4.870833 | Female | T3 | N1 | M0 | III | 0.660373 | 2.045737 |
| GSM734170 | 0 | 4.345 | 0 | 4.345 | Female | T3 | N0 | M0 | II | -1.58084 | -0.44107 |


| GSM734171 | 0 | 8.536667 | 0 | 5.405 | Male | T4 | N0 | M0 | II | -1.20354 | 0.998171 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM734172 | 0 | 4.155833 | 0 | 3.0625 | Female | T3 | N0 | M0 | II | 1.221077 | 0.059992 |
| GSM734173 | 1 | 1.273333 | NA | NA | Male | T3 | N0 | M1 | IV | 0.224988 | 0.343584 |
| GSM734174 | 0 | 4.545 | 0 | 2.243333 | Female | T3 | N1 | M0 | III | -0.30395 | -0.14181 |
| GSM734175 | 1 | 0.98 | 1 | 0.684167 | Male | T3 | N2 | M0 | III | 2.577809 | -0.19132 |

Table 4. Information of patient samples from GSE38832

| ID | DFS | DFS.time | DSS | DSS.time | Stage | TXNIP | GDF15 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM950411 | NA | NA | 1 | 0.130833333 | IV | 0.228936499 | 1.583136447 |
| GSM950412 | NA | NA | 1 | 1.466666667 | IV | 0.177766916 | -0.520849181 |
| GSM950413 | NA | NA | 1 | 1.055833333 | IV | $0.045104297$ | 1.275806193 |
| GSM950414 | NA | NA | 1 | 0.569166667 | IV | $0.282642004$ | -0.750102844 |
| GSM950415 | NA | NA | 1 | 2.710833333 | IV | $0.373194554$ | 1.316795384 |
| GSM950416 | NA | NA | 1 | 1.341666667 | IV | 0.135575225 | 1.571889282 |
| GSM950417 | 0 | 0.035833333 | 0 | 0.035833333 | II | 0.127046161 | 0.644385211 |
| GSM950418 | 0 | 7.035833333 | 0 | 7.035833333 | II | $0.395881947$ | 1.034811432 |
| GSM950419 | 0 | 3.6525 | 0 | 3.6525 | III | 0.365583287 | 1.341932706 |
| GSM950420 | 0 | 6.758333333 | 0 | 6.758333333 | II | $0.480669722$ | 0.092105309 |
| GSM950421 | 1 | 0.3225 | 1 | 1.1525 | III | $0.436809936$ | 0.554216099 |
| GSM950422 | 0 | 9.0475 | 0 | 9.0475 | III | 1.256641199 | -0.693377173 |
| GSM950423 | 0 | 2.3 | 0 | 2.3 | II | 0.591657994 | 1.141293245 |
| GSM950424 | 0 | 3.455833333 | 0 | 3.455833333 | III | 0.166308956 | -0.333781833 |
| GSM950425 | 0 | 3.416666667 | 0 | 3.416666667 | III | 0.445220696 | -1.549557739 |
| GSM950426 | 0 | 4.5 | 0 | 4.5 | III | $0.824894908$ | -0.018204972 |
| GSM950427 | NA | NA | 1 | 1.069166667 | IV | $0.071062069$ | -1.820657463 |
| GSM950428 | 0 | 0.2975 | 0 | 0.2975 | I | $2.022652372$ | 0.060116991 |
| GSM950429 | 0 | 9.060833333 | 0 | 9.060833333 | III | $0.440542002$ | -1.310041006 |
| GSM950430 | 0 | 3.85 | 0 | 3.85 | II | 1.12922372 | -0.134005278 |
| GSM950431 | 0 | 5.883333333 | 0 | 5.883333333 | III | -0.84667235 | -1.01817447 |
| GSM950432 | 0 | 8.8 | 0 | 8.8 | III | $1.909002192$ | 0.366223042 |
| GSM950433 | 1 | 5 | 1 | 5.764166667 | III | $0.558683413$ | -0.164293513 |
| GSM950434 | 0 | 7.135833333 | 0 | 7.135833333 | III | $0.933209875$ | -0.488227085 |
| GSM950435 | 0 | 7.919166667 | 0 | 7.919166667 | 11 | -0.43312882 | 0.389173615 |
| GSM950436 | 0 | 4.558333333 | 0 | 4.558333333 | III | $0.383708347$ | -0.701500675 |
| GSM950437 | 0 | 7.6975 | 0 | 7.6975 | 11 | $0.913439888$ | -0.678906115 |
| GSM950438 | 1 | 3.460833333 | 1 | 4.019166667 | III | 0.166308956 | -1.417224483 |
| GSM950439 | 0 | 4.766666667 | 0 | 4.766666667 | III | $0.489279046$ | -0.84538344 |
| GSM950440 | 0 | 8.441666667 | 0 | 8.441666667 | 1 | $0.558683413$ | 0.009256557 |
| GSM950441 | 0 | 8.1275 | 0 | 8.1275 | I | 2.234815172 | -2.212528192 |


| GSM950442 | 0 | 8.925 | 0 | 8.925 | 1 | $0.722883417$ | 0.50173558 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM950443 | 0 | 4.539166667 | 0 | 4.539166667 | 1 | 0.506889431 | -0.220377053 |
| GSM950444 | 0 | 6.980833333 | 0 | 6.980833333 | II | 1.408938841 | -0.232753833 |
| GSM950445 | 0 | 2.916666667 | 0 | 2.916666667 | 1 | 1.397309359 | 1.022981391 |
| GSM950446 | 0 | 2.5775 | 0 | 2.5775 | III | 0.370987339 | 0.433781366 |
| GSM950447 | 0 | 1.219166667 | 0 | 1.219166667 | 1 | $0.087764739$ | 0.270151851 |
| GSM950448 | 0 | 1.014166667 | 0 | 1.014166667 | II | $2.597948541$ | 1.239903605 |
| GSM950449 | 0 | 0.025 | 0 | 0.025 | III | 0.080085375 | -0.633779373 |
| GSM950450 | 0 | 2.5275 | 0 | 2.5275 | III | -0.32328667 | 0.886870392 |
| GSM950451 | NA | NA | 1 | 0.710833333 | IV | $0.612042274$ | 1.380600101 |
| GSM950452 | 1 | 1.505833333 | 0 | 1.591666667 | III | 0.772647433 | 0.750741546 |
| GSM950453 | 0 | 2.614166667 | 0 | 2.614166667 | II | $0.510572793$ | -0.447139265 |
| GSM950454 | 0 | 0.9525 | 0 | 0.9525 | II | $0.322023581$ | 1.060245815 |
| GSM950455 | 0 | 1.9025 | 0 | 1.9025 | III | $0.189756194$ | 0.761597221 |
| GSM950456 | NA | NA | 1 | 0.080833333 | IV | $1.179928319$ | -0.295394235 |
| GSM950457 | 1 | 0.810833333 | 0 | 2.233333333 | III | 0.968520534 | -1.992866635 |
| GSM950458 | NA | NA | 0 | 2.258333333 | IV | 0.422845571 | 0.178831541 |
| GSM950459 | 0 | 1.730833333 | 0 | 1.730833333 | III | 0.324702083 | -0.720061874 |
| GSM950460 | 0 | 5.294166667 | 0 | 5.294166667 | II | 1.053100873 | 1.011237776 |
| GSM950461 | 0 | 3.0975 | 0 | 3.0975 | II | 2.210940136 | 0.284189229 |
| GSM950462 | 0 | 3.3725 | 0 | 3.3725 | II | 1.260757757 | -0.718970508 |
| GSM950463 | 0 | 0.614166667 | 0 | 0.614166667 | III | 0.037471704 | 0.928655978 |
| GSM950464 | NA | NA | 1 | 0.789166667 | IV | -0.29559334 | -1.225738335 |
| GSM950465 | 0 | 2.069166667 | 0 | 2.069166667 | II | 0.158774948 | 0.972505658 |
| GSM950466 | NA | NA | 1 | 3 | IV | 0.166308956 | 0.980688364 |
| GSM950467 | 0 | 3.083333333 | 0 | 3.083333333 | I | 0.116663454 | -0.10827794 |
| GSM950468 | 0 | 0.319166667 | 0 | 0.319166667 | II | 0.453045413 | 0.206396998 |
| GSM950469 | 0 | 1.155833333 | 0 | 1.155833333 | 1 | $0.545465775$ | -0.596646063 |
| GSM950470 | 0 | 2.091666667 | 0 | 2.091666667 | III | 0.534913178 | 0.794653476 |
| GSM950471 | 0 | 9.208333333 | 0 | 9.208333333 | III | 1.27061564 | 0.805417807 |
| GSM950472 | 0 | 2.610833333 | 0 | 2.610833333 | 1 | $1.472497042$ | -0.048299829 |
| GSM950473 | NA | NA | 0 | 3.010833333 | IV | 0.320257466 | 1.304270389 |
| GSM950474 | 0 | 3.5725 | 0 | 3.5725 | II | 0.413456573 | 0.983948708 |
| GSM950475 | 0 | 4.591666667 | 0 | 4.591666667 | I | 0.896799514 | 0.247536336 |
| GSM950476 | 0 | 4.919166667 | 0 | 4.919166667 | 1 | 0.435511174 | -1.089449886 |
| GSM950477 | 0 | 1.8025 | 0 | 1.8025 | 1 | -0.15298936 | 1.728054626 |
| GSM950478 | 1 | 1.910833333 | 0 | 3.0025 | III | 1.595202554 | 0.34305088 |
| GSM950479 | 0 | 1.735833333 | 0 | 1.735833333 | II | 0.720653755 | -0.456144756 |
| GSM950480 | 0 | 1.080833333 | 0 | 1.080833333 | III | $0.489279046$ | 0.658726869 |
| GSM950481 | 0 | 4.7 | 0 | 4.7 | II | 0.431270116 | -0.94614713 |


| GSM950482 | NA | NA | 1 | 1.35 | IV | $0.322023581$ | -0.240746346 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM950483 | 0 | 2.566666667 | 0 | 2.566666667 | 1 | $0.642063706$ | -0.027235816 |
| GSM950484 | 0 | 1.7025 | 0 | 1.7025 | III | 0.846982288 | 0.800997582 |
| GSM950485 | 0 | 1.6475 | 0 | 1.6475 | II | $0.732876811$ | 0.596398063 |
| GSM950486 | 1 | 0.975 | 0 | 1.505833333 | III | 0.408963314 | -0.663277932 |
| GSM950487 | 1 | 1.216666667 | 0 | 1.764166667 | II | 0.124585455 | -0.705313562 |
| GSM950488 | NA | NA | 0 | 1.614166667 | IV | $0.763439389$ | -0.82601364 |
| GSM950489 | 0 | 3.339166667 | 0 | 3.339166667 | I | 2.70198355 | -1.955320106 |
| GSM950490 | 0 | 4.419166667 | 0 | 4.419166667 | II | 0.226499576 | 0.223603499 |
| GSM950491 | NA | NA | 1 | 0.091666667 | IV | 0.761335632 | -0.741002686 |
| GSM950492 | 0 | 3.725 | 0 | 3.725 | III | 2.234815172 | -1.608041335 |
| GSM950493 | NA | NA | 1 | 1.5 | IV | 1.631642852 | -1.684232215 |
| GSM950494 | NA | NA | 1 | 1.064166667 | IV | 2.306114689 | -2.64063546 |
| GSM950495 | 0 | 0.766666667 | 0 | 0.766666667 | II | 1.441040656 | -0.854155466 |
| GSM950496 | 0 | 2.0275 | 0 | 2.0275 | 1 | $0.257086946$ | -0.866013406 |
| GSM950497 | 0 | 0.360833333 | 0 | 0.360833333 | II | 1.648375221 | 1.614923135 |
| GSM950498 | NA | NA | 0 | 4.7025 | IV | -1.00013932 | 0.971621554 |
| GSM950499 | 0 | 2.008333333 | 0 | 2.008333333 | 1 | $1.170036885$ | 0.114760627 |
| GSM950500 | 0 | 1.694166667 | 0 | 1.694166667 | II | $0.373194554$ | -1.380826918 |
| GSM950501 | NA | NA | 0 | 0.0975 | IV | $1.408683598$ | 0.317101837 |
| GSM950502 | NA | NA | 1 | 0.169166667 | IV | $1.269091051$ | 0.731683417 |
| GSM950503 | 0 | 4.125 | 0 | 4.125 | 1 | 1.101954935 | -1.392785845 |
| GSM950504 | 1 | 0.8775 | 0 | 2.9475 | II | $2.140664002$ | -0.033677693 |
| GSM950505 | 0 | 0.9525 | 0 | 0.9525 | III | $1.472497042$ | -0.303543938 |
| GSM950506 | 0 | 0.7025 | 0 | 0.7025 | II | $0.645722158$ | 1.070308999 |
| GSM950507 | 0 | 0.8 | 0 | 0.8 | II | 1.231799066 | 0.980688364 |
| GSM950508 | NA | NA | 1 | 3.414166667 | IV | $0.536833316$ | 1.912617684 |
| GSM950509 | 0 | 4.514166667 | 0 | 4.514166667 | III | 1.627845351 | -1.337772415 |
| GSM950510 | NA | NA | 1 | 0.683333333 | IV | 0.888660471 | -2.443080056 |
| GSM950511 | NA | NA | 1 | 0.2975 | IV | $1.861229889$ | -2.580712744 |
| GSM950512 | 0 | 6.6975 | 0 | 6.6975 | II | $0.995770608$ | 0.871075263 |
| GSM950513 | 0 | 7.919166667 | 0 | 7.919166667 | II | 0.668525979 | -0.712495789 |
| GSM950514 | 0 | 4.180833333 | 0 | 4.180833333 | III | 1.779192944 | 0.237988031 |
| GSM950515 | NA | NA | 1 | 2.566666667 | IV | $0.801343676$ | 1.70281209 |
| GSM950516 | 0 | 7.430833333 | 0 | 7.430833333 | II | -0.33190818 | -0.654902815 |
| GSM950517 | 0 | 4.339166667 | 0 | 4.339166667 | III | 0.330466748 | 0.638151544 |
| GSM950518 | NA | NA | 1 | 0.433333333 | IV | 0.90779298 | -0.315150267 |
| GSM950519 | 0 | 7.016666667 | 0 | 7.016666667 | II | $0.245568303$ | 0.521075091 |
| GSM950520 | 0 | 9.283333333 | 0 | 9.283333333 | III | 1.340650717 | 0.583986918 |


| GSM950521 | 0 | 0.6525 | 0 | 0.6525 | III | 0.045104297 | -0.393558834 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| GSM950522 | 0 | 7.955833333 | 0 | 7.955833333 | III | 1.008985377 | 0.066773464 |
| GSM950523 | 0 | 8.8725 | 0 | 8.8725 | II | 0.202184265 | 0.498769511 |
| GSM950524 | NA | NA | 1 | 0.533333333 | IV | 0.743101699 | 1.08597556 |
| GSM950525 | 0 | 7.705833333 | 0 | 7.705833333 | III | 0.030330618 | 0.561325111 |
| GSM950526 | NA | NA | 1 | 7.730833333 | IV | -0.33190818 | 0.250463744 |
| GSM950527 | NA | NA | 1 | 4.083333333 | IV | -0.30502323 | 0.304399299 |
| GSM950528 | 0 | 7.683333333 | 0 | 7.683333333 | III | 0.359957161 | -0.234690234 |
| GSM950529 | 0 | 7.65 | 0 | 7.65 | III | 1.479728489 | 0.927804761 |
| GSM950530 | NA | NA | 1 | 1.95 | IV | 0.846982288 | 0.706260614 |
| GSM950531 | 0 | 1.7975 | 0 | 1.7975 | III | 1.334208643 | -0.74690238 |
| GSM950532 | 0 | 2.755833333 | 0 | 2.755833333 | II | 0.422845571 | 0.321469297 |

Table 5. Information of patient samples from GSE52735

| ID | ACT response | TXNIP | GDF15 |
| :---: | :---: | :---: | :---: |
| GSM1275067 | NR | -0.453588 | 1.911558 |
| GSM1275068 | NR | 0.741675 | 0.272435 |
| GSM1275069 | R | -1.527873 | -0.834293 |
| GSM1275070 | R | 0.503087 | 1.779891 |
| GSM1275071 | NR | -0.15211 | 0.986188 |
| GSM1275072 | NR | -1.68777 | 0.631303 |
| GSM1275073 | NR | 0.299146 | 0.182579 |
| GSM1275074 | NR | 1.874411 | 0.075166 |
| GSM1275075 | R | -0.271545 | -0.906072 |
| GSM1275076 | NR | -2.813699 | 1.35069 |
| GSM1275077 | R | 0.558166 | 0.49383 |
| GSM1275078 | R | -0.293038 | -0.462063 |
| GSM1275079 | R | 1.347586 | -1.118223 |
| GSM1275080 | R | -1.657522 | -0.575103 |
| GSM1275081 | R | 0.458082 | 0.946724 |
| GSM1275082 | R | -0.687145 | 0.212632 |
| GSM1275083 | R | -0.665227 | -1.117578 |
| GSM1275084 | R | 0.172792 | -2.379292 |
| GSM1275085 | NR | -0.655423 | 0.697212 |
| GSM1275086 | R | 0.102255 | 0.921207 |
| GSM1275087 | NR | -0.640448 | -1.1809 |
| GSM1275088 | R | 0.320025 | 1.061141 |
| GSM1275089 | NR | 0.929067 | -0.163991 |
| GSM1275090 | R | 0.651024 | -0.768571 |
| GSM1275091 | R | 0.938855 | -1.016959 |
| GSM1275092 | NR | 0.153157 | 1.11456 |
| GSM1275093 | R | 0.799161 | -0.273163 |
| GSM1275094 | R | 1.071156 | -0.578287 |


| GSM1275095 | R | 0.713962 | -1.360835 |
| :---: | :---: | :---: | :---: |
| GSM1275096 | NR | -0.687145 | 0.463133 |
| GSM1275097 | R | -0.384918 | 1.19474 |
| GSM1275098 | NR | -1.659706 | 0.894535 |
| GSM1275099 | R | 1.197858 | -0.322389 |
| GSM1275100 | R | 1.054219 | -0.019074 |
| GSM1275101 | R | -0.054504 | -0.537994 |
| GSM1275102 | NR | -0.35798 | -1.616903 |
| GSM1275103 | R | 0.763957 | 0.042167 |

Table 6. Information of patient samples from GSE6988

| ID | Type | GDF15 |
| :---: | :--- | :---: |
| AD15889L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.437729 |
| AD15889N | human normal colorectal mucosa | 1.297665 |
| AD15889T | human colorectal primary tumour (adenocarcinoma) | 1.929246 |
| AD15889T2 | human colorectal primary tumour (adenocarcinoma) | 1.763517 |
| AD15889Y | human normal liver tissue | 3.574398 |
| AX11903L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.573805 |
| AX11903T | human colorectal primary tumour (adenocarcinoma) | 1.523402 |
| BF95674L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.807717 |
| BF95674N | human normal colorectal mucosa | 2.272595 |
| BF95674T | human colorectal primary tumour (adenocarcinoma) | 2.393257 |
| BH27060L | human colorectal liver metastasis tumour (adenocarcinoma) | 3.451118 |
| BH27060N | human normal colorectal mucosa | 1.666417 |
| BH27060T | human colorectal primary tumour (adenocarcinoma) | 2.129928 |
| CA75662L | human colorectal liver metastasis tumour (adenocarcinoma) | 3.40047 |
| CA75662N | human normal colorectal mucosa | 1.570837 |
| CA75662T | human colorectal primary tumour (adenocarcinoma) | 3.195132 |
| CA75662Y | human normal liver tissue | 3.944034 |
| CH76639L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.234958 |
| CH76639N | human normal colorectal mucosa | 1.185903 |
| CH76639T | human colorectal primary tumour (adenocarcinoma) | 2.062743 |
| CH76639Y | human normal liver tissue | 3.972991 |
| DA09647L | human colorectal liver metastasis tumour (invasive squamous cell carcinoma) | 1.61401 |
| DA09647N | human normal colorectal mucosa | 1.644748 |
| DA09647T | human colorectal primary tumour (invasive squamous cell carcinoma) | 2.412006 |
| DA09647T2 | human colorectal primary tumour (invasive squamous cell carcinoma) | 2.857492 |
| DA09647Y | human normal liver tissue | 4.584387 |
| DA85401L | human colorectal liver metastasis tumour (adenocarcinoma) | 3.185002 |
| DA85401N | human normal colorectal mucosa | 1.690391 |
| DA85401T | human colorectal primary tumour (adenocarcinoma) | 2.335573 |
| DA85401Y | human normal liver tissue | 5.994388 |
| DA86595L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.944078 |
| DA86595N | human normal colorectal mucosa | 1.675662 |
| DA86595N2 | human normal colorectal mucosa | 1.789686 |


| DA86595T | human colorectal primary tumour (adenocarcinoma) | 1.367762 |
| :---: | :---: | :---: |
| DA86595T2 | human colorectal primary tumour (adenocarcinoma) | 1.639317 |
| DA86595Y | human normal liver tissue | 3.491193 |
| DB14731L | human colorectal liver metastasis tumour (adenocarcinoma) | 3.477558 |
| DB14731N | human normal colorectal mucosa | 1.704383 |
| DB14731T | human colorectal primary tumour (adenocarcinoma) | 2.64972 |
| DB14731Y | human normal liver tissue | 3.185925 |
| DB33368L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.798984 |
| DB33368N | human normal colorectal mucosa | 2.430789 |
| DB33368T | human colorectal primary tumour (adenocarcinoma) | 3.189344 |
| DB33368Y | human normal liver tissue | 4.379159 |
| DC10136L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.972484 |
| DC10136N | human normal colorectal mucosa | 1.756299 |
| DC10136T | human colorectal primary tumour (adenocarcinoma) | 1.892931 |
| DC54343L | human colorectal liver metastasis tumour (adenocarcinoma) | 0.18005 |
| DC54343N | human normal colorectal mucosa | 1.984971 |
| DC54343T | human colorectal primary tumour (adenocarcinoma) | 1.520653 |
| DD13676L | human colorectal liver metastasis tumour (adenocarcinoma after chemoradiation therapy) | 1.919197 |
| DD13676N | human normal colorectal mucosa | 2.070493 |
| DD13676T | human colorectal primary tumour (adenocarcinoma after chemoradiation therapy) | 5.796173 |
| DD13676Y | human normal liver tissue | 5.235613 |
| DX14048T | human colorectal primary tumour (adenocarcinoma) | 2.509886 |
| DX16165T | human colorectal primary tumour (adenocarcinoma) | 1.504442 |
| DX18306T | human colorectal primary tumour (adenocarcinoma) | -0.351 |
| DX18618T | human colorectal primary tumour (adenocarcinoma) | 0.261456 |
| DX18679T | human colorectal primary tumour (adenocarcinoma) | 2.670293 |
| DX22237T | human colorectal primary tumour (adenocarcinoma) | 3.172609 |
| DX24121T | human colorectal primary tumour (adenocarcinoma) | 1.075656 |
| DX25011T | human colorectal primary tumour (adenocarcinoma) | 1.719013 |
| DX26025T | human colorectal primary tumour (adenocarcinoma) | 3.068779 |
| DX27754L | human colorectal liver metastasis tumour (gastrointestinal stromal tumour) | 1.364322 |
| DX27754N | human normal colorectal mucosa | 1.574519 |
| DX27754T | human colorectal primary tumour (gastrointestinal stromal tumour) | 1.904249 |
| DX28973T | human colorectal primary tumour (adenocarcinoma) | 2.5637 |
| DX31056T | human colorectal primary tumour (adenocarcinoma) | 1.748598 |
| DX31470T | human colorectal primary tumour (adenocarcinoma) | 3.416421 |
| DX33570T | human colorectal primary tumour (adenocarcinoma) | 1.294134 |
| DX33882T | human colorectal primary tumour (adenocarcinoma) | 1.628017 |
| DX33896T | human colorectal primary tumour (adenocarcinoma) | 2.289097 |
| DX36208T | human colorectal primary tumour (adenocarcinoma) | 3.174302 |
| DX45134T | human colorectal primary tumour (adenocarcinoma) | 2.12642 |
| DX46644L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.282871 |
| DX46644L2 | human colorectal liver metastasis tumour (adenocarcinoma) | 2.180125 |
| DX46644N | human normal colorectal mucosa | 2.776432 |
| DX46644N2 | human normal colorectal mucosa | 2.612871 |
| DX46644T | human colorectal primary tumour (adenocarcinoma) | 2.679253 |


| DX46644T2 | human colorectal primary tumour (adenocarcinoma) | 2.630854 |
| :---: | :---: | :---: |
| DX52497T | human colorectal primary tumour (adenocarcinoma) | 0.620962 |
| DX57828L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.110447 |
| DX57828L2 | human colorectal liver metastasis tumour (adenocarcinoma) | 2.82083 |
| DX57828N | human normal colorectal mucosa | 2.332805 |
| DX57828N2 | human normal colorectal mucosa | 2.559739 |
| DX57828T | human colorectal primary tumour (adenocarcinoma) | 4.138434 |
| DX57828T2 | human colorectal primary tumour (adenocarcinoma) | 3.97004 |
| DX62184T | human colorectal primary tumour (adenocarcinoma) | 2.170682 |
| DX63421L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.256163 |
| DX63421N | human normal colorectal mucosa | 2.611123 |
| DX63421T | human colorectal primary tumour (adenocarcinoma) | 3.368063 |
| DX64153L | human colorectal liver metastasis tumour (adenocarcinoma) | 3.257078 |
| DX64153N | human normal colorectal mucosa | 2.486665 |
| DX64153T | human colorectal primary tumour (adenocarcinoma) | 2.14822 |
| DX67096L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.563062 |
| DX67096N | human normal colorectal mucosa | 3.001181 |
| DX67096T | human colorectal primary tumour (adenocarcinoma) | 2.127045 |
| DX68531T | human colorectal primary tumour (adenocarcinoma) | 0.733839 |
| DX70008L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.003639 |
| DX70008N | human normal colorectal mucosa | 1.830151 |
| DX70008T | human colorectal primary tumour (adenocarcinoma) | 3.174756 |
| DX70008Y | human normal liver tissue | 2.352135 |
| DX72875L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.933767 |
| DX72875N | human normal colorectal mucosa | 1.33371 |
| DX72875T | human colorectal primary tumour (adenocarcinoma) | 1.547777 |
| DX72875T2 | human colorectal primary tumour (adenocarcinoma) | 1.536613 |
| DX73169L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.977251 |
| DX73169N | human normal colorectal mucosa | 2.907815 |
| DX73169T | human colorectal primary tumour (adenocarcinoma) | 2.718055 |
| DX73339L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.90262 |
| DX73339N | human normal colorectal mucosa | 1.496952 |
| DX73339T | human colorectal primary tumour (adenocarcinoma) | 3.164846 |
| DX73339Y | human normal liver tissue | 2.361714 |
| DX86797L | human colorectal liver metastasis tumour (adenocarcinoma) | 3.68982 |
| DX86797N | human normal colorectal mucosa | 1.854225 |
| DX86797T | human colorectal primary tumour (adenocarcinoma) | 2.557598 |
| DX86797Y | human normal liver tissue | 3.126623 |
| EA71820L | human colorectal liver metastasis tumour (adenocarcinoma) | 2.537432 |
| EA71820T | human colorectal primary tumour (adenocarcinoma) | 0.758211 |
| EX36605L | human colorectal liver metastasis tumour (adenocarcinoma) | 1.239077 |
| EX36605N | human normal colorectal mucosa | 2.164224 |
| EX36605T | human colorectal primary tumour (adenocarcinoma) | 1.354372 |
| EX36605Y | human normal liver tissue | 2.370023 |

Table 7. DLD1 RNA-seq data

| Gene symbols (Protein coding) | Ctrl (FPKM) | Oxaliplatin (FPKM) | log2 FoldChange | P-adj |
| :---: | :---: | :---: | :---: | :---: |
| PRR35 | 0 | 28.54604642 | 7.266648694 | 4.05E-07 |
| LCN10 | 0.348551657 | 19.81510099 | 5.77798115 | 0.000165013 |
| KCNB2 | 0 | 9.706757472 | 5.710984401 | 0.000944421 |
| MSLNL | 1.404126458 | 67.71865034 | 5.648547106 | $1.39 \mathrm{E}-10$ |
| ARHGDIG | 0 | 8.572541077 | 5.535993911 | 0.002144401 |
| LCN6 | 0 | 7.722649387 | 5.382576736 | 0.003533255 |
| DIRAS1 | 0.358471485 | 14.16813813 | 5.291236529 | 0.001478102 |
| AZU1 | 0.348551657 | 13.53987207 | 5.22439553 | 0.001381992 |
| CCDC27 | 0.606003494 | 20.50235029 | 4.952011819 | 0.000369608 |
| TXNIP | 269.1314923 | 5656.84046 | 4.393907246 | 3.23E-05 |
| TBXA2R | 2.287421445 | 39.23883874 | 4.079540413 | 4.03E-07 |
| KRTAP3-1 | 1.736887689 | 26.77862079 | 3.986304302 | $8.66 \mathrm{E}-05$ |
| C16orf90 | 1.404126458 | 20.143357 | 3.886848878 | 0.000404855 |
| LYPD1 | 0.697103315 | 9.959528556 | 3.878697138 | 0.02031963 |
| ATAD3C | 0.651553405 | 9.393553402 | 3.819505399 | 0.020045939 |
| FCGRT | 0.707023143 | 9.525458512 | 3.815109141 | 0.018535348 |
| PAX5 | 0.606003494 | 8.417741357 | 3.690189167 | 0.032800515 |
| RGS22 | 4.483800267 | 52.87831485 | 3.584576576 | $2.38 \mathrm{E}-08$ |
| LYPD5 | 0.716942971 | 8.107733749 | 3.56726866 | 0.040775101 |
| IGF2 | 1.01002489 | 11.52926475 | 3.521303794 | 0.00988745 |
| CPA4 | 15.4650591 | 176.1615753 | 3.495720114 | $1.17 \mathrm{E}-16$ |
| RASD2 | 1.368496375 | 14.72266598 | 3.446066645 | 0.00318405 |
| ANK1 | 1.782437599 | 18.66984546 | 3.444763727 | 0.001488446 |
| PTX4 | 1.378416203 | 14.40864557 | 3.420790593 | 0.00581604 |
| SNAI2 | 0.909005242 | 9.918793717 | 3.354114189 | 0.026429436 |
| PDE6G | 4.095569298 | 40.67562823 | 3.33126446 | $2.98 \mathrm{E}-07$ |
| RGS11 | 2.424071176 | 22.24152997 | 3.226885568 | 0.000327353 |
| PKDREJ | 4.202459545 | 37.95424359 | 3.209201115 | 2.52E-05 |
| ANO2 | 5.828407757 | 53.14717945 | 3.207502448 | 4.64E-08 |
| DACT3 | 3.287526507 | 28.42075948 | 3.104053822 | 0.000150843 |
| CHRD | 1.792357427 | 14.03861315 | 3.027956708 | 0.014782567 |
| C11orf94 | 1.414046286 | 10.5277698 | 2.938353804 | 0.033496993 |
| CHGA | 1.762597943 | 12.01272864 | 2.803494298 | 0.024200189 |
| ARRDC4 | 172.9196795 | 1160.017472 | 2.747058788 | 9.63E-10 |
| PDCL2 | 4.584819916 | 29.59693522 | 2.727474801 | 0.000558821 |
| INHA | 2.06559969 | 13.16222222 | 2.702016776 | 0.021122924 |
| PDE10A | 33.72891497 | 219.3575194 | 2.698430287 | 4.67E-19 |
| PNMA2 | 34.13487213 | 212.2371324 | 2.648639507 | $1.36 \mathrm{E}-15$ |
| GPR137C | 53.21070562 | 327.5893119 | 2.625864776 | 1.23E-28 |
| KCNG2 | 2.727072923 | 16.54052704 | 2.608860065 | 0.008565108 |
| AP3B2 | 4.121279552 | 24.60793412 | 2.59037783 | 0.001500428 |
| RPP25 | 4.646103054 | 27.91417573 | 2.581616636 | 0.000282438 |
| HCAR3 | 2.782542661 | 16.16328535 | 2.569844393 | 0.008287204 |
| PLPPR3 | 32.04344779 | 184.3770951 | 2.519142127 | $1.80 \mathrm{E}-17$ |
| 03-Sep | 46.08095523 | 259.0874552 | 2.492684351 | $1.69 \mathrm{E}-16$ |
| RASGRP3 | 17.57849375 | 97.74761476 | 2.482790473 | 8.06E-11 |
| COL1A1 | 4.701572792 | 25.75155698 | 2.46304087 | 0.001463559 |
| ADRB2 | 2.212112051 | 12.34161806 | 2.441564692 | 0.039888572 |
| UCN2 | 7.852506767 | 42.20998093 | 2.438021162 | $2.71 \mathrm{E}-05$ |
| WNT16 | 21.07210879 | 111.6133627 | 2.412413619 | $1.72 \mathrm{E}-09$ |
| COL20A1 | 2.974604932 | 15.87256772 | 2.410925128 | 0.014015023 |
| FGF2 | 20.98687957 | 110.6226099 | 2.404684243 | $1.76 \mathrm{E}-10$ |
| HTR1D | 16.32675026 | 86.00456706 | 2.39451671 | $2.69 \mathrm{E}-10$ |
| ENHO | 3.737097813 | 19.3498855 | 2.385035867 | 0.004632392 |
| LYG2 | 6.44433108 | 33.07425299 | 2.365799283 | 0.000225897 |
| PTGER2 | 49.36096136 | 252.6579753 | 2.36338399 | $6.61 \mathrm{E}-15$ |
| B3GAT1 | 5.737307937 | 29.20504976 | 2.355497201 | 0.000916199 |


| VWA5B2 | 71.94579383 | 363.3904149 | 2.341373811 | $4.40 \mathrm{E}-26$ |
| :---: | :---: | :---: | :---: | :---: |
| APLP1 | 31.76427773 | 160.5659135 | 2.334114287 | 1.50E-12 |
| DMC1 | 3.645997992 | 18.37407345 | 2.326246992 | 0.007022647 |
| RNF152 | 2.671603185 | 12.87830568 | 2.275684362 | 0.035165482 |
| C1QTNF2 | 10.90647032 | 52.48962585 | 2.274847592 | 0.000442427 |
| PTGES3L | 5.085754532 | 23.88552657 | 2.245402325 | 0.002812597 |
| CALHM4 | 3.469726148 | 16.14399537 | 2.238344759 | 0.022181972 |
| TMEM210 | 8.197009195 | 38.14018876 | 2.232089349 | 0.000205831 |
| BAIAP3 | 95.55803419 | 449.3300405 | 2.227374929 | 8.13E-29 |
| FOXD4 | 25.24891528 | 115.4144015 | 2.206209116 | $9.08 \mathrm{E}-08$ |
| C5AR1 | 36.72341675 | 167.3002168 | 2.189493266 | $2.49 \mathrm{E}-10$ |
| TMEM217 | 14.195761 | 64.67923249 | 2.17759175 | 4.62E-07 |
| PEAR1 | 9.474348551 | 43.05626799 | 2.166610104 | 0.000112887 |
| ZNF345 | 4.505461292 | 19.73496986 | 2.152066644 | 0.020399001 |
| AKAP12 | 161.3512784 | 710.9110899 | 2.140314549 | 8.15E-21 |
| CYR61 | 1387.786154 | 5945.598838 | 2.09882266 | 2.32E-30 |
| GNG13 | 20.64824774 | 88.15655484 | 2.098670663 | $2.66 \mathrm{E}-07$ |
| MSLN | 29.64514406 | 126.016474 | 2.094460483 | $1.86 \mathrm{E}-10$ |
| TMEM249 | 7.923709733 | 33.90392433 | 2.082351912 | 0.002093715 |
| NHLRC4 | 3.368706499 | 14.24681952 | 2.0716486 | 0.049706111 |
| TTLL6 | 8.206871824 | 34.41968929 | 2.055674805 | 0.000701974 |
| S1PR5 | 9.286392708 | 37.91228424 | 2.0513492 | 0.001149187 |
| NLRP3 | 9.67051725 | 39.62299273 | 2.035369389 | 0.000701974 |
| SDR42E1 | 3.99454965 | 16.25765209 | 2.025376411 | 0.023999986 |
| MEIS3 | 5.267896975 | 21.34142809 | 2.014893529 | 0.020466476 |
| MDK | 153.3590238 | 619.3048721 | 2.014090386 | 8.06E-33 |
| HUNK | 76.78407355 | 306.7319811 | 2.00450603 | $3.99 \mathrm{E}-16$ |
| EDN1 | 37.0381025 | 148.0219175 | 1.996296943 | 8.15E-12 |
| FAM131B | 12.51839228 | 49.52045562 | 1.98291888 | 0.001513213 |
| RAET1G | 6.418620825 | 25.11853067 | 1.968452596 | 0.006578295 |
| TMEM191B | 30.92664705 | 119.8950032 | 1.966111755 | 1.11E-09 |
| PRSS51 | 4.075729642 | 15.62618957 | 1.953151378 | 0.034506787 |
| TTLL10 | 28.17562804 | 107.9926925 | 1.937098146 | 4.65E-09 |
| JSRP1 | 11.55990229 | 43.79558539 | 1.936210823 | 0.005122722 |
| SLC25A42 | 129.0556141 | 493.1417646 | 1.931233215 | 3.73E-20 |
| CLDN1 | 61.60781835 | 234.1572764 | 1.927424103 | 4.63E-11 |
| NRIP3 | 4.57079366 | 17.52377359 | 1.925881049 | 0.03274181 |
| USH1G | 4.939184973 | 18.97160223 | 1.925754698 | 0.018268125 |
| TMEM200B | 11.34788597 | 43.19043918 | 1.924822638 | 0.000192967 |
| CYP1A1 | 22.31346877 | 84.36250008 | 1.918444943 | 0.000115162 |
| CALD1 | 198.9113473 | 751.8590677 | 1.915608314 | $3.76 \mathrm{E}-13$ |
| MDGA1 | 11.05480405 | 41.36897349 | 1.906702483 | 0.000486714 |
| LOXL3 | 163.2145467 | 611.1277337 | 1.906242878 | $6.06 \mathrm{E}-26$ |
| B3GALT5 | 260.4299322 | 974.6133288 | 1.905323052 | $1.48 \mathrm{E}-38$ |
| INAFM2 | 60.93830386 | 227.4034844 | 1.90167873 | $1.06 \mathrm{E}-15$ |
| PLAT | 25.83496472 | 95.34326406 | 1.887519419 | 5.24E-07 |
| TEX14 | 43.56008523 | 160.133776 | 1.885510482 | $2.64 \mathrm{E}-07$ |
| ADAMTS15 | 33.13699493 | 121.6255928 | 1.884467063 | $1.31 \mathrm{E}-07$ |
| HIST1H2BJ | 25.70424278 | 94.09208045 | 1.877554323 | 1.69E-07 |
| TCHH | 38.2839754 | 140.7522917 | 1.877286477 | 7.32E-10 |
| EFCAB5 | 3.984629822 | 14.52672325 | 1.860925313 | 0.049255327 |
| FGF22 | 27.33429742 | 98.40720919 | 1.855436317 | $3.48 \mathrm{E}-06$ |
| BDNF | 87.41655193 | 316.3280954 | 1.852677967 | 2.87E-18 |
| TLX2 | 6.125538906 | 22.01804642 | 1.852031724 | 0.014247921 |
| MYL9 | 5.010445138 | 17.78799198 | 1.830685975 | 0.048032622 |
| ADGRF1 | 30.41339315 | 108.2559805 | 1.822480176 | $4.66 \mathrm{E}-07$ |
| PHACTR3 | 24.26214399 | 86.38128654 | 1.819532219 | $1.28 \mathrm{E}-05$ |
| CD37 | 18.76661186 | 65.96278605 | 1.815446766 | 8.57E-06 |
| CILP2 | 24.16928 | 84.98645638 | 1.805077479 | 3.09E-06 |
| HSD17B6 | 25.22491199 | 87.01873381 | 1.788298574 | 3.37E-07 |
| SYNE1 | 148.5065463 | 514.8940288 | 1.787871159 | 4.79E-19 |


| DMBX1 | 79.52448025 | 272.1625916 | 1.776480795 | $2.05 \mathrm{E}-15$ |
| :---: | :---: | :---: | :---: | :---: |
| IFITM5 | 13.28270653 | 45.5742754 | 1.771402425 | 0.000598628 |
| ZMYND15 | 32.04162642 | 109.4008279 | 1.768335722 | $1.56 \mathrm{E}-07$ |
| PRICKLE1 | 20.56888911 | 69.84756059 | 1.765677018 | $1.77 \mathrm{E}-05$ |
| DQX1 | 24.94585633 | 82.28570026 | 1.730356319 | $2.88 \mathrm{E}-05$ |
| NR2E3 | 30.67101658 | 100.8429306 | 1.723896018 | 4.76E-06 |
| APBB1 | 18.0893482 | 59.59504832 | 1.719965589 | $4.06 \mathrm{E}-05$ |
| FAM69B | 135.1867887 | 443.8235012 | 1.715737884 | 1.11E-22 |
| C1orf105 | 53.15112946 | 174.6585244 | 1.715579022 | $6.83 \mathrm{E}-11$ |
| P2RX2 | 12.83142825 | 41.43301111 | 1.709348197 | 0.004496059 |
| HAP1 | 10.96781066 | 35.38684233 | 1.706438642 | 0.007187446 |
| CHST3 | 35.69936561 | 116.4161217 | 1.703205579 | 1.85E-08 |
| CCNI2 | 17.92293898 | 58.47187106 | 1.702258094 | 6.73E-05 |
| NDRG2 | 21.40252776 | 69.86097985 | 1.697615465 | 2.16E-05 |
| DPF1 | 69.64440333 | 224.863738 | 1.69650418 | 7.41E-13 |
| ADGRB2 | 311.5585553 | 1008.750798 | 1.695840738 | 2.53E-31 |
| KCNJ8 | 73.99132507 | 239.012064 | 1.687450358 | $4.99 \mathrm{E}-11$ |
| CCDC102A | 82.58396511 | 265.7553013 | 1.686574224 | $4.38 \mathrm{E}-12$ |
| PLK2 | 762.9028719 | 2445.10974 | 1.679753363 | 4.19E-33 |
| IGF2BP1 | 7.464218599 | 24.01824802 | 1.665378021 | 0.022185345 |
| AC010325.1 | 6.06014934 | 19.18363847 | 1.664487178 | 0.034590839 |
| PCDH7 | 140.3398174 | 444.8782199 | 1.660791906 | $1.22 \mathrm{E}-15$ |
| VASH1 | 10.52410995 | 33.24131635 | 1.659995005 | 0.007289915 |
| CLDN5 | 77.64518662 | 244.6872728 | 1.656911908 | 8.82E-15 |
| KIF17 | 44.70618177 | 140.987559 | 1.655307621 | 2.21E-07 |
| C1QTNF9B | 15.1304765 | 48.10373012 | 1.654171642 | 0.000713547 |
| SPIB | 9.735964014 | 30.15610928 | 1.654025118 | 0.015804225 |
| PALLD | 349.83206 | 1100.109196 | 1.653907679 | $1.62 \mathrm{E}-22$ |
| RNF151 | 8.119878431 | 25.34521068 | 1.643777031 | 0.02417374 |
| SLC19A3 | 10.39333082 | 32.24283494 | 1.638337184 | 0.005257939 |
| STAB1 | 8.85255463 | 27.82341363 | 1.636271238 | 0.017540724 |
| TCEA2 | 30.39583855 | 94.49604662 | 1.635871821 | 1.72E-06 |
| SYNGR3 | 11.48858493 | 35.22802981 | 1.629131442 | 0.007752867 |
| PPP1R27 | 7.216743788 | 22.14716323 | 1.627089692 | 0.034927542 |
| DACT1 | 20.50344235 | 63.251102 | 1.620091932 | 0.000157986 |
| FOXA3 | 31.17412186 | 95.35523074 | 1.616312051 | 8.19E-06 |
| GPRIN3 | 12.78587834 | 38.23652745 | 1.601148889 | 0.016880868 |
| PLPPR2 | 258.9872553 | 783.67346 | 1.597796051 | $1.26 \mathrm{E}-21$ |
| NBPF1 | 971.1307141 | 2936.141555 | 1.596245141 | $2.70 \mathrm{E}-31$ |
| MYBL1 | 239.2678859 | 720.762793 | 1.591413483 | $5.26 \mathrm{E}-15$ |
| RAB3D | 24.13541408 | 72.90381941 | 1.582922696 | 0.000209785 |
| SLC1A3 | 72.75042267 | 215.4198181 | 1.571817072 | $3.67 \mathrm{E}-05$ |
| GVQW2 | 32.0831271 | 95.48668536 | 1.568613219 | 5.76E-06 |
| CDH7 | 12.22531036 | 36.35388132 | 1.565969523 | 0.024068896 |
| CTGF | 268.9479165 | 790.6073811 | 1.555329385 | 0.00803267 |
| GGT7 | 52.86551072 | 156.1532933 | 1.554239481 | $1.84 \mathrm{E}-06$ |
| ZSCAN12 | 136.2996546 | 398.6652727 | 1.550091871 | $8.21 \mathrm{E}-16$ |
| BRSK1 | 12.59552304 | 36.92584123 | 1.547525489 | 0.004779943 |
| TMEM99 | 275.3249672 | 804.1366206 | 1.547092901 | 8.56E-27 |
| TMEM191C | 51.85794248 | 151.0641237 | 1.540711042 | $6.78 \mathrm{E}-08$ |
| C1R | 40.76516609 | 118.771529 | 1.538656372 | $2.66 \mathrm{E}-05$ |
| PLEKHD1 | 25.04276955 | 72.21512036 | 1.536359499 | 7.97E-05 |
| RDH5 | 48.74674501 | 140.8158494 | 1.532960141 | $1.71 \mathrm{E}-07$ |
| HPCAL4 | 20.84025281 | 59.88413327 | 1.520649371 | 0.002627942 |
| CLGN | 19.70132735 | 55.90086517 | 1.509183172 | 0.001534354 |
| MORN2 | 105.5082996 | 298.164876 | 1.502148625 | $1.46 \mathrm{E}-08$ |
| NOTCH4 | 14.67503459 | 41.84883276 | 1.499519579 | 0.0084431 |
| KBTBD8 | 43.58226714 | 122.1600143 | 1.494759045 | 0.001818953 |
| HIST1H4H | 18.77071829 | 52.51891339 | 1.492835735 | 0.001381992 |
| CCDC148 | 24.60898867 | 69.02428218 | 1.491212339 | 0.000154648 |
| ACTA2 | 42.85476906 | 120.648331 | 1.490220685 | 5.69E-07 |


| HPX | 27.73004877 | 78.42969105 | 1.490017167 | 6.32E-05 |
| :---: | :---: | :---: | :---: | :---: |
| ATF5 | 380.9388232 | 1062.717948 | 1.479861021 | 7.07E-14 |
| PAX6 | 13.72640724 | 38.16772958 | 1.477824208 | 0.009925088 |
| REEP2 | 49.54668935 | 136.8619829 | 1.472098729 | 3.73E-07 |
| CYP2W1 | 11.19550301 | 30.80767812 | 1.467284662 | 0.021854318 |
| SOWAHA | 10.76172213 | 29.55538404 | 1.4659163 | 0.017852404 |
| MOSPD1 | 720.2241398 | 1982.438024 | 1.460137459 | $2.70 \mathrm{E}-27$ |
| KISS1R | 11.95394666 | 32.46591032 | 1.458959191 | 0.022472711 |
| NPTX2 | 11.84118582 | 32.34586069 | 1.457540221 | 0.033545655 |
| NKX3-1 | 431.1222601 | 1182.763338 | 1.456708899 | $2.68 \mathrm{E}-28$ |
| CSPG5 | 39.88826259 | 109.0522827 | 1.454433949 | 0.000103385 |
| KRT5 | 15.06508693 | 41.58955754 | 1.451765359 | 0.009038804 |
| LPAR6 | 16.19602832 | 44.2402864 | 1.447929827 | 0.004584182 |
| ZNF488 | 111.8737929 | 304.0888697 | 1.44547129 | $2.46 \mathrm{E}-08$ |
| KIAA0319 | 116.6857271 | 317.1802137 | 1.442500138 | $5.76 \mathrm{E}-13$ |
| KATNAL1 | 192.893093 | 522.9167334 | 1.440848807 | $2.34 \mathrm{E}-18$ |
| CRABP2 | 82.5960556 | 223.705853 | 1.440376088 | 3.86E-08 |
| DAB2 | 102.5534771 | 278.3022233 | 1.439347055 | 7.95E-08 |
| FAM126A | 151.6329834 | 410.3408639 | 1.437249124 | 2.47E-11 |
| ZNF132 | 10.4983997 | 28.32256287 | 1.436376866 | 0.030643379 |
| PBX3 | 28.94211295 | 78.26047281 | 1.433957669 | $8.47 \mathrm{E}-05$ |
| SLFNL1 | 63.40803934 | 170.7959688 | 1.433132745 | 3.89E-06 |
| SEMA3G | 67.08955302 | 180.0559127 | 1.427916056 | $1.25 \mathrm{E}-08$ |
| FAM13B | 546.7388225 | 1467.242252 | 1.423171578 | 7.37E-20 |
| MSANTD1 | 41.13190763 | 110.0344453 | 1.41996731 | $1.16 \mathrm{E}-05$ |
| PPP1R14C | 185.7339896 | 495.5843266 | 1.41704785 | $2.36 \mathrm{E}-14$ |
| IFRD1 | 2569.86777 | 6861.626155 | 1.417021631 | $1.61 \mathrm{E}-26$ |
| FAM71F2 | 53.0971318 | 141.3522695 | 1.41002112 | 0.00071383 |
| MRC2 | 12.64107295 | 33.41016875 | 1.407655801 | 0.032771739 |
| INKA1 | 11.71046388 | 30.62916745 | 1.405872017 | 0.033058979 |
| MYLK2 | 17.63390629 | 46.60609946 | 1.402556538 | 0.006346161 |
| OBSL1 | 11.76182719 | 30.87409586 | 1.396361846 | 0.017494963 |
| REEP1 | 44.24321949 | 115.4345501 | 1.392552395 | $5.88 \mathrm{E}-05$ |
| ZNF467 | 55.41425553 | 145.3365526 | 1.391891547 | $6.24 \mathrm{E}-05$ |
| NRP1 | 675.5141138 | 1771.659131 | 1.39088456 | $1.94 \mathrm{E}-16$ |
| NKX6-1 | 23.42679837 | 60.89685028 | 1.390230314 | 0.00483803 |
| FAM57B | 17.14647705 | 44.78864657 | 1.380162693 | 0.010518107 |
| COL28A1 | 23.19083596 | 60.6412909 | 1.37815479 | 0.00102821 |
| TPH1 | 65.67961316 | 170.5425643 | 1.376559625 | $1.91 \mathrm{E}-05$ |
| LRRN4 | 81.06566292 | 210.2558392 | 1.374736053 | $4.98 \mathrm{E}-07$ |
| ALPP | 224.5874049 | 581.8585645 | 1.374294021 | $2.89 \mathrm{E}-10$ |
| EPPK1 | 427.9867733 | 1108.184846 | 1.373090547 | 5.82E-26 |
| GJC2 | 12.75788303 | 33.01021537 | 1.372495351 | 0.026895285 |
| RNF227 | 284.3973506 | 734.0357961 | 1.366399118 | 5.65E-17 |
| RRM2 | 3911.385706 | 10083.73489 | 1.366328089 | 0.000163207 |
| WNT8B | 17.04369323 | 44.01279005 | 1.365098169 | 0.006626952 |
| ACBD7 | 30.03143927 | 77.24370068 | 1.354519131 | 0.001029508 |
| CDC14A | 482.7671778 | 1230.413822 | 1.349974419 | 3.83E-18 |
| LRRC8C | 159.3292295 | 404.9787028 | 1.347976734 | $1.79 \mathrm{E}-09$ |
| MYLPF | 16.52474032 | 41.86667299 | 1.346607543 | 0.007568888 |
| BTNL9 | 137.565602 | 349.1266827 | 1.343174481 | $3.33 \mathrm{E}-10$ |
| SLC51B | 27.31217271 | 68.76244391 | 1.336935581 | 0.001617407 |
| SAMHD1 | 632.8583194 | 1596.63732 | 1.335352533 | 3.16E-11 |
| RARRES2 | 297.2527822 | 748.4086601 | 1.332821137 | $2.24 \mathrm{E}-13$ |
| TUBB2B | 20.86784163 | 52.52571448 | 1.329975397 | 0.003931575 |
| WDFY4 | 66.3409148 | 166.7559146 | 1.32804275 | $6.90 \mathrm{E}-07$ |
| E2F2 | 370.355056 | 925.0101948 | 1.321495395 | $1.65 \mathrm{E}-14$ |
| ZNF491 | 19.13500317 | 47.46104554 | 1.316874492 | 0.005448941 |
| ZNF559 | 23.17322416 | 57.77213287 | 1.313429031 | 0.007457759 |
| DZIP1L | 140.2850402 | 348.6186492 | 1.313264107 | 2.93E-08 |
| GLIPR2 | 37.50175726 | 92.38839831 | 1.312227773 | 0.000292926 |


| NANOS1 | 220.106239 | 545.8199015 | 1.312072181 | $9.64 \mathrm{E}-12$ |
| :---: | :---: | :---: | :---: | :---: |
| EEF1A2 | 218.4332415 | 542.193347 | 1.311685216 | 5.12E-07 |
| CLSPN | 1551.785259 | 3850.932325 | 1.31140341 | 0.001439321 |
| CCDC151 | 15.9840692 | 39.70167411 | 1.310112008 | 0.012379544 |
| IKBIP | 227.9098513 | 564.0945611 | 1.307480679 | $1.39 \mathrm{E}-07$ |
| ANKRD2 | 44.22497241 | 109.6654545 | 1.301091499 | 8.62E-05 |
| ADAMTSL2 | 17.19601899 | 42.40800682 | 1.291113356 | 0.024814033 |
| CCDC15 | 124.4569967 | 304.5232367 | 1.290026196 | $1.67 \mathrm{E}-10$ |
| OAS2 | 25.95588122 | 63.02018394 | 1.287992929 | 0.004743197 |
| ZNF540 | 17.89728593 | 43.49178778 | 1.287339404 | 0.007752867 |
| TMEM240 | 27.54215012 | 66.67077508 | 1.285816441 | 0.002036535 |
| HDAC9 | 32.87708644 | 80.25056565 | 1.28157314 | 0.001010591 |
| SLC35G6 | 41.56528202 | 100.8794274 | 1.279358671 | 0.000695783 |
| SHOX2 | 37.05207156 | 89.94669215 | 1.27881977 | 0.000120206 |
| KRT71 | 12.48464076 | 30.14466197 | 1.278637439 | 0.038090051 |
| TPM2 | 73.14906707 | 177.9311293 | 1.277645623 | $4.84 \mathrm{E}-06$ |
| PPARA | 632.2246542 | 1531.882706 | 1.276753377 | $1.36 \mathrm{E}-24$ |
| DDIAS | 574.518766 | 1383.758162 | 1.268382214 | 5.73E-09 |
| FRMPD3 | 18.54296873 | 44.47265421 | 1.266679041 | 0.018813592 |
| ZNF695 | 85.50749882 | 205.6341963 | 1.264485258 | 2.09E-08 |
| RYR3 | 63.35479746 | 151.5200467 | 1.261791111 | 0.000170731 |
| GPR179 | 14.89292151 | 35.55431386 | 1.258824917 | 0.020775519 |
| PIGW | 541.0232302 | 1289.368733 | 1.253573831 | 1.23E-10 |
| SLC12A4 | 680.2427723 | 1620.198759 | 1.252744811 | 5.88E-24 |
| MATN2 | 188.5510694 | 450.385435 | 1.251919916 | 8.43E-09 |
| FAM111B | 1602.119935 | 3811.122313 | 1.250319516 | 0.002679659 |
| RASGRF1 | 27.85854284 | 66.62940682 | 1.248055305 | 0.008583637 |
| ARHGDIB | 60.21286204 | 143.8183623 | 1.246472271 | 0.000959727 |
| DENND2C | 101.9080231 | 240.3254696 | 1.244353371 | 3.83E-06 |
| AC093512.2 | 39.97537038 | 93.95772633 | 1.242187438 | 0.000582571 |
| TUBB2A | 141.5665432 | 334.5298259 | 1.241436014 | 1.13E-06 |
| DCLK2 | 103.4982268 | 243.8292414 | 1.238097246 | 5.12E-07 |
| PMEPA1 | 253.644943 | 597.8770973 | 1.236636511 | 6.44E-06 |
| TAS1R3 | 58.02269701 | 136.760884 | 1.233374712 | $2.46 \mathrm{E}-05$ |
| RGS9 | 93.34615093 | 218.6154588 | 1.233155386 | $1.76 \mathrm{E}-07$ |
| CYTIP | 14.24131091 | 33.52040375 | 1.233066865 | 0.030238544 |
| FRMPD2 | 14.90284134 | 34.83272265 | 1.232489879 | 0.026176393 |
| ZNF620 | 334.3563314 | 785.2674107 | 1.232195565 | $3.37 \mathrm{E}-15$ |
| IRF8 | 76.36539061 | 179.415383 | 1.229505463 | $1.56 \mathrm{E}-06$ |
| ITPKA | 141.9931196 | 332.97124 | 1.229412697 | $1.20 \mathrm{E}-09$ |
| KITLG | 1411.770007 | 3304.364903 | 1.22683276 | $1.60 \mathrm{E}-14$ |
| TMEM38A | 55.05390548 | 128.6320446 | 1.223305427 | 0.000177901 |
| GNB3 | 19.41628669 | 45.56788248 | 1.221718308 | 0.02916432 |
| ARAP3 | 176.9032676 | 411.2191551 | 1.221574733 | 9.18E-10 |
| ESR2 | 20.45207904 | 47.73503623 | 1.219300456 | 0.032599992 |
| CXCR6 | 217.6778387 | 508.0128374 | 1.219204866 | 8.19E-12 |
| FOXD1 | 449.0938708 | 1044.446333 | 1.218626378 | 1.94E-18 |
| C18orf54 | 423.324007 | 983.9286836 | 1.21827735 | $7.00 \mathrm{E}-08$ |
| SPTBN5 | 276.9871808 | 643.4660486 | 1.217560777 | $1.50 \mathrm{E}-12$ |
| CRIP2 | 18.80224194 | 43.45384124 | 1.213970869 | 0.014034223 |
| DBN1 | 36.71925313 | 85.25967307 | 1.21291947 | 0.00074486 |
| FBXO5 | 1010.814858 | 2340.369369 | 1.211107674 | $2.60 \mathrm{E}-12$ |
| DYRK3 | 21.40076359 | 49.54434949 | 1.208605891 | 0.017806858 |
| ENPEP | 125.7059342 | 291.0652425 | 1.207847131 | $9.50 \mathrm{E}-09$ |
| DLK2 | 59.64471039 | 137.5758003 | 1.20539901 | 8.52E-05 |
| GFI1 | 46.19605833 | 105.7616152 | 1.203163625 | 0.000654213 |
| CD101 | 28.62748441 | 65.44899304 | 1.202172305 | 0.005440602 |
| MFSD2A | 250.2520018 | 574.290542 | 1.201277827 | 4.13E-07 |
| SPTB | 1269.314765 | 2918.530204 | 1.201031173 | $2.61 \mathrm{E}-24$ |
| CARD9 | 167.2344001 | 384.153742 | 1.19986916 | 6.76E-10 |
| REN | 17.07926611 | 39.246048 | 1.191848915 | 0.030482606 |


| COPZ2 | 44.62893661 | 102.4489807 | 1.190140017 | 0.000633365 |
| :---: | :---: | :---: | :---: | :---: |
| KRTAP2-3 | 30.60956185 | 69.95070037 | 1.18984798 | 0.001778992 |
| NOTUM | 64.09664381 | 146.9261699 | 1.189227493 | 4.13E-05 |
| STXBP5L | 29.59777279 | 67.48011485 | 1.18756576 | 0.002930181 |
| CDKL2 | 27.30624491 | 62.18731615 | 1.185507765 | 0.002654467 |
| CAVIN1 | 2067.449859 | 4677.257517 | 1.178264239 | 6.57E-17 |
| LSMEM2 | 17.49332173 | 39.31874463 | 1.176658647 | 0.034846083 |
| CLDN18 | 20.96709711 | 47.07469434 | 1.17182607 | 0.041711985 |
| TCF19 | 940.9514538 | 2117.082201 | 1.17031645 | 1.72E-09 |
| E2F8 | 732.0153023 | 1647.710292 | 1.169964658 | $1.41 \mathrm{E}-11$ |
| FOXL2NB | 17.61001741 | 39.71951434 | 1.169479088 | 0.020387717 |
| WDR53 | 252.7720077 | 566.7138798 | 1.165000943 | 7.47E-12 |
| SPATA33 | 181.9836724 | 407.1155698 | 1.16490102 | $2.58 \mathrm{E}-07$ |
| NCAPH2 | 1313.780376 | 2944.440947 | 1.164593783 | $9.16 \mathrm{E}-15$ |
| RAD9B | 38.68389037 | 86.70831804 | 1.162096938 | 0.000417464 |
| SLC35E4 | 105.5078359 | 235.6740141 | 1.161441144 | $6.27 \mathrm{E}-06$ |
| KLHL4 | 420.3059172 | 940.1202829 | 1.159790677 | $1.50 \mathrm{E}-13$ |
| ZNF462 | 134.2444956 | 299.2486836 | 1.158606294 | $1.74 \mathrm{E}-07$ |
| HEG1 | 570.3116696 | 1269.675754 | 1.154321797 | 9.82E-18 |
| TP73 | 422.4984396 | 939.160819 | 1.153974074 | 4.47E-13 |
| RTKN2 | 857.0107123 | 1904.951219 | 1.152319786 | $1.69 \mathrm{E}-09$ |
| CENPO | 782.7153077 | 1737.743592 | 1.151250113 | 2.91E-09 |
| AC131097.2 | 19.19640071 | 42.26041636 | 1.14807555 | 0.037131475 |
| SYNJ1 | 583.101796 | 1291.325232 | 1.14737447 | $2.16 \mathrm{E}-15$ |
| CBR3 | 17.51891759 | 38.8459117 | 1.146935111 | 0.032049789 |
| C9orf43 | 20.90746374 | 46.57658668 | 1.146114734 | 0.016002107 |
| FHDC1 | 532.4936313 | 1174.929163 | 1.143169202 | 3.68E-09 |
| SLC35D3 | 20.34695296 | 45.28076948 | 1.141612216 | 0.023209018 |
| AC020915.1 | 38.37689659 | 84.07449903 | 1.135401895 | 0.0011619 |
| CCP110 | 727.8480875 | 1595.519883 | 1.132426735 | 9.37E-10 |
| ULBP2 | 162.3503989 | 356.2182778 | 1.132358442 | 1.51E-09 |
| ZNF584 | 200.761333 | 437.3196655 | 1.125764955 | $2.04 \mathrm{E}-11$ |
| IL11 | 29.35206215 | 63.78633987 | 1.125072073 | 0.004450211 |
| EXO1 | 1212.051205 | 2642.715556 | 1.124683424 | 0.005113326 |
| ERFE | 69.47576625 | 151.1558161 | 1.124659037 | $1.46 \mathrm{E}-05$ |
| FAM189A2 | 77.62711114 | 169.2063487 | 1.121463196 | $9.44 \mathrm{E}-05$ |
| TSACC | 21.2560726 | 46.13066117 | 1.120607631 | 0.015804225 |
| CENPL | 577.8254063 | 1256.30197 | 1.120100865 | $1.98 \mathrm{E}-15$ |
| TLE2 | 58.01847618 | 126.3348465 | 1.119776562 | 0.004225832 |
| UNC79 | 16.36238034 | 35.68662713 | 1.119201641 | 0.038462567 |
| MID1 | 572.5135221 | 1243.280158 | 1.118785096 | $9.41 \mathrm{E}-10$ |
| TMCC2 | 52.8778872 | 114.635913 | 1.118680746 | 0.000527994 |
| CCDC142 | 383.4317823 | 830.9238609 | 1.117315457 | 8.85E-13 |
| S100A5 | 38.87418847 | 84.00604045 | 1.11696118 | 0.005336755 |
| RAB9B | 57.56543373 | 124.9588558 | 1.115704365 | 0.000167688 |
| HELLS | 2247.850903 | 4869.472297 | 1.115457996 | $2.00 \mathrm{E}-09$ |
| TMOD2 | 130.2586524 | 282.6435995 | 1.114541904 | 5.41E-06 |
| TCF7L1 | 54.50571398 | 117.815895 | 1.114245186 | 0.000107412 |
| RAB30 | 662.3784582 | 1430.936153 | 1.111779409 | 7.18E-20 |
| CIP2A | 1457.075254 | 3147.123117 | 1.111206452 | 5.82E-08 |
| CENPU | 1468.825252 | 3172.53312 | 1.111098421 | 1.49E-16 |
| UTP4 | 2356.55574 | 5073.391803 | 1.106514365 | $7.76 \mathrm{E}-13$ |
| ZNF180 | 341.5327034 | 735.1401762 | 1.105142518 | 1.09E-14 |
| AIF1L | 520.248659 | 1118.03416 | 1.104784891 | $1.18 \mathrm{E}-07$ |
| MITF | 687.6147805 | 1478.820791 | 1.104030501 | $2.80 \mathrm{E}-12$ |
| SCNM1 | 414.4305957 | 891.3514801 | 1.103488618 | 4.89E-15 |
| NOCT | 205.4098355 | 440.3069012 | 1.103226822 | 1.72E-09 |
| ELFN2 | 34.16046799 | 73.2091808 | 1.100528172 | 0.003507821 |
| PLCE1 | 547.1811145 | 1173.809609 | 1.099601529 | $2.58 \mathrm{E}-11$ |
| CSRP2 | 295.6670913 | 632.335624 | 1.097904209 | $2.58 \mathrm{E}-08$ |
| TAS2R5 | 40.7297076 | 87.13216528 | 1.095886428 | 0.001439321 |


| NR2F1 | 322.2682788 | 689.1071895 | 1.09537268 | 4.08E-12 |
| :---: | :---: | :---: | :---: | :---: |
| CHRM5 | 30.39002515 | 64.81916319 | 1.092155916 | 0.012190786 |
| CHRNB1 | 592.3873607 | 1262.779754 | 1.090940896 | $1.32 \mathrm{E}-10$ |
| CCND3 | 795.9934714 | 1694.228796 | 1.090477628 | $7.35 \mathrm{E}-07$ |
| 06-Sep | 347.1249833 | 740.4577303 | 1.090221994 | 6.62E-09 |
| AK1 | 47.64978393 | 100.8527452 | 1.088893772 | 0.003607441 |
| CPA5 | 26.35756036 | 56.23941286 | 1.08836314 | 0.015415243 |
| CNTNAP3 | 22.12357716 | 46.8643331 | 1.086067523 | 0.025632262 |
| MCM8 | 1796.304276 | 3811.597985 | 1.085605399 | $2.43 \mathrm{E}-10$ |
| CEP19 | 70.77523032 | 149.4813075 | 1.082149384 | 5.72E-05 |
| STX11 | 68.52908077 | 145.2590957 | 1.081218271 | 0.000132229 |
| IGFBP3 | 36.68778667 | 77.56876022 | 1.079307269 | 0.003961959 |
| ADCY9 | 171.8285617 | 362.4971113 | 1.07735193 | 9.57E-09 |
| MRPL53 | 74.77160134 | 157.2908891 | 1.075564697 | $1.50 \mathrm{E}-05$ |
| SLC25A19 | 226.7759535 | 476.9580071 | 1.074828865 | 3.83E-05 |
| CSRNP1 | 370.7976006 | 780.7647493 | 1.074145546 | $1.01 \mathrm{E}-13$ |
| TMEM255B | 47.77422877 | 100.3040881 | 1.074130529 | 0.002776961 |
| B2M | 1628.964839 | 3428.595046 | 1.073695964 | 8.36E-19 |
| TXNDC16 | 520.5807638 | 1095.897967 | 1.073569732 | 1.13E-11 |
| DIRAS2 | 44.51634735 | 93.88219908 | 1.072844589 | 0.001095752 |
| LRRN1 | 140.616874 | 295.9081 | 1.070770026 | $1.08 \mathrm{E}-06$ |
| FADS1 | 172.6327902 | 362.774749 | 1.070490782 | $4.56 \mathrm{E}-09$ |
| PXMP2 | 128.8280361 | 270.1819742 | 1.06971578 | $2.30 \mathrm{E}-05$ |
| XRCC2 | 1077.593467 | 2260.623249 | 1.069346394 | $1.62 \mathrm{E}-07$ |
| TMPRSS9 | 119.8539236 | 251.1719326 | 1.067015464 | $1.01 \mathrm{E}-05$ |
| GJA3 | 203.4495967 | 425.551343 | 1.066545065 | 1.52E-06 |
| MFHAS1 | 2697.639395 | 5647.721506 | 1.065779913 | $3.04 \mathrm{E}-25$ |
| CCNE2 | 379.5461792 | 793.6920672 | 1.065755585 | 2.22E-12 |
| DENND5B | 83.22418381 | 174.0156146 | 1.065219998 | $1.95 \mathrm{E}-05$ |
| TMPRSS6 | 39.36121122 | 82.03419601 | 1.065150656 | 0.005336755 |
| ZNF718 | 206.348543 | 431.2910242 | 1.063602958 | $1.57 \mathrm{E}-07$ |
| PKMYT1 | 1569.596539 | 3278.163 | 1.06287064 | 4.01E-08 |
| TRABD2A | 107.4198093 | 223.6209193 | 1.061436216 | 0.000158899 |
| MOB3B | 277.4257606 | 577.7401626 | 1.060325974 | 1.03E-05 |
| ENO2 | 399.511804 | 831.5520259 | 1.058037106 | 1.23E-05 |
| CPNE7 | 31.79015958 | 65.94152412 | 1.057967575 | 0.014178359 |
| SKIDA1 | 50.21039044 | 104.3857357 | 1.055903796 | 0.004957649 |
| OGDHL | 51.45996328 | 106.3860514 | 1.055557 | 0.001374234 |
| CMTM1 | 39.86049607 | 82.3178873 | 1.055344677 | 0.013554949 |
| ANKDD1B | 36.12328386 | 75.14128967 | 1.055124316 | 0.006670907 |
| SECTM1 | 160.1819581 | 332.4528008 | 1.052024419 | $1.27 \mathrm{E}-07$ |
| SAC3D1 | 319.1277556 | 660.7719548 | 1.051550772 | 7.53E-07 |
| PTAFR | 21.23441157 | 43.96060791 | 1.051121014 | 0.041289357 |
| CHRNA1 | 123.9064057 | 256.1806052 | 1.049549689 | $9.81 \mathrm{E}-06$ |
| TIMM8A | 273.9717104 | 565.6294654 | 1.047894622 | 1.89E-06 |
| POPDC2 | 41.80324349 | 86.63580433 | 1.047838476 | 0.003803614 |
| SCNN1D | 101.7742664 | 210.3087688 | 1.045864464 | 3.32E-05 |
| KRT10 | 368.397033 | 758.8291718 | 1.045053625 | 2.59E-08 |
| AC011043.1 | 196.5845265 | 405.3286289 | 1.043736971 | 7.61E-10 |
| AFAP1L2 | 107.0143458 | 221.1168505 | 1.041785285 | 0.000360299 |
| CAMK1 | 144.1427052 | 296.3070118 | 1.04098186 | 1.19E-06 |
| TUFT1 | 875.5552008 | 1801.741581 | 1.040747698 | 2.31E-15 |
| MCM10 | 1186.321475 | 2439.978694 | 1.040539557 | 0.009499875 |
| ATAD5 | 775.5055573 | 1594.100871 | 1.040210432 | $2.89 \mathrm{E}-10$ |
| PLCD4 | 112.3329348 | 230.2760641 | 1.039857836 | $1.51 \mathrm{E}-05$ |
| HHIP | 23.11552657 | 47.57592675 | 1.036913635 | 0.048941507 |
| SNPH | 21.89770618 | 44.88423781 | 1.03683145 | 0.035398971 |
| ICAM2 | 20.5291526 | 42.35519126 | 1.036699487 | 0.04183557 |
| LMF2 | 1742.772718 | 3572.950393 | 1.036084721 | 3.50E-16 |
| CDH24 | 1175.865243 | 2409.872761 | 1.035850011 | $1.35 \mathrm{E}-11$ |
| P2RY2 | 72.1728509 | 148.5031153 | 1.035242216 | 0.000136246 |


| CDIP1 | 44.8194635 | 91.43246733 | 1.033328732 | 0.002651022 |
| :---: | :---: | :---: | :---: | :---: |
| ACSS1 | 82.09341401 | 167.1710311 | 1.0312598 | 0.000212414 |
| PLIN4 | 54.14313606 | 110.8096684 | 1.028373017 | 0.000817096 |
| APC2 | 88.53306057 | 180.9047628 | 1.028125842 | 0.000155703 |
| NAGS | 28.85107033 | 58.49673762 | 1.026935264 | 0.024255362 |
| ZNF850 | 183.8055605 | 373.8199881 | 1.025656081 | 6.87E-06 |
| F3 | 2209.566192 | 4495.874606 | 1.024614359 | $1.20 \mathrm{E}-12$ |
| BRIP1 | 841.9794219 | 1711.755997 | 1.024322576 | $3.68 \mathrm{E}-09$ |
| AC240274.1 | 697.8359214 | 1419.077085 | 1.024212698 | $3.41 \mathrm{E}-11$ |
| FIGNL1 | 715.6248634 | 1455.342427 | 1.023849139 | $2.20 \mathrm{E}-11$ |
| ZNF420 | 195.0890714 | 396.9864837 | 1.022376737 | 8.09E-08 |
| PCLAF | 584.3914308 | 1186.050936 | 1.022220704 | $1.03 \mathrm{E}-06$ |
| MAB21L4 | 1381.086707 | 2803.004108 | 1.020887333 | 1.49E-13 |
| BLOC1S1-RDH5 | 39.08039139 | 78.67443654 | 1.020313492 | 0.021480345 |
| LIPC | 27.35766542 | 55.50410825 | 1.019374833 | 0.018820716 |
| RAD51AP1 | 979.0239759 | 1984.094939 | 1.019111659 | $6.72 \mathrm{E}-07$ |
| ESCO2 | 825.6946993 | 1672.258394 | 1.018486131 | $4.71 \mathrm{E}-07$ |
| NLRC5 | 215.4137219 | 435.4373852 | 1.013409243 | 3.67E-08 |
| ACP7 | 65.78986015 | 133.0227695 | 1.011899794 | 0.001342804 |
| OVOL2 | 379.1352515 | 764.6559387 | 1.010774533 | $1.20 \mathrm{E}-12$ |
| NXF1 | 1844.480758 | 3708.093649 | 1.007492266 | $9.94 \mathrm{E}-12$ |
| PACSIN3 | 190.9643207 | 383.2723813 | 1.005879676 | 3.52E-06 |
| ACP4 | 33.24382798 | 66.33043835 | 1.002922256 | 0.012073234 |
| CRY1 | 625.5284771 | 1251.742663 | 1.002421305 | $6.27 \mathrm{E}-13$ |
| HCFC2 | 235.4978162 | 471.9121776 | 1.002201493 | $2.36 \mathrm{E}-10$ |
| TUBB6 | 1955.29615 | 3910.337683 | 1.000101189 | $1.56 \mathrm{E}-07$ |
| FAM122C | 147.9562985 | 295.5887311 | 0.997660354 | 2.27E-07 |
| UPF3B | 1000.383771 | 1996.448214 | 0.997206449 | 7.20E-12 |
| ITGA10 | 109.3184789 | 218.0566506 | 0.996851401 | $6.41 \mathrm{E}-06$ |
| RAB36 | 89.46419053 | 178.3227177 | 0.994002647 | $1.98 \mathrm{E}-05$ |
| EEPD1 | 169.4013687 | 336.7700127 | 0.993113432 | 1.71E-06 |
| MYH15 | 135.6640121 | 269.8988051 | 0.992277344 | $6.60 \mathrm{E}-05$ |
| DOK3 | 353.4571467 | 702.2869843 | 0.991871161 | $8.46 \mathrm{E}-06$ |
| DLC1 | 192.5508756 | 381.6867345 | 0.989638315 | 6.32E-07 |
| STRIP2 | 336.0802346 | 666.1461119 | 0.987927817 | 1.29E-06 |
| AGFG2 | 227.5645359 | 450.9649434 | 0.986587466 | $2.11 \mathrm{E}-08$ |
| SPAG1 | 664.8419227 | 1317.089738 | 0.986427136 | $2.64 \mathrm{E}-13$ |
| ARHGAP24 | 33.66523237 | 67.1395952 | 0.986120529 | 0.02412871 |
| UBA7 | 29.5620855 | 58.77990671 | 0.985803813 | 0.03594426 |
| LIMK2 | 817.1805205 | 1618.408171 | 0.985787473 | 1.08E-09 |
| ZNF433 | 36.57285516 | 72.04248041 | 0.985527272 | 0.008833062 |
| KCNC4 | 132.5292117 | 261.2352766 | 0.982782842 | $2.41 \mathrm{E}-06$ |
| STON2 | 159.3063551 | 314.8656947 | 0.980874953 | $9.29 \mathrm{E}-08$ |
| AEN | 996.6992986 | 1966.284468 | 0.980464526 | 0.015858008 |
| POLD3 | 1149.415518 | 2266.254004 | 0.979505818 | $4.94 \mathrm{E}-09$ |
| DTL | 1284.180923 | 2529.018141 | 0.978198998 | 9.03E-08 |
| TNFRSF11A | 65.9486346 | 129.6032105 | 0.975415066 | 0.000731885 |
| CCNE1 | 527.478038 | 1034.678878 | 0.973501948 | 1.98E-09 |
| C12orf4 | 646.5697097 | 1268.587788 | 0.972319086 | 1.02E-09 |
| AKAP5 | 82.47166795 | 161.7123513 | 0.972203151 | 0.000256509 |
| KSR1 | 162.9897474 | 320.2217147 | 0.971010729 | $3.30 \mathrm{E}-07$ |
| MFSD6L | 42.852484 | 84.23650801 | 0.970940166 | 0.008276517 |
| CCDC18 | 716.0357399 | 1402.765265 | 0.969937186 | $1.97 \mathrm{E}-08$ |
| UBXN11 | 376.2820268 | 737.203782 | 0.969583467 | $6.91 \mathrm{E}-10$ |
| LRFN1 | 43.45490196 | 84.97337641 | 0.968300538 | 0.005321492 |
| TNNT1 | 96.34360297 | 188.3298246 | 0.967083095 | 0.006240577 |
| GPR161 | 384.3831883 | 749.7803015 | 0.964680757 | $6.77 \mathrm{E}-10$ |
| TNIK | 674.2375901 | 1317.236205 | 0.964509366 | 3.04E-10 |
| CGAS | 41.9988341 | 82.3293346 | 0.963315009 | 0.024860138 |
| DYRK1B | 123.9481924 | 241.4136981 | 0.962373066 | 0.000148251 |
| ZNF107 | 768.7864547 | 1497.537078 | 0.962166669 | 4.91E-07 |


| ZDHHC14 | 346.6788982 | 674.304464 | 0.961055916 | 7.26E-09 |
| :---: | :---: | :---: | :---: | :---: |
| CLCN2 | 515.0592171 | 1001.04935 | 0.96003642 | $1.56 \mathrm{E}-11$ |
| LGR5 | 1210.250758 | 2353.510341 | 0.959618577 | 0.043632828 |
| GDPD5 | 681.8733205 | 1325.919846 | 0.95885925 | $1.62 \mathrm{E}-11$ |
| DCLRE1B | 532.3938611 | 1033.716819 | 0.958201141 | $1.66 \mathrm{E}-07$ |
| ZNF780B | 283.2578471 | 550.6581129 | 0.956362345 | 3.54E-09 |
| RUBCNL | 82.26535063 | 159.8691466 | 0.955243535 | 0.000577237 |
| DONSON | 1120.654213 | 2170.116174 | 0.95375108 | $1.57 \mathrm{E}-11$ |
| MYBL2 | 2050.646952 | 3971.189934 | 0.953638336 | 3.56E-07 |
| GP1BA | 123.905942 | 240.4448407 | 0.953507454 | $8.09 \mathrm{E}-06$ |
| ARL13B | 615.0841445 | 1190.655402 | 0.952982385 | $1.09 \mathrm{E}-09$ |
| DIAPH3 | 1571.929001 | 3040.770625 | 0.951622793 | $2.39 \mathrm{E}-07$ |
| SCML1 | 513.8749467 | 992.3881059 | 0.95145106 | 4.52E-07 |
| BARX2 | 178.162131 | 344.7517121 | 0.950173327 | 3.32E-06 |
| HECTD2 | 97.59980219 | 188.8326473 | 0.949983702 | 4.75E-05 |
| GAMT | 163.2558758 | 314.6935504 | 0.949260205 | 0.000157649 |
| LAMB2 | 6297.044907 | 12156.39953 | 0.948875543 | $2.20 \mathrm{E}-11$ |
| BRICD5 | 383.8104428 | 739.5899295 | 0.948198479 | $1.36 \mathrm{E}-08$ |
| TYRO3 | 803.0276962 | 1548.32969 | 0.947892841 | $2.54 \mathrm{E}-08$ |
| WDR76 | 911.6550629 | 1757.885497 | 0.947724127 | 2.72E-08 |
| FAM71E1 | 71.60036402 | 138.3506152 | 0.947662435 | 0.004422798 |
| TSNAXIP1 | 22.33142986 | 43.14784643 | 0.946620923 | 0.049969428 |
| CCDC74A | 57.6248955 | 111.1937535 | 0.945584783 | 0.004299021 |
| CENPK | 1027.613991 | 1974.454841 | 0.942231338 | 4.57E-08 |
| CXCL16 | 530.0735609 | 1017.783139 | 0.939758997 | 8.62E-10 |
| CGRRF1 | 194.9939795 | 373.8854038 | 0.938231809 | $3.48 \mathrm{E}-07$ |
| SOX15 | 48.26929279 | 92.58760638 | 0.93814102 | 0.0089672 |
| TMA7 | 300.2087608 | 573.8073751 | 0.936414843 | 5.57E-05 |
| CLDN9 | 94.90031809 | 181.1549708 | 0.932741263 | 0.000227804 |
| ORC6 | 1115.100454 | 2127.467813 | 0.932679185 | $9.39 \mathrm{E}-07$ |
| PLEKHB1 | 249.2573968 | 476.1248423 | 0.932456429 | 1.12E-07 |
| PSMB9 | 95.11661854 | 181.2936053 | 0.931131732 | 0.001904922 |
| NEIL3 | 449.1907724 | 856.3914748 | 0.930532819 | 4.87E-05 |
| NUP210L | 89.55598283 | 170.4946202 | 0.930259683 | 0.003721975 |
| UHRF1 | 2892.923787 | 5506.866077 | 0.928896075 | $2.08 \mathrm{E}-07$ |
| C19orf47 | 545.7677246 | 1037.750411 | 0.92810138 | $1.19 \mathrm{E}-07$ |
| RELL2 | 137.987464 | 261.5964248 | 0.926822753 | $1.45 \mathrm{E}-05$ |
| ZWINT | 2738.169615 | 5197.552655 | 0.924723593 | 6.18E-06 |
| MTCL1 | 580.8506971 | 1101.180093 | 0.924123352 | 9.18E-09 |
| TOP3A | 1410.617507 | 2675.258568 | 0.923601959 | 1.13E-10 |
| LRRC8E | 27.13003027 | 51.28352917 | 0.923559874 | 0.049457105 |
| RUSC2 | 97.22559748 | 184.5107892 | 0.922486657 | 4.87E-05 |
| LAMP3 | 127.1458624 | 240.5929533 | 0.921462314 | 2.72E-05 |
| UPK3B | 86.39831418 | 164.103325 | 0.92102914 | 0.002638499 |
| MPP2 | 147.2617723 | 278.4352575 | 0.920269917 | 0.000482975 |
| KCNJ14 | 114.057732 | 215.2166661 | 0.919886791 | 0.000491143 |
| TRIM36 | 291.2222718 | 550.0130905 | 0.919519356 | $2.38 \mathrm{E}-08$ |
| CCDC150 | 463.2053361 | 875.5413359 | 0.919054214 | 3.11E-09 |
| CD8A | 78.78769762 | 148.8508865 | 0.918300544 | 0.000348295 |
| RCBTB2 | 231.5984728 | 437.3603552 | 0.916290683 | $1.14 \mathrm{E}-07$ |
| CCDC138 | 605.638306 | 1142.329148 | 0.916070636 | 1.85E-08 |
| POLA1 | 1411.697571 | 2660.624803 | 0.914369402 | 0.022019711 |
| ERP27 | 45.5004332 | 86.22165768 | 0.913666724 | 0.038209288 |
| ZNF10 | 345.724951 | 651.1160042 | 0.913106573 | 1.43E-09 |
| KIRREL1 | 552.0587515 | 1039.003071 | 0.912295517 | $1.10 \mathrm{E}-08$ |
| CCDC74B | 33.81003776 | 63.77994695 | 0.912226377 | 0.025970701 |
| KIFC2 | 2762.876343 | 5196.18692 | 0.911330033 | $1.90 \mathrm{E}-19$ |
| USP11 | 1687.066404 | 3172.683597 | 0.910896193 | 4.27E-16 |
| GPC4 | 203.177369 | 381.7652753 | 0.91059617 | 3.28E-05 |
| MAP7D1 | 1297.553076 | 2432.265777 | 0.907369965 | $1.39 \mathrm{E}-10$ |
| SLC23A3 | 34.14866959 | 64.28310899 | 0.906822739 | 0.027007799 |


| KLHL23 | 740.9255301 | 1387.613146 | 0.906515548 | 2.02E-10 |
| :---: | :---: | :---: | :---: | :---: |
| ZNF552 | 253.6625881 | 474.9051011 | 0.905275101 | $4.86 \mathrm{E}-09$ |
| GDF11 | 403.1186592 | 754.5364843 | 0.904902079 | 7.33E-05 |
| FAM161B | 79.70251626 | 149.4670719 | 0.903376843 | 0.000555687 |
| LAMB1 | 5427.394756 | 10151.32141 | 0.903188253 | $2.18 \mathrm{E}-13$ |
| WDR62 | 1224.966092 | 2289.902673 | 0.902677313 | 0.031103856 |
| CITED2 | 2749.251337 | 5140.489982 | 0.902606643 | 1.03E-12 |
| HIST1H2AC | 101.0710004 | 188.9712395 | 0.901835616 | 0.00853218 |
| FANCI | 4102.282616 | 7660.304338 | 0.9010162 | 7.17E-09 |
| CATSPERG | 46.44711868 | 86.56013649 | 0.900974253 | 0.009669509 |
| P2RX5 | 93.42374538 | 173.9677422 | 0.899186093 | 0.001106238 |
| ZNF26 | 555.3103796 | 1035.19367 | 0.898277165 | $1.23 \mathrm{E}-11$ |
| RAB15 | 497.5450834 | 927.6135706 | 0.898217978 | 4.89E-09 |
| HAS3 | 122.522983 | 227.6262657 | 0.897945346 | 0.004862299 |
| GPR143 | 33.47152033 | 62.08295186 | 0.897694402 | 0.032599992 |
| CX3CL1 | 81.84987403 | 151.8815765 | 0.897392598 | 0.004510763 |
| GPR3 | 143.3095874 | 265.7348291 | 0.895416358 | 0.001750428 |
| RAD51C | 1028.347651 | 1911.980001 | 0.894838344 | 4.28E-06 |
| JUN | 1104.433113 | 2053.416898 | 0.894512225 | 0.000120344 |
| SPHK1 | 41.31410727 | 76.36288878 | 0.894014923 | 0.01732921 |
| YAE1 | 231.7372931 | 430.7355394 | 0.893803031 | $1.50 \mathrm{E}-07$ |
| ATAD2 | 5456.203878 | 10134.51516 | 0.893359476 | $9.45 \mathrm{E}-07$ |
| CD83 | 106.2332266 | 197.2651465 | 0.893210312 | 0.003041436 |
| SIX4 | 204.7871775 | 380.210774 | 0.892935697 | $1.08 \mathrm{E}-06$ |
| TNFAIP3 | 122.9908946 | 228.9334161 | 0.890899703 | 0.000130095 |
| GPR75 | 176.0654653 | 326.0166339 | 0.889715071 | 2.32E-05 |
| GIPR | 161.8895439 | 298.7282063 | 0.887878643 | 7.09E-05 |
| RP9 | 195.3511444 | 360.6179586 | 0.886782478 | $1.77 \mathrm{E}-05$ |
| IQCC | 145.4021407 | 268.1818443 | 0.885985051 | $1.41 \mathrm{E}-05$ |
| SURF2 | 358.6046779 | 662.2600678 | 0.885402236 | $1.74 \mathrm{E}-08$ |
| ISG15 | 1075.296306 | 1983.739733 | 0.883852711 | 1.27E-08 |
| CALCA | 46.48850497 | 86.17709297 | 0.883297752 | 0.027129665 |
| ZNF503 | 559.7103928 | 1030.991043 | 0.882425165 | $3.32 \mathrm{E}-10$ |
| MTSS1L | 427.9469796 | 789.2000576 | 0.882207047 | $1.16 \mathrm{E}-08$ |
| COTL1 | 1579.145227 | 2905.536184 | 0.87960875 | $1.30 \mathrm{E}-07$ |
| PSMC3IP | 320.0944585 | 588.2017455 | 0.879037408 | 0.000150244 |
| ZNF324 | 508.0479899 | 933.7329876 | 0.87790286 | 4.47E-11 |
| ADAMTS16 | 62.99968272 | 116.0077345 | 0.87768708 | 0.003819129 |
| MAGI3 | 1423.960124 | 2616.120034 | 0.877243937 | 6.76E-10 |
| RFC2 | 1024.58596 | 1880.842362 | 0.87681494 | 5.91E-08 |
| MYL6B | 877.6290345 | 1608.634222 | 0.875304745 | $9.66 \mathrm{E}-11$ |
| ZWILCH | 1426.367864 | 2614.901627 | 0.874571893 | 0.000103385 |
| ITGA1 | 99.01026293 | 181.2873981 | 0.874270498 | 0.000580855 |
| SDR16C5 | 111.9281065 | 205.3399881 | 0.873909849 | 0.000241237 |
| KIF26A | 173.7980612 | 318.3399273 | 0.873762692 | 0.000152011 |
| AMH | 735.3987725 | 1347.256675 | 0.873274909 | 3.32E-07 |
| AC004233.2 | 68.03366746 | 124.6342045 | 0.872120524 | 0.006394133 |
| FOXM1 | 3087.969314 | 5649.507749 | 0.871456211 | 5.75E-08 |
| PPP1R18 | 938.1483334 | 1714.543304 | 0.870948088 | $4.77 \mathrm{E}-10$ |
| LTK | 36.87767828 | 67.37708911 | 0.870573241 | 0.039274709 |
| SLC39A1 | 36.24989936 | 66.37901587 | 0.870558565 | 0.023313238 |
| FLRT1 | 138.6174708 | 253.0165181 | 0.870289042 | 0.000298642 |
| MAP3K14 | 928.2230286 | 1695.811668 | 0.869671523 | $1.42 \mathrm{E}-11$ |
| SKA3 | 888.6508945 | 1623.655207 | 0.869467648 | $9.44 \mathrm{E}-05$ |
| PROZ | 44.60761877 | 80.94368566 | 0.868573862 | 0.03387231 |
| C4orf46 | 939.8252268 | 1712.24574 | 0.865874845 | 1.13E-06 |
| KLHDC7A | 98.08248973 | 179.1910803 | 0.865650777 | 0.019771781 |
| IL3RA | 143.3255222 | 261.545719 | 0.864685148 | 0.002514103 |
| FAM222A | 181.4745821 | 329.2537118 | 0.86273787 | 0.000208756 |
| DSCC1 | 921.166547 | 1674.351911 | 0.862341455 | $1.96 \mathrm{E}-05$ |
| FAM227A | 81.30873921 | 148.0976994 | 0.862225698 | 0.001196644 |


| ZDHHC11 | 232.2088687 | 421.242859 | 0.860750238 | 5.84E-06 |
| :---: | :---: | :---: | :---: | :---: |
| ICAM1 | 418.0412735 | 758.5976598 | 0.859653046 | 5.41E-06 |
| RAD18 | 1273.134145 | 2307.686829 | 0.858084797 | 2.07E-06 |
| TMEM79 | 314.4520374 | 569.6855865 | 0.857922287 | 4.94E-09 |
| EVA1A | 94.85118264 | 171.9585846 | 0.857841562 | 0.000289408 |
| ARL3 | 549.7968054 | 995.7725304 | 0.857396239 | 4.19E-09 |
| AP1S2 | 412.63471 | 747.1271954 | 0.856733645 | 2.06E-08 |
| WDFY2 | 247.4420718 | 447.2990751 | 0.855718176 | $1.18 \mathrm{E}-07$ |
| RAD1 | 1011.898816 | 1829.104317 | 0.854486032 | 4.15E-08 |
| TTLL11 | 43.96182157 | 79.30433527 | 0.8542259 | 0.018600371 |
| SLC39A5 | 31.25524465 | 56.65296841 | 0.854137903 | 0.044189175 |
| KIF1A | 49.95053915 | 90.59826099 | 0.853277308 | 0.011387174 |
| ACOT4 | 44.54200041 | 80.36689662 | 0.851368715 | 0.023416361 |
| FSD1L | 128.2556636 | 230.7009558 | 0.849906426 | 0.000629831 |
| BTN2A2 | 358.7863628 | 646.1043044 | 0.84876814 | $2.26 \mathrm{E}-07$ |
| CTXN1 | 326.6176845 | 587.4252262 | 0.848679719 | $4.98 \mathrm{E}-05$ |
| RPP30 | 956.6338517 | 1722.342657 | 0.848484302 | $3.22 \mathrm{E}-08$ |
| ATP6V0E2 | 609.3161197 | 1096.073873 | 0.847714958 | 2.33E-06 |
| SMIM4 | 188.5164117 | 338.0446103 | 0.846809964 | 0.000179891 |
| ZNF714 | 622.8826808 | 1118.826508 | 0.845336129 | $6.68 \mathrm{E}-06$ |
| TIMM9 | 500.5670596 | 899.5203914 | 0.844363775 | $1.51 \mathrm{E}-08$ |
| AASS | 339.0828648 | 609.113747 | 0.844307092 | 8.83E-08 |
| ANKRD36C | 187.7104824 | 336.4532757 | 0.844203377 | $1.24 \mathrm{E}-05$ |
| KIF18A | 903.3422942 | 1621.710766 | 0.843659906 | $1.97 \mathrm{E}-08$ |
| ARHGEF40 | 100.855805 | 180.6081055 | 0.843219729 | 0.003054485 |
| ZBTB46 | 176.685209 | 316.7085336 | 0.843150537 | $1.66 \mathrm{E}-05$ |
| CYBRD1 | 50.05555083 | 89.81925034 | 0.843007749 | 0.046579296 |
| ADAL | 324.0771763 | 580.9996874 | 0.842750682 | $1.79 \mathrm{E}-08$ |
| CHML | 4580.056684 | 8208.298496 | 0.841610293 | 4.83E-12 |
| EED | 833.2648747 | 1492.128998 | 0.841126313 | $2.75 \mathrm{E}-07$ |
| TMEM201 | 845.4670398 | 1512.81442 | 0.840131466 | $1.95 \mathrm{E}-06$ |
| CHST7 | 69.13343449 | 123.55362 | 0.84005873 | 0.006081622 |
| SPRN | 157.3383611 | 281.3475571 | 0.839207198 | 4.94E-05 |
| INCA1 | 96.49890627 | 172.4443146 | 0.838465434 | 0.001615264 |
| RFC3 | 1003.608576 | 1792.226505 | 0.836858116 | 6.62E-05 |
| CASC10 | 151.1507261 | 270.0029707 | 0.836468639 | 0.000432815 |
| TNC | 311.1193736 | 555.7166242 | 0.836370974 | 0.000206605 |
| AAMDC | 70.22411848 | 125.3436432 | 0.835089792 | 0.004741405 |
| SERHL2 | 130.5827072 | 232.8542793 | 0.834954023 | 0.000492231 |
| PARD6A | 200.0856619 | 357.2581991 | 0.834216809 | $2.31 \mathrm{E}-06$ |
| CDC6 | 2595.282931 | 4626.229014 | 0.834181322 | 2.64E-06 |
| EMC6 | 55.28217591 | 98.13054424 | 0.833511939 | 0.011221897 |
| VAMP1 | 269.9502372 | 479.8274592 | 0.830886658 | $4.91 \mathrm{E}-07$ |
| LRR1 | 556.5929006 | 988.2162393 | 0.828804553 | $1.09 \mathrm{E}-05$ |
| ARHGEF3 | 1072.601817 | 1903.935586 | 0.828705139 | $3.51 \mathrm{E}-09$ |
| ZSCAN22 | 210.2336252 | 373.3487455 | 0.828703925 | $4.08 \mathrm{E}-05$ |
| ISX | 177.9420163 | 316.1915864 | 0.828687665 | 0.000357031 |
| PPP1R3F | 114.2869025 | 203.2309589 | 0.828566651 | 0.000340729 |
| POLD1 | 2268.71337 | 4028.067203 | 0.828383829 | 1.63E-08 |
| CEND1 | 40.99895783 | 72.47149608 | 0.82754567 | 0.047941443 |
| EN2 | 72.34576599 | 127.9234222 | 0.82723521 | 0.005473883 |
| LRRC61 | 303.490561 | 538.4583257 | 0.826467224 | 6.42E-08 |
| MSH2 | 4870.380358 | 8628.136188 | 0.82510478 | $1.71 \mathrm{E}-06$ |
| IRX5 | 160.2431208 | 283.6555002 | 0.82481016 | $2.44 \mathrm{E}-05$ |
| RNF207 | 607.830626 | 1076.499311 | 0.824692854 | $1.42 \mathrm{E}-06$ |
| TCF7 | 915.223954 | 1620.412794 | 0.824690765 | 5.51E-10 |
| SLC22A4 | 50.23792206 | 88.90022432 | 0.824446085 | 0.013993454 |
| NXPH4 | 121.4229872 | 214.5100579 | 0.824269539 | 0.000279532 |
| C12orf45 | 1039.186937 | 1839.490707 | 0.824261914 | $3.16 \mathrm{E}-05$ |
| TRIM15 | 941.2242562 | 1665.73534 | 0.824236321 | 3.02E-08 |
| KIAA0895 | 180.6163621 | 319.0238 | 0.824129935 | $3.06 \mathrm{E}-05$ |


| CDCA5 | 1636.840336 | 2895.656292 | 0.823073149 | 0.044170767 |
| :---: | :---: | :---: | :---: | :---: |
| LY6G5B | 97.03587746 | 171.1999773 | 0.822526626 | 0.001038399 |
| SLC43A2 | 145.938591 | 257.8670383 | 0.821983001 | 5.79E-05 |
| ZNF527 | 126.2489476 | 223.5444617 | 0.821398839 | 0.00033361 |
| CFAP44 | 573.0396399 | 1011.94201 | 0.820350499 | $6.59 \mathrm{E}-07$ |
| CIT | 3582.114877 | 6321.667774 | 0.819334662 | $3.01 \mathrm{E}-10$ |
| MROH8 | 38.57295089 | 68.26782685 | 0.819164086 | 0.046684765 |
| HCCS | 627.559323 | 1104.955422 | 0.817141691 | 2.87E-07 |
| NXT1 | 423.5345179 | 745.2369612 | 0.817062981 | 1.23E-05 |
| RFWD3 | 2978.0224 | 5245.123577 | 0.816745604 | $1.94 \mathrm{E}-06$ |
| SLC45A2 | 68.0307172 | 119.3786049 | 0.815669937 | 0.034987015 |
| NNAT | 104.0269219 | 182.3068022 | 0.81414004 | 0.004106646 |
| SLC2A3 | 324.0882822 | 569.4146065 | 0.813842634 | $1.19 \mathrm{E}-05$ |
| IL1R2 | 258.5124375 | 454.2669441 | 0.813757782 | $2.14 \mathrm{E}-06$ |
| TMEM56 | 645.7926424 | 1135.852556 | 0.813686539 | $1.88 \mathrm{E}-10$ |
| SHANK3 | 106.5086906 | 186.4528239 | 0.812607517 | 0.008206168 |
| DYNLL1 | 4951.748314 | 8686.152764 | 0.810907221 | 3.19E-09 |
| C12orf75 | 1511.524688 | 2650.342221 | 0.810428479 | 5.67E-08 |
| SLC25A45 | 82.4173843 | 144.8555377 | 0.810373472 | 0.011604838 |
| POLR3K | 420.307501 | 736.6332719 | 0.810363233 | 0.000811053 |
| TNNI2 | 124.6585723 | 218.8036278 | 0.810227475 | 0.000154709 |
| KIF24 | 559.0634278 | 979.8590449 | 0.809093257 | 2.21E-05 |
| IQCJ-SCHIP1 | 84.33704971 | 147.3956234 | 0.808619834 | 0.001593336 |
| CMC2 | 652.410786 | 1141.784336 | 0.8082775 | 8.95E-06 |
| KHK | 320.2108048 | 559.6570348 | 0.806861302 | $5.90 \mathrm{E}-05$ |
| GPR37 | 142.0451182 | 247.6761146 | 0.806139329 | 0.000154722 |
| ITGB8 | 217.1915595 | 379.4392538 | 0.80533698 | 0.000250966 |
| HRH1 | 281.7611998 | 491.3938542 | 0.803366297 | 2.13E-07 |
| TRAM2 | 1626.905621 | 2838.47694 | 0.802917036 | $4.79 \mathrm{E}-12$ |
| NEMP1 | 3011.456622 | 5247.603377 | 0.801274659 | 8.90E-09 |
| THAP10 | 224.7679098 | 392.1443707 | 0.800941695 | $1.57 \mathrm{E}-05$ |
| CYB5RL | 498.9942089 | 869.762407 | 0.800924449 | $1.55 \mathrm{E}-07$ |
| ASIC3 | 177.3438763 | 309.0465001 | 0.799095555 | 5.00E-05 |
| UACA | 2061.042103 | 3583.080725 | 0.797574378 | $1.83 \mathrm{E}-10$ |
| SUV39H2 | 697.3293273 | 1211.25602 | 0.797462345 | $3.26 \mathrm{E}-06$ |
| ING3 | 378.8022615 | 659.0638811 | 0.79683653 | 3.47E-07 |
| CDKN2C | 255.9664414 | 444.759734 | 0.796835814 | 0.000163591 |
| TRIM35 | 651.3929214 | 1131.750306 | 0.796656216 | 6.66E-09 |
| ZNF79 | 121.2088002 | 210.3543328 | 0.796331279 | 0.000201231 |
| 03-Mar | 47.66141073 | 82.95365958 | 0.795757857 | 0.045093993 |
| DNAH12 | 82.01182752 | 141.8865504 | 0.795657556 | 0.006275953 |
| IRF1 | 295.6618226 | 512.2358389 | 0.795115149 | $1.34 \mathrm{E}-06$ |
| ZNRF2 | 116.905321 | 202.5453846 | 0.794843375 | 0.000384078 |
| COL18A1 | 160.8184374 | 278.7038545 | 0.793256131 | 0.009458476 |
| CREB3 | 1392.495985 | 2411.199257 | 0.791785896 | $1.67 \mathrm{E}-08$ |
| STYK1 | 334.174189 | 577.5143892 | 0.791032522 | 6.87E-06 |
| LAT2 | 200.9415968 | 347.3627505 | 0.790835302 | $1.27 \mathrm{E}-05$ |
| MYRIP | 416.3293225 | 720.5879925 | 0.79043917 | $3.70 \mathrm{E}-06$ |
| GTF2A2 | 845.5485812 | 1461.292936 | 0.789845856 | $6.00 \mathrm{E}-05$ |
| ZNF260 | 837.2493567 | 1446.780093 | 0.789288591 | $6.54 \mathrm{E}-10$ |
| HHEX | 55.55353961 | 95.88262593 | 0.78874573 | 0.028954962 |
| RHOD | 939.9690715 | 1622.715889 | 0.787794261 | 2.59E-09 |
| C1orf35 | 714.3241711 | 1231.26149 | 0.786469921 | $2.04 \mathrm{E}-05$ |
| POLE | 4411.763273 | 7603.842553 | 0.785555432 | $1.60 \mathrm{E}-07$ |
| ASB16 | 157.362536 | 270.078612 | 0.783698471 | 0.001485521 |
| TMEM67 | 230.7163067 | 397.1693493 | 0.781709752 | 0.000116022 |
| TMEM200A | 2749.490581 | 4726.870242 | 0.781467447 | 4.58E-09 |
| RASL10A | 80.34472792 | 138.0535047 | 0.780260164 | 0.00939954 |
| ABHD8 | 124.7754968 | 213.8719772 | 0.779017674 | 0.000416896 |
| PGBD1 | 220.546589 | 377.7573953 | 0.778593321 | 0.000170544 |
| PRKACA | 1661.201475 | 2847.020086 | 0.777453376 | 5.12E-07 |


| TAP2 | 571.7414886 | 980.0303012 | 0.776568058 | $1.38 \mathrm{E}-05$ |
| :---: | :---: | :---: | :---: | :---: |
| HSPA14 | 721.3671868 | 1234.417056 | 0.776144487 | $3.18 \mathrm{E}-07$ |
| TOP2A | 16059.99918 | 27503.70204 | 0.77614036 | $6.60 \mathrm{E}-07$ |
| CENPN | 874.4522582 | 1495.72659 | 0.774748065 | $9.75 \mathrm{E}-06$ |
| RABIF | 422.52135 | 722.599236 | 0.774259109 | 7.05E-07 |
| SEMA3C | 573.2967486 | 980.3945374 | 0.77380694 | 4.29E-07 |
| CEP128 | 404.2305467 | 691.4962658 | 0.773796285 | 0.000169817 |
| SOAT1 | 594.8890475 | 1015.516475 | 0.772949971 | 8.21E-08 |
| ANKRD1 | 196.0287362 | 335.6252766 | 0.772424336 | 0.006432642 |
| LRRC45 | 900.9364279 | 1538.7221 | 0.772152413 | 6.24E-06 |
| MAMLD1 | 155.1918675 | 264.3270596 | 0.771790048 | 0.001205525 |
| TRPV3 | 620.4448148 | 1058.560503 | 0.770211162 | 4.40E-09 |
| SLC10A3 | 554.3995864 | 944.650785 | 0.769050314 | 7.06E-07 |
| SIVA1 | 1483.506142 | 2526.444159 | 0.768525598 | $1.70 \mathrm{E}-05$ |
| FAM50A | 1474.692044 | 2509.64062 | 0.767783931 | 1.32E-10 |
| EZH2 | 1955.491815 | 3328.557088 | 0.767641713 | 2.95E-06 |
| STARD9 | 141.956189 | 241.2771202 | 0.767229466 | 0.00080056 |
| ZHX1 | 698.7276703 | 1188.787795 | 0.766448801 | $1.48 \mathrm{E}-07$ |
| ZNF827 | 509.4574088 | 866.8398846 | 0.766311509 | $1.64 \mathrm{E}-08$ |
| IDH3A | 953.5740448 | 1620.094785 | 0.765040646 | 7.23E-05 |
| PHLDB2 | 1139.354652 | 1936.051443 | 0.7649476 | $1.19 \mathrm{E}-10$ |
| BCAM | 2073.822573 | 3523.517792 | 0.764507995 | $1.46 \mathrm{E}-06$ |
| GINS3 | 454.9702674 | 772.1846173 | 0.763505004 | 0.000168881 |
| CRCP | 648.2389167 | 1098.91901 | 0.761907012 | 8.23E-07 |
| FN3KRP | 833.9578655 | 1413.12128 | 0.761459355 | $1.91 \mathrm{E}-06$ |
| GFOD1 | 611.6147554 | 1036.670288 | 0.761415642 | $1.01 \mathrm{E}-05$ |
| SYT12 | 602.1398587 | 1019.705609 | 0.760861879 | $1.58 \mathrm{E}-07$ |
| CNKSR3 | 590.5335275 | 1000.20958 | 0.760663578 | 0.000405338 |
| CDKN2AIP | 1058.071765 | 1791.874082 | 0.76043896 | $6.41 \mathrm{E}-07$ |
| IRX3 | 246.7098593 | 417.5841311 | 0.760415455 | 2.87E-05 |
| NUTM2G | 52.71164958 | 88.87877946 | 0.759247428 | 0.038303533 |
| PRKAR1B | 430.5098352 | 728.1691796 | 0.759136753 | 0.000118225 |
| XRCC1 | 582.3308043 | 985.5328729 | 0.759001969 | 1.97E-08 |
| KRBOX4 | 298.4969208 | 505.4966162 | 0.758121388 | $1.69 \mathrm{E}-05$ |
| UAP1L1 | 99.71870096 | 168.4817891 | 0.756830948 | 0.004695574 |
| CCDC3 | 374.6895081 | 632.2887243 | 0.756390382 | 0.000903256 |
| HES7 | 122.0309836 | 205.1672792 | 0.75600414 | 0.009217337 |
| USP1 | 3250.376859 | 5488.051593 | 0.755878267 | $1.41 \mathrm{E}-07$ |
| CERS6 | 1151.936646 | 1944.231341 | 0.754997501 | 9.96E-08 |
| ARHGAP23 | 466.3386249 | 786.9762375 | 0.754657186 | 2.16E-06 |
| FLNA | 9945.032919 | 16776.6612 | 0.754474844 | $1.60 \mathrm{E}-11$ |
| TRMT6 | 1448.617727 | 2444.052971 | 0.754393788 | $2.10 \mathrm{E}-08$ |
| CCDC58 | 620.0897274 | 1045.573073 | 0.753732458 | $1.01 \mathrm{E}-08$ |
| SLC41A2 | 357.7465151 | 602.6446613 | 0.753509653 | 2.87E-07 |
| ACD | 1008.758124 | 1699.181693 | 0.752143876 | $7.00 \mathrm{E}-08$ |
| TNS1 | 93.74366644 | 157.9075249 | 0.752100615 | 0.008230914 |
| E2F1 | 1084.655103 | 1825.176584 | 0.751601697 | 4.42E-06 |
| ARSK | 302.3199975 | 508.7999583 | 0.751121848 | 6.80E-07 |
| BLOC1S1 | 160.0280398 | 269.0412113 | 0.750735566 | 0.000824861 |
| SPINDOC | 679.2598188 | 1142.086191 | 0.750418147 | $1.67 \mathrm{E}-05$ |
| SLC30A4 | 98.87708435 | 166.4923296 | 0.748824913 | 0.005316257 |
| TGFB1I1 | 85.61985318 | 143.8870461 | 0.748619872 | 0.027457442 |
| ESAM | 67.64818523 | 113.2654272 | 0.748279976 | 0.027792805 |
| SPICE1 | 141.1518462 | 237.1467387 | 0.747639953 | 0.000504354 |
| NDUFAF8 | 494.0660938 | 828.7087631 | 0.747462079 | 3.10E-05 |
| ARR3 | 61.76806487 | 103.3092781 | 0.74631309 | 0.02233996 |
| SEMA6C | 139.5060583 | 233.8820906 | 0.746184709 | 0.000432272 |
| MAST2 | 2947.693503 | 4941.825386 | 0.745409184 | $2.08 \mathrm{E}-12$ |
| SERTAD1 | 382.6795586 | 640.5603938 | 0.744605968 | 1.95E-05 |
| DGKH | 1510.173932 | 2529.43917 | 0.744426547 | 5.72E-05 |
| TIPIN | 481.0907304 | 805.1830884 | 0.744196627 | 0.000204697 |


| ZNF141 | 141.8849288 | 237.5175186 | 0.744144235 | 0.000911178 |
| :---: | :---: | :---: | :---: | :---: |
| PRXL2B | 582.5438563 | 974.5892125 | 0.743853638 | $2.36 \mathrm{E}-06$ |
| ZGRF1 | 609.5520882 | 1020.621272 | 0.743771365 | 0.000234174 |
| NIFK | 1199.78927 | 2008.636718 | 0.743602308 | $2.60 \mathrm{E}-06$ |
| ZNF44 | 279.3023987 | 468.2833255 | 0.742681842 | $4.78 \mathrm{E}-05$ |
| TNFRSF12A | 2534.072991 | 4238.650902 | 0.742565918 | $1.74 \mathrm{E}-07$ |
| EDRF1 | 1207.566754 | 2019.758799 | 0.742563744 | $6.14 \mathrm{E}-07$ |
| CHAC2 | 458.12675 | 766.0192124 | 0.742526082 | 0.005388616 |
| C4BPB | 1214.809005 | 2032.724893 | 0.742474821 | 8.39E-09 |
| SFXN5 | 614.8308562 | 1028.430145 | 0.742287859 | 3.14E-06 |
| FAM89A | 158.8972128 | 265.0912858 | 0.742093952 | 0.001276062 |
| CENPT | 789.6047271 | 1320.517286 | 0.74191222 | 2.21E-07 |
| MOK | 67.93487567 | 113.7332058 | 0.741247187 | 0.012870079 |
| NDUFAF6 | 444.0644051 | 742.3321227 | 0.740517669 | $2.18 \mathrm{E}-06$ |
| PEA15 | 1336.454625 | 2232.264226 | 0.740427267 | $1.45 \mathrm{E}-07$ |
| MECOM | 166.3022617 | 277.4451675 | 0.740100123 | 0.004006519 |
| LY6G5C | 113.0192542 | 189.1024423 | 0.739858239 | 0.003144849 |
| ALOXE3 | 210.0544392 | 351.4095369 | 0.739518905 | 0.000610947 |
| TOMM40L | 277.5817924 | 462.9360068 | 0.739439549 | 0.001218047 |
| CDK2 | 1453.564177 | 2426.139236 | 0.739291556 | 0.000283553 |
| FAM216A | 188.8271115 | 315.5065186 | 0.739279819 | 0.000444736 |
| PLAGL1 | 1448.128317 | 2418.033941 | 0.739256434 | 1.13E-08 |
| TONSL | 2649.915402 | 4419.870381 | 0.738242477 | 0.000115153 |
| CORO2A | 267.0824952 | 445.7737207 | 0.738079881 | 0.0014633 |
| STAMBPL1 | 787.2896658 | 1313.307542 | 0.737992863 | 1.03E-05 |
| BLCAP | 1973.641398 | 3289.088847 | 0.736752167 | $2.58 \mathrm{E}-11$ |
| PDX1 | 335.9811446 | 558.7300255 | 0.736434433 | 0.000443796 |
| WDHD1 | 1529.642799 | 2545.360884 | 0.734705576 | 9.87E-05 |
| CCDC69 | 277.0733101 | 460.3991599 | 0.73346822 | 5.17E-05 |
| FKBPL | 190.5723837 | 316.2649459 | 0.732967421 | 0.000414666 |
| ZBTB2 | 907.8814015 | 1507.464385 | 0.731910384 | 1.23E-06 |
| C2orf72 | 254.4457276 | 421.8115508 | 0.731749744 | 0.00069963 |
| PHLDB3 | 97.65362215 | 161.9427499 | 0.731656449 | 0.003450562 |
| ALDOC | 49.1285845 | 81.63156837 | 0.730692144 | 0.040711232 |
| SLC16A2 | 170.0463018 | 282.2552498 | 0.730641576 | 0.000842616 |
| FAM161A | 639.663774 | 1059.045533 | 0.728253705 | 3.13E-06 |
| RAB5IF | 587.3196157 | 971.6125756 | 0.727561207 | 0.000218154 |
| AUNIP | 430.4144001 | 711.7335096 | 0.726912355 | $4.66 \mathrm{E}-05$ |
| PCM1 | 4706.721843 | 7781.93652 | 0.725242747 | 7.99E-12 |
| LNPK | 1010.563677 | 1670.250451 | 0.724759925 | 3.73E-05 |
| IRAK1 | 3576.731349 | 5910.561045 | 0.72472979 | 4.85E-07 |
| RASSF5 | 315.4827721 | 521.0250596 | 0.724629747 | 0.000109342 |
| TRPC1 | 162.6687845 | 269.0413253 | 0.724421902 | 0.001117652 |
| AP4E1 | 679.4773352 | 1122.732587 | 0.724212377 | $3.65 \mathrm{E}-08$ |
| ZNF778 | 394.3966216 | 651.8217932 | 0.72341428 | $2.31 \mathrm{E}-06$ |
| IL17RB | 263.217045 | 433.6039234 | 0.723112556 | 0.000249155 |
| DOCK11 | 131.0048613 | 215.6669437 | 0.722705449 | 0.008018126 |
| GALNT18 | 85.14897014 | 140.6290879 | 0.722629189 | 0.00785126 |
| SERTAD4 | 442.2941152 | 729.4591362 | 0.721722963 | 0.000180718 |
| TMSB4Y | 368.7090966 | 607.8000178 | 0.721526974 | 0.000435567 |
| CCDC136 | 281.3193777 | 463.2219642 | 0.720590068 | $2.43 \mathrm{E}-05$ |
| DUSP7 | 489.7022528 | 806.0430466 | 0.720401308 | 0.001505868 |
| ZGLP1 | 70.94175393 | 116.5656418 | 0.720319871 | 0.040849374 |
| ACAP3 | 2504.952728 | 4121.092232 | 0.718480216 | $3.49 \mathrm{E}-08$ |
| CEP152 | 986.7842717 | 1623.657773 | 0.718448481 | 5.63E-06 |
| GRK4 | 131.8018281 | 216.5419272 | 0.718094154 | 0.003576352 |
| NEO1 | 513.7952809 | 844.2737456 | 0.716226766 | 5.32E-07 |
| GPR153 | 247.2885088 | 405.7529001 | 0.716176524 | 0.003689157 |
| SNAP29 | 851.6600332 | 1397.107894 | 0.713634062 | $1.25 \mathrm{E}-08$ |
| CSPP1 | 862.0592047 | 1412.668076 | 0.712768997 | $2.90 \mathrm{E}-07$ |
| C1orf122 | 569.6587858 | 932.7669902 | 0.712122406 | $1.89 \mathrm{E}-06$ |


| RASSF1 | 548.9185442 | 898.5060869 | 0.712043461 | 0.000116122 |
| :---: | :---: | :---: | :---: | :---: |
| ITGB1BP1 | 1257.442643 | 2058.67459 | 0.711895896 | 6.81E-08 |
| GPRASP1 | 99.25186715 | 162.8909071 | 0.710833954 | 0.012526907 |
| SGCB | 727.040505 | 1189.981392 | 0.710628249 | $4.40 \mathrm{E}-08$ |
| DNMT1 | 8006.089942 | 13099.40366 | 0.710374836 | 0.00018458 |
| BAD | 297.9351667 | 487.5038395 | 0.709916969 | 4.64E-05 |
| ZNF35 | 394.9348061 | 645.9625717 | 0.709700697 | 0.000489319 |
| SLF1 | 703.3263211 | 1149.696634 | 0.709279514 | 0.000192475 |
| LYSMD2 | 233.4130693 | 381.0406282 | 0.708810269 | 0.00014179 |
| PDSS1 | 410.0049268 | 669.9339172 | 0.708629642 | 0.004227779 |
| SLC41A1 | 982.4923859 | 1605.374319 | 0.708316652 | $1.77 \mathrm{E}-08$ |
| SOCS4 | 1800.130699 | 2938.723814 | 0.707312032 | $1.68 \mathrm{E}-07$ |
| C21orf58 | 477.4471107 | 778.8805394 | 0.706042726 | $1.94 \mathrm{E}-05$ |
| LONRF3 | 376.8782187 | 614.4181759 | 0.706038183 | 2.93E-05 |
| PDGFRL | 115.7982685 | 188.6520958 | 0.70594291 | 0.004362289 |
| CDR2L | 760.6774473 | 1239.463222 | 0.705111538 | $2.42 \mathrm{E}-05$ |
| NCAPG | 3180.249525 | 5184.25147 | 0.704982806 | 3.16E-05 |
| PRKD3 | 1301.753413 | 2120.920356 | 0.704466443 | 2.93E-07 |
| DUSP2 | 122.7838488 | 199.6152714 | 0.704433312 | 0.014336996 |
| STK39 | 551.0108747 | 897.4989013 | 0.703650016 | 0.000170544 |
| STIL | 1608.61167 | 2619.14736 | 0.703432856 | 3.16E-05 |
| TTYH1 | 118.7289672 | 193.273063 | 0.702738348 | 0.014037936 |
| LPAR1 | 238.35419 | 387.3893701 | 0.702349582 | 0.000278726 |
| ZNF431 | 387.5712007 | 630.3521787 | 0.701832045 | 8.99E-05 |
| ZNF655 | 851.707079 | 1385.202617 | 0.701230535 | $2.90 \mathrm{E}-06$ |
| C15orf41 | 354.9858112 | 577.9757562 | 0.701105046 | 8.69E-05 |
| TRAIP | 606.236452 | 984.1922391 | 0.699160786 | 0.000374307 |
| PITX1 | 850.626577 | 1380.483703 | 0.698530444 | 7.18E-09 |
| DOCK4 | 293.6013201 | 475.9960225 | 0.698046295 | 0.001589832 |
| RBL1 | 774.1130638 | 1255.147833 | 0.697459644 | 0.000126196 |
| CADM4 | 179.9740932 | 291.4078876 | 0.696807071 | 0.000605221 |
| IGFBP4 | 448.9414034 | 727.4067948 | 0.696059204 | 0.003217077 |
| IQCB1 | 1139.129131 | 1845.538628 | 0.696000159 | 1.37E-09 |
| CEP57L1 | 414.2488598 | 671.0098261 | 0.695357381 | $1.39 \mathrm{E}-05$ |
| NYAP2 | 290.7019339 | 470.9576964 | 0.694818783 | 5.77E-05 |
| ZDHHC11B | 147.7683999 | 239.0203148 | 0.694188624 | 0.001380291 |
| PCNX2 | 909.1192358 | 1470.913294 | 0.693394184 | $9.49 \mathrm{E}-08$ |
| CSNK2B | 257.9669947 | 416.6709492 | 0.693117028 | 0.000467439 |
| C2CD3 | 1483.217904 | 2398.112525 | 0.692879091 | 7.51E-08 |
| RFC1 | 3695.152671 | 5971.18121 | 0.692451982 | 3.37E-07 |
| MELTF | 57.04653803 | 92.17799474 | 0.692068099 | 0.031308104 |
| ANKRD42 | 266.6402428 | 430.8490132 | 0.691919978 | 0.000107412 |
| C17orf53 | 337.1981643 | 544.8280354 | 0.691770637 | $8.48 \mathrm{E}-05$ |
| DPH3 | 420.5436077 | 678.3841132 | 0.691309287 | 4.75E-05 |
| RNF167 | 2228.929929 | 3597.675826 | 0.690591067 | 8.98E-08 |
| SLC25A20 | 232.7314704 | 376.1267756 | 0.690573244 | 0.000175021 |
| XPA | 471.400897 | 761.1284079 | 0.690106229 | $2.18 \mathrm{E}-05$ |
| STIM2 | 1340.425707 | 2163.091301 | 0.689567031 | 8.58E-08 |
| AMDHD1 | 110.5736364 | 178.2396154 | 0.689260737 | 0.005519075 |
| GGNBP2 | 2863.071142 | 4615.976573 | 0.688833359 | 2.48E-09 |
| SPC25 | 403.7214564 | 650.7253139 | 0.688605046 | 0.000979607 |
| SYNPO | 257.8749402 | 415.8431358 | 0.687852621 | 0.016601282 |
| STK17A | 1229.180894 | 1978.87534 | 0.687135689 | $1.68 \mathrm{E}-08$ |
| SLC30A6 | 1816.745146 | 2925.456151 | 0.687012046 | $1.57 \mathrm{E}-07$ |
| BLM | 885.3548842 | 1424.588975 | 0.686621043 | 0.003135347 |
| GPATCH4 | 1492.785301 | 2400.569272 | 0.685692958 | 0.000544607 |
| MED27 | 602.0254814 | 967.8317442 | 0.685432073 | 1.33E-05 |
| ZNF346 | 447.3279794 | 718.8628711 | 0.685308232 | $1.10 \mathrm{E}-06$ |
| TXNL4B | 252.7757709 | 406.6357077 | 0.684587184 | 0.003254169 |
| TEAD2 | 223.1225856 | 358.2257338 | 0.683473375 | 0.003018414 |
| KREMEN2 | 233.0054624 | 373.2896668 | 0.682917695 | 0.003082285 |


| KCNC3 | 279.8729437 | 450.0355806 | 0.682865018 | 0.000141909 |
| :---: | :---: | :---: | :---: | :---: |
| ARL16 | 493.9672748 | 792.2097854 | 0.6817712 | 4.75E-07 |
| TCOF1 | 6162.143607 | 9881.554117 | 0.681371136 | 0.000306162 |
| LYAR | 1054.053851 | 1689.672805 | 0.681115498 | 0.002718062 |
| FANCM | 663.822183 | 1064.117732 | 0.680797853 | 0.000384863 |
| GLRX2 | 635.5641555 | 1018.316405 | 0.680262123 | 5.11E-05 |
| ASF1B | 1640.554673 | 2627.966671 | 0.680115554 | 0.002568204 |
| URB2 | 1182.372119 | 1891.194126 | 0.678023618 | 0.003244385 |
| CHAF1A | 1811.430059 | 2895.862741 | 0.677279346 | 0.001599306 |
| FGD3 | 645.664979 | 1032.341125 | 0.676595005 | 8.21E-06 |
| ABCB1 | 876.3422486 | 1399.343705 | 0.67579641 | 0.003540471 |
| ATL1 | 208.0454654 | 332.282838 | 0.675582793 | 0.000458875 |
| DCLRE1C | 460.0428897 | 734.5620515 | 0.675369092 | $7.78 \mathrm{E}-06$ |
| COQ10A | 133.3825756 | 212.726764 | 0.675142209 | 0.005464516 |
| URB1 | 2961.990576 | 4728.506526 | 0.67495784 | 6.70E-06 |
| SPNS3 | 128.5713639 | 205.4316777 | 0.674809094 | 0.02142996 |
| WNT7B | 232.1424945 | 370.1085953 | 0.674017777 | 0.00318405 |
| RUSC1 | 1374.521325 | 2192.393633 | 0.673916545 | $6.78 \mathrm{E}-05$ |
| GINS4 | 880.5367302 | 1404.097847 | 0.673644149 | 0.004149028 |
| RNF25 | 655.7063204 | 1045.799305 | 0.673549696 | 3.35E-07 |
| ZNF789 | 498.1384395 | 793.6601054 | 0.673197603 | 2.83E-06 |
| ZNF250 | 328.7714064 | 523.6668353 | 0.672960595 | 0.000100663 |
| MICB | 488.0591054 | 776.4499175 | 0.671187715 | 0.008702649 |
| ZNF34 | 104.7692891 | 166.5316147 | 0.67104791 | 0.005978654 |
| SCIN | 314.2458917 | 500.2562966 | 0.670447881 | $1.27 \mathrm{E}-05$ |
| SAP30 | 280.780212 | 446.3460436 | 0.670304276 | 0.002555333 |
| TGM1 | 224.9975951 | 358.2783478 | 0.669024974 | 0.001573067 |
| WDR90 | 2652.959385 | 4217.09595 | 0.668858793 | 3.61E-05 |
| FLVCR2 | 213.0768791 | 339.6657417 | 0.668817402 | 0.000782323 |
| MYO7A | 261.5867915 | 416.1849251 | 0.668703888 | 0.006143669 |
| C5 | 281.9749864 | 447.9493477 | 0.667846256 | 0.000375021 |
| CHCHD3 | 1764.652268 | 2802.014075 | 0.667292577 | $2.74 \mathrm{E}-05$ |
| ASAH2 | 64.74238381 | 103.1898618 | 0.667059861 | 0.045721744 |
| MPC1 | 590.6289237 | 937.1617013 | 0.666920296 | 0.000517406 |
| SPRED3 | 89.75498739 | 142.6466075 | 0.666643535 | 0.040711359 |
| RTTN | 666.6419483 | 1057.177123 | 0.665617134 | 0.000257092 |
| HILPDA | 364.8491915 | 577.4135155 | 0.665162777 | 0.000188845 |
| LYSMD3 | 1196.41693 | 1896.817916 | 0.664437358 | 2.26E-08 |
| CHN1 | 479.083614 | 759.4963385 | 0.664424874 | 0.000484278 |
| TRIAP1 | 495.6706159 | 785.0606541 | 0.664381634 | 0.000925922 |
| CCDC134 | 272.707184 | 431.8196173 | 0.664320759 | 0.000257844 |
| PHKG2 | 724.0541228 | 1146.890883 | 0.664004638 | 4.55E-06 |
| TIMM29 | 424.6841489 | 672.4205245 | 0.663843225 | $1.26 \mathrm{E}-05$ |
| MIB2 | 1278.927111 | 2026.609433 | 0.663516755 | 4.83E-05 |
| NT5C3A | 836.6631357 | 1324.140461 | 0.663254176 | $9.04 \mathrm{E}-07$ |
| SWI5 | 248.630196 | 394.0492752 | 0.66276575 | 0.000594437 |
| ATAD3A | 1844.666962 | 2919.363827 | 0.662722613 | 0.000836933 |
| MAP3K3 | 667.6298935 | 1055.87539 | 0.662545934 | 3.41E-05 |
| SLC39A8 | 541.7627976 | 857.2606508 | 0.662495983 | 0.000693026 |
| DNAJC1 | 933.3719931 | 1478.194458 | 0.662481444 | $7.00 \mathrm{E}-07$ |
| ZNF48 | 534.960648 | 845.7602654 | 0.662297561 | 2.67E-05 |
| PRDM11 | 227.6750056 | 359.5148188 | 0.661375549 | 0.000722835 |
| LUZP1 | 2672.539633 | 4221.833928 | 0.659785487 | $1.87 \mathrm{E}-06$ |
| CAMSAP2 | 2672.856356 | 4221.830894 | 0.659298915 | $5.78 \mathrm{E}-10$ |
| CSGALNACT1 | 242.8899044 | 383.7244773 | 0.659188875 | 0.002493554 |
| CPSF7 | 3673.779212 | 5798.814228 | 0.658451341 | $2.69 \mathrm{E}-10$ |
| MRM2 | 1121.831454 | 1770.015736 | 0.658246865 | 0.000108778 |
| RPP40 | 178.2026172 | 280.9189496 | 0.65753238 | 0.006762672 |
| KPTN | 483.1615953 | 762.5759029 | 0.657501358 | 2.01E-06 |
| HAUS5 | 1204.78046 | 1899.638383 | 0.657200922 | 4.59E-05 |
| SKA2 | 1417.571726 | 2232.544565 | 0.655415238 | $1.66 \mathrm{E}-05$ |


| ZMAT5 | 124.609494 | 196.1333791 | 0.65449682 | 0.004947129 |
| :---: | :---: | :---: | :---: | :---: |
| ST7L | 420.802917 | 662.6295091 | 0.653274523 | 7.25E-05 |
| CCDC84 | 1541.333898 | 2422.41725 | 0.653000319 | 9.79E-07 |
| NOP56 | 6937.223638 | 10907.53051 | 0.652948346 | $9.58 \mathrm{E}-05$ |
| TNK1 | 711.8743923 | 1119.03253 | 0.652387756 | 8.16E-07 |
| FHL3 | 609.663253 | 958.1575103 | 0.651750603 | $9.08 \mathrm{E}-06$ |
| RGS12 | 381.3946144 | 598.8825655 | 0.6510777 | $5.00 \mathrm{E}-05$ |
| DFFA | 1734.326521 | 2721.925975 | 0.65069199 | $2.19 \mathrm{E}-06$ |
| LRRFIP2 | 1204.890938 | 1891.684041 | 0.650467209 | $1.87 \mathrm{E}-08$ |
| LIN52 | 323.329059 | 506.927649 | 0.649920184 | 7.23E-05 |
| VEGFB | 378.9212361 | 594.7530455 | 0.649789676 | 1.97E-05 |
| TMEM131L | 1284.416431 | 2014.65862 | 0.649210402 | 6.05E-06 |
| NLGN2 | 415.6943664 | 650.8877339 | 0.647988728 | $2.84 \mathrm{E}-05$ |
| CENPI | 776.1732055 | 1215.969655 | 0.647648059 | 0.003700549 |
| PLXND1 | 268.1865403 | 419.6428095 | 0.647570484 | 0.002461046 |
| CDC42EP3 | 5060.143428 | 7927.529752 | 0.647506856 | $2.08 \mathrm{E}-08$ |
| PCNT | 5462.697652 | 8556.564118 | 0.647328344 | $6.25 \mathrm{E}-07$ |
| PLXNA3 | 3381.718905 | 5294.539625 | 0.646715154 | 5.95E-08 |
| GLUL | 757.8350962 | 1186.093502 | 0.646597714 | $7.28 \mathrm{E}-05$ |
| TYMS | 1308.12305 | 2047.665985 | 0.646593957 | 0.005363655 |
| PRTFDC1 | 1087.657237 | 1702.749968 | 0.64646603 | 0.000259032 |
| NRM | 723.2163838 | 1131.681413 | 0.646379031 | 2.05E-05 |
| KCNH2 | 122.9590217 | 192.2857771 | 0.646376805 | 0.029807895 |
| ZNF519 | 140.3939234 | 219.6024506 | 0.646192915 | 0.010687473 |
| ICA1L | 122.5730757 | 192.2663307 | 0.646127887 | 0.00559497 |
| MFSD12 | 1578.798415 | 2469.945106 | 0.645795007 | $2.08 \mathrm{E}-05$ |
| USP37 | 747.0768365 | 1167.67046 | 0.645251246 | $1.19 \mathrm{E}-05$ |
| NR4A3 | 133.4568134 | 208.4103261 | 0.644928019 | 0.035074324 |
| SERPINH1 | 2458.559056 | 3844.228409 | 0.6447024 | $3.41 \mathrm{E}-06$ |
| ZNF367 | 910.0601448 | 1422.191899 | 0.644533398 | 0.00167436 |
| NEDD9 | 568.1535552 | 887.8956229 | 0.644329268 | 8.48E-06 |
| CCDC86 | 819.1181559 | 1279.640838 | 0.644278687 | 0.002217769 |
| GNAI1 | 431.2082512 | 674.1026506 | 0.644165665 | 0.001286083 |
| PCGF6 | 309.7074857 | 483.2911748 | 0.643774934 | 0.000135461 |
| MRPS11 | 625.2651369 | 976.5263335 | 0.643414628 | 0.001161827 |
| ZNF256 | 103.1532035 | 161.0256242 | 0.642711839 | 0.008083518 |
| ERI1 | 1398.078965 | 2182.287079 | 0.642701124 | 0.000269262 |
| EFR3B | 122.803574 | 191.526083 | 0.642254164 | 0.016847037 |
| KANK2 | 2074.980271 | 3237.144567 | 0.641765633 | $2.29 \mathrm{E}-06$ |
| GEMIN6 | 547.798772 | 854.940137 | 0.64148778 | 0.000544607 |
| LRRC37A2 | 345.4709976 | 538.3330388 | 0.641487639 | 0.000478154 |
| USP36 | 2300.659187 | 3588.51462 | 0.641324416 | $1.00 \mathrm{E}-07$ |
| MMP24 | 396.806832 | 618.4184679 | 0.640925467 | 7.62E-05 |
| COL11A2 | 271.1771705 | 422.844194 | 0.6398044 | 0.000259031 |
| RASAL2 | 746.7601999 | 1164.24587 | 0.639388317 | 1.17E-05 |
| ZNF724 | 127.4280733 | 198.395419 | 0.638821116 | 0.027772502 |
| BRCC3 | 1449.866794 | 2257.030567 | 0.638803165 | $3.42 \mathrm{E}-06$ |
| SMCHD1 | 5284.50719 | 8228.328592 | 0.638675351 | $1.24 \mathrm{E}-08$ |
| PEAK1 | 491.552401 | 764.9794373 | 0.638580368 | 0.000136962 |
| SLC35D1 | 797.5013927 | 1240.972327 | 0.637540403 | $2.59 \mathrm{E}-06$ |
| ATP6V1D | 1014.214528 | 1577.669067 | 0.637486171 | 3.48E-06 |
| CENPM | 803.7204405 | 1249.826717 | 0.637372548 | 0.006890721 |
| FANCB | 300.4959721 | 466.701368 | 0.636950466 | 0.011277553 |
| PRDM1 | 89.94123626 | 139.7887856 | 0.635344026 | 0.03201247 |
| C22orf46 | 1064.589873 | 1654.020225 | 0.635204259 | 5.69E-07 |
| FAM204A | 1154.497499 | 1792.229916 | 0.634741096 | 2.54E-08 |
| CEP85L | 153.1157126 | 237.6551803 | 0.634676692 | 0.003638127 |
| CPTP | 929.5894748 | 1442.612303 | 0.634617421 | 6.82E-07 |
| RAD54L | 1056.470959 | 1639.665461 | 0.634582437 | 0.003359342 |
| LAMB3 | 5059.467607 | 7852.709485 | 0.634159251 | 0.00064127 |
| ZNF385A | 367.5140661 | 570.3677097 | 0.634108372 | 0.000114606 |


| RELT | 432.3359441 | 669.9979283 | 0.633798375 | 0.001854424 |
| :---: | :---: | :---: | :---: | :---: |
| ABCG2 | 108.9006029 | 168.6382215 | 0.633363783 | 0.013924765 |
| NDC80 | 1061.992875 | 1647.756982 | 0.633287228 | 3.29E-05 |
| CYP26B1 | 667.4108742 | 1034.526426 | 0.633248188 | 0.000134034 |
| POLA2 | 294.5187669 | 456.0484224 | 0.633029963 | 0.009785142 |
| C1orf112 | 554.2985429 | 859.2339744 | 0.63268183 | 0.010512729 |
| LHX4 | 421.9158041 | 653.6501023 | 0.632599717 | 0.000117806 |
| MCM2 | 3686.971763 | 5713.875682 | 0.632130596 | 0.002807718 |
| ING2 | 417.4274398 | 646.9264989 | 0.632002716 | 2.85E-05 |
| WDR4 | 690.102772 | 1068.552908 | 0.631506542 | 0.000801387 |
| DZANK1 | 75.70232481 | 117.014989 | 0.631347814 | 0.037370579 |
| GPSM1 | 301.6571904 | 466.9025186 | 0.630981522 | 0.007164059 |
| GKAP1 | 159.3719163 | 246.688516 | 0.630837731 | 0.002011002 |
| SOGA1 | 390.4300277 | 604.2001619 | 0.630481085 | 0.004391866 |
| NDP | 207.9746988 | 322.2334031 | 0.62961211 | 0.027415592 |
| ARHGEF26 | 626.3250197 | 969.0227438 | 0.629478461 | 8.12E-05 |
| BMP1 | 1430.955265 | 2214.134594 | 0.629284091 | $4.92 \mathrm{E}-08$ |
| SSX2IP | 1153.213408 | 1783.552682 | 0.629162355 | 1.91E-05 |
| KCND1 | 155.0784141 | 239.8939174 | 0.629022908 | 0.004284769 |
| CLTB | 1646.787216 | 2546.184141 | 0.62871256 | $6.51 \mathrm{E}-06$ |
| NUPL2 | 891.609594 | 1376.963948 | 0.628064552 | $1.20 \mathrm{E}-05$ |
| ZRANB3 | 432.8107408 | 669.3875685 | 0.62769863 | $3.07 \mathrm{E}-05$ |
| NVL | 996.394171 | 1539.804153 | 0.627606223 | 1.12E-05 |
| PA2G4 | 5119.790042 | 7909.079162 | 0.627508772 | 0.00125557 |
| SH3GL2 | 789.4652381 | 1220.01963 | 0.62740382 | 5.87E-06 |
| ALKBH1 | 380.384996 | 587.4301242 | 0.62686986 | $3.01 \mathrm{E}-05$ |
| SUPT6H | 5117.779958 | 7902.257743 | 0.626713696 | $4.88 \mathrm{E}-08$ |
| SLC35E3 | 514.2842333 | 792.9028789 | 0.625952451 | $1.71 \mathrm{E}-05$ |
| CDC7 | 1283.531441 | 1980.600052 | 0.625538551 | 0.000108792 |
| ZMPSTE24 | 2316.703162 | 3573.100933 | 0.625148548 | 0.000105299 |
| QKI | 246.8921733 | 380.0343759 | 0.624768142 | 0.001521827 |
| ATAD3B | 1710.233671 | 2636.26436 | 0.62467434 | 0.000410636 |
| CHSY3 | 114.7608836 | 176.4848616 | 0.624104063 | 0.025632262 |
| NTAN1 | 374.2838096 | 576.3762289 | 0.624041085 | 0.000108778 |
| POLQ | 1724.868241 | 2657.05428 | 0.623527776 | 0.004999879 |
| IL11RA | 175.3120282 | 270.337365 | 0.623106234 | 0.003807251 |
| BAZ1A | 2421.782603 | 3725.657008 | 0.621657478 | 0.000257092 |
| TFPT | 235.0903808 | 361.3514476 | 0.6215136 | 0.001044037 |
| UBR1 | 1559.669665 | 2399.930129 | 0.621266621 | 2.33E-05 |
| GSTT2B | 83.40045565 | 128.3523238 | 0.620761946 | 0.033138209 |
| CDH3 | 2598.86249 | 3995.387755 | 0.620222336 | $2.34 \mathrm{E}-07$ |
| VRK1 | 875.7605492 | 1345.808881 | 0.619965343 | 0.000703919 |
| AMOT | 549.7311298 | 844.9449968 | 0.619215728 | 0.000274481 |
| TRIM3 | 480.1189998 | 736.987073 | 0.619186572 | 0.000163886 |
| CAV1 | 828.8661048 | 1272.261473 | 0.6181523 | $2.48 \mathrm{E}-06$ |
| MCM3 | 5941.855798 | 9117.025372 | 0.617738941 | 0.001446131 |
| RUNDC1 | 771.4967764 | 1183.292634 | 0.617412304 | 3.16E-06 |
| MASP2 | 148.4393353 | 228.557399 | 0.617249799 | 0.018462781 |
| THBS1 | 4285.836432 | 6571.674069 | 0.616741141 | 3.02E-05 |
| ENO3 | 347.211272 | 532.8653341 | 0.616702836 | 0.000827294 |
| SAMD9 | 417.3768683 | 640.3973404 | 0.615429664 | 0.005530719 |
| NRIP1 | 256.3609733 | 393.1975256 | 0.615232372 | 0.002405579 |
| KIF4A | 1737.980798 | 2661.888115 | 0.61476791 | 0.000134682 |
| E2F7 | 882.5728802 | 1350.88584 | 0.614702107 | 0.000796804 |
| LIG1 | 2315.380727 | 3543.625347 | 0.614134071 | 0.001460126 |
| PRR36 | 178.2925609 | 273.1566098 | 0.613913731 | 0.002508492 |
| TMEM251 | 178.693918 | 272.5647688 | 0.613630778 | 0.014733983 |
| CCDC88A | 439.251628 | 671.2168108 | 0.612907398 | 0.003558165 |
| SORBS3 | 866.4596843 | 1324.361522 | 0.612117076 | $1.52 \mathrm{E}-06$ |
| ZFAND2A | 313.416245 | 479.497006 | 0.61204051 | 0.000182211 |
| TMEM39B | 557.6940613 | 852.7940622 | 0.611801632 | 0.000198631 |


| ARHGAP25 | 110.7101145 | 169.3910005 | 0.611792612 | 0.031308104 |
| :---: | :---: | :---: | :---: | :---: |
| ZNF296 | 154.3854172 | 235.8340116 | 0.611305249 | 0.005007701 |
| ITPRIP | 361.0584514 | 550.9167253 | 0.610594329 | 0.000263612 |
| MRPL33 | 718.4825888 | 1096.407297 | 0.610434045 | $1.53 \mathrm{E}-05$ |
| ELL2 | 804.1979975 | 1227.176424 | 0.610062809 | $3.57 \mathrm{E}-06$ |
| HAUS2 | 1305.693056 | 1991.581687 | 0.609771245 | 0.000377548 |
| GRK5 | 100.9609311 | 153.6370326 | 0.609297643 | 0.026874609 |
| TUBG1 | 1052.46197 | 1604.28515 | 0.608672443 | 0.001446131 |
| HAUS8 | 588.688639 | 896.8927853 | 0.608024516 | 0.005352449 |
| TMEM140 | 262.1502798 | 399.9723837 | 0.607430159 | 0.000573957 |
| STOM | 285.1995228 | 434.4470829 | 0.607185854 | 0.002411752 |
| ELOVL7 | 674.2423196 | 1026.811652 | 0.60679615 | 1.33E-06 |
| ATP5IF1 | 2396.271006 | 3647.808272 | 0.606778145 | 0.000212021 |
| JPT1 | 2688.252113 | 4092.872307 | 0.606629904 | 0.000302702 |
| DDX11 | 3199.959598 | 4871.713135 | 0.606469204 | 0.000479419 |
| PPP1R13B | 631.0850064 | 960.2906191 | 0.606355226 | 5.12E-06 |
| SMAD3 | 1936.701242 | 2948.99484 | 0.606164852 | $1.08 \mathrm{E}-07$ |
| PINX1 | 213.1400108 | 324.170344 | 0.606164019 | 0.016808566 |
| MCOLN3 | 354.0812283 | 538.9235118 | 0.605508752 | 0.003506183 |
| GPATCH11 | 833.5341099 | 1268.294115 | 0.605250914 | 0.000153794 |
| PSMC5 | 2800.927587 | 4260.193983 | 0.605079437 | 8.03E-05 |
| IQGAP3 | 3162.418077 | 4809.073626 | 0.604646717 | 0.000759112 |
| BARD1 | 1219.47447 | 1854.269483 | 0.604510307 | 0.000128142 |
| RECQL4 | 2583.463738 | 3926.683699 | 0.604174404 | 0.003678802 |
| RFC4 | 1514.528351 | 2301.477406 | 0.604059029 | 0.001333197 |
| FKBP5 | 1589.413903 | 2415.093298 | 0.604004816 | 0.009192435 |
| RPF2 | 1234.452494 | 1875.780156 | 0.603629173 | 7.69E-05 |
| BX255925.3 | 782.7475776 | 1188.722251 | 0.603317104 | 8.39E-06 |
| IRS2 | 518.6518887 | 788.3349633 | 0.603225817 | 0.000257244 |
| MEA1 | 1168.077919 | 1773.204578 | 0.602843567 | 0.000886704 |
| RAB27A | 387.6400614 | 588.095971 | 0.602424754 | 0.000440252 |
| LTB4R2 | 214.0756203 | 324.8055223 | 0.602078523 | 0.003984282 |
| POLR3C | 990.8357025 | 1504.500338 | 0.601745986 | $1.30 \mathrm{E}-05$ |
| CLCN4 | 380.8419732 | 578.5230059 | 0.601366043 | 0.00010741 |
| ITGAE | 287.024554 | 434.5157696 | 0.601090233 | 0.00753634 |
| DPF2 | 1822.790124 | 2763.875143 | 0.600155329 | $1.54 \mathrm{E}-07$ |
| NIP7 | 1273.304501 | 1929.302546 | 0.599730522 | $6.09 \mathrm{E}-05$ |
| ATP6V1A | 3209.477096 | 4859.852505 | 0.598736933 | $1.54 \mathrm{E}-06$ |
| RPUSD1 | 1034.158281 | 1565.054514 | 0.598307381 | $8.00 \mathrm{E}-05$ |
| PXMP4 | 143.2311861 | 216.6217614 | 0.598177635 | 0.015415243 |
| NSL1 | 834.6077601 | 1263.560674 | 0.598059866 | 0.000244726 |
| IFFO2 | 626.0855228 | 946.959401 | 0.597990939 | 0.00022422 |
| RNFT1 | 323.5541803 | 489.9441676 | 0.597677052 | 0.000217214 |
| CKAP2 | 3668.819601 | 5552.329801 | 0.597659009 | 0.000383934 |
| RINT1 | 952.5175153 | 1441.394674 | 0.597528759 | $1.68 \mathrm{E}-05$ |
| KLC3 | 104.8399712 | 158.5861152 | 0.597349172 | 0.046897457 |
| CABP4 | 244.4530974 | 369.8865643 | 0.596960755 | 0.001106301 |
| BMPR1B | 327.5843028 | 495.9049228 | 0.596343898 | 0.000816539 |
| RPRD1B | 1578.198658 | 2385.604591 | 0.596046939 | 4.51E-07 |
| ARPC5L | 1512.232184 | 2283.810911 | 0.595323315 | 0.000522507 |
| NOSIP | 1004.371415 | 1517.016724 | 0.594786054 | $6.47 \mathrm{E}-05$ |
| RMI1 | 1040.19953 | 1569.094708 | 0.59363682 | 0.001488448 |
| ZSWIM9 | 246.5828945 | 371.1753552 | 0.593047252 | 0.002535155 |
| SERPINE2 | 448.3756062 | 676.3221106 | 0.592598247 | 0.004569132 |
| KIF23 | 2678.066039 | 4038.343492 | 0.592480694 | 0.000760627 |
| UTP23 | 545.500675 | 822.5932081 | 0.592424333 | $5.64 \mathrm{E}-05$ |
| ACYP1 | 260.6918398 | 392.2986934 | 0.592357608 | 0.003062212 |
| GEN1 | 1471.921866 | 2218.429502 | 0.591848627 | $9.78 \mathrm{E}-05$ |
| TOE1 | 717.2016639 | 1080.591653 | 0.591319997 | 0.000299376 |
| MRPL37 | 3254.695656 | 4903.464432 | 0.59129514 | $4.31 \mathrm{E}-05$ |
| PHF19 | 2868.628192 | 4321.362266 | 0.591036554 | $5.69 \mathrm{E}-06$ |


| INAVA | 2958.957781 | 4456.323524 | 0.590366282 | 7.23E-05 |
| :---: | :---: | :---: | :---: | :---: |
| PAX9 | 267.4215036 | 402.6360124 | 0.590327848 | 0.00446551 |
| COX19 | 770.7531958 | 1160.404025 | 0.590106315 | $1.38 \mathrm{E}-05$ |
| NCAPD3 | 4441.940491 | 6686.093066 | 0.590068847 | 0.002454193 |
| TMEM14A | 926.2390276 | 1393.184708 | 0.589441002 | 0.000238075 |
| HSPA4L | 793.8498197 | 1193.816165 | 0.588913765 | 0.011483871 |
| TMEM205 | 159.3299519 | 239.4720421 | 0.588647777 | 0.007234511 |
| CCDC137 | 1021.259498 | 1535.084241 | 0.588578051 | 0.000921793 |
| C19orf25 | 1098.196225 | 1650.87995 | 0.588555534 | 0.000282325 |
| RRP36 | 1247.821129 | 1876.0015 | 0.588502792 | 0.000176641 |
| DMXL2 | 2500.408101 | 3758.782742 | 0.588057507 | 0.000498395 |
| LMCD1 | 901.9428127 | 1355.709762 | 0.58805411 | 8.50E-06 |
| KLF10 | 2092.001854 | 3143.991041 | 0.587642719 | $1.20 \mathrm{E}-06$ |
| FAM200B | 479.4011295 | 719.6891603 | 0.586875017 | 0.000130649 |
| POLR2I | 123.7419323 | 185.8112526 | 0.586332452 | 0.011496498 |
| ZNF678 | 637.9669449 | 958.8469732 | 0.586326785 | 0.000218497 |
| ETFRF1 | 229.1939552 | 344.6042357 | 0.586119164 | 0.002598609 |
| WDR92 | 268.5778693 | 403.3459706 | 0.585900474 | 0.003886928 |
| FAM122B | 2272.767457 | 3410.781059 | 0.585705177 | 0.000491305 |
| KIFC3 | 1970.960405 | 2958.078666 | 0.585644918 | 6.99E-06 |
| NAT1 | 387.8683045 | 581.9662917 | 0.585475401 | 0.000583394 |
| ECI2 | 261.7685608 | 392.8457839 | 0.585099262 | 0.004695011 |
| ITGA7 | 128.7978129 | 193.6326897 | 0.585065973 | 0.012309137 |
| NDOR1 | 1342.828216 | 2013.572588 | 0.584894428 | $2.47 \mathrm{E}-05$ |
| SCN8A | 452.8658191 | 679.1838958 | 0.584870509 | 0.000969577 |
| YJEFN3 | 386.0829739 | 579.4657006 | 0.584663949 | 0.000330616 |
| AUP1 | 2681.511511 | 4021.598207 | 0.58440711 | 8.18E-08 |
| QTRT1 | 1263.544964 | 1893.718614 | 0.583841007 | 7.53E-07 |
| ST3GAL2 | 250.4267109 | 374.8013739 | 0.583081008 | 0.002657169 |
| DISC1 | 431.8882302 | 647.5374018 | 0.583016481 | 0.000259257 |
| KIF1C | 5474.74989 | 8200.356006 | 0.582945675 | $6.31 \mathrm{E}-07$ |
| 11-Sep | 6735.89645 | 10087.43243 | 0.582670199 | $4.61 \mathrm{E}-05$ |
| ZBTB40 | 1257.841179 | 1883.96405 | 0.58254877 | $4.38 \mathrm{E}-06$ |
| WNT10A | 212.0780684 | 317.5423317 | 0.582406461 | 0.034646332 |
| TEX30 | 281.4696234 | 421.0692915 | 0.582180858 | 0.018906398 |
| ANKRD44 | 135.1750475 | 202.3207454 | 0.581853978 | 0.01454484 |
| TAOK2 | 2661.481788 | 3982.685093 | 0.581659644 | 5.55E-06 |
| COL7A1 | 505.5031976 | 756.1911119 | 0.581105889 | 0.003170187 |
| CEP78 | 1952.059776 | 2919.550144 | 0.581005839 | 0.00075876 |
| WDR31 | 211.1632558 | 316.4310788 | 0.580453296 | 0.01957503 |
| MEIS2 | 178.783925 | 267.755911 | 0.579583395 | 0.008359071 |
| MSH6 | 847.2205907 | 1266.231382 | 0.579415099 | $1.68 \mathrm{E}-05$ |
| HRAS | 1593.144593 | 2379.287259 | 0.579140586 | 0.000405243 |
| PDLIM2 | 395.6657419 | 590.7970241 | 0.579137724 | 0.000151817 |
| RRS1 | 924.8343021 | 1380.645438 | 0.57864951 | 0.007128476 |
| ZC3H8 | 637.2684206 | 950.941177 | 0.57742373 | 7.24E-05 |
| POP7 | 751.8461173 | 1121.183405 | 0.5772791 | 0.006653714 |
| GON7 | 196.1814896 | 292.3638451 | 0.576171767 | 0.041234294 |
| BTC | 437.4446689 | 652.8565168 | 0.575955651 | 0.016246798 |
| SLF2 | 1531.049698 | 2281.397552 | 0.575577591 | 1.92E-06 |
| FBXO9 | 1853.886239 | 2762.765409 | 0.575566993 | 1.55E-06 |
| FANCD2 | 2187.409707 | 3258.879416 | 0.57536447 | 0.000486608 |
| MICALL2 | 1549.955476 | 2309.411074 | 0.575163025 | $6.97 \mathrm{E}-07$ |
| FGFR4 | 176.0646012 | 262.1868584 | 0.574925116 | 0.015639067 |
| PRIM2 | 755.6034973 | 1125.238037 | 0.574741172 | 0.001152992 |
| MKRN3 | 162.897055 | 242.7078109 | 0.574714854 | 0.005176117 |
| MRPS6 | 625.8997437 | 932.1413533 | 0.574446258 | 0.002051284 |
| CAP2 | 419.6172494 | 625.1911711 | 0.574376473 | 0.000167688 |
| MPP1 | 520.6617362 | 774.7123705 | 0.57434812 | 0.00431695 |
| C1orf109 | 920.5114557 | 1369.821944 | 0.573620611 | $1.49 \mathrm{E}-05$ |
| TYW1B | 177.0797171 | 263.4163267 | 0.57308663 | 0.023505634 |


| ADSSL1 | 209.9156188 | 312.2027446 | 0.57267451 | 0.027055726 |
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| BRPF3 | 1796.420121 | 2670.051765 | 0.571356125 | 0.000665567 |
| RFC5 | 1667.268742 | 2475.799689 | 0.570682501 | 0.005109598 |
| TELO2 | 2233.482795 | 3316.102078 | 0.570527075 | 0.000508835 |
| ASB9 | 189.4501488 | 281.6448929 | 0.570342014 | 0.007711359 |
| PLEKHA4 | 237.5269789 | 352.6839939 | 0.570245733 | 0.025847166 |
| CASP8AP2 | 1109.418468 | 1646.49899 | 0.570211281 | 0.000674654 |
| TLN2 | 713.3263 | 1058.977416 | 0.570094449 | 0.014819727 |
| TAF3 | 608.3233635 | 903.4569722 | 0.570054526 | 0.00209285 |
| LIN9 | 580.020313 | 861.2000622 | 0.570013643 | 0.000969799 |
| TEFM | 234.5713135 | 348.2269467 | 0.569248599 | 0.002326366 |
| MED26 | 166.563007 | 246.7042013 | 0.568934279 | 0.007846706 |
| UNC119B | 2059.208528 | 3052.112726 | 0.568158878 | $3.30 \mathrm{E}-06$ |
| ATP6V0B | 2002.056484 | 2966.121021 | 0.567592108 | 8.87E-05 |
| APOPT1 | 235.5494655 | 349.10642 | 0.567028798 | 0.005910148 |
| SEC61A2 | 462.4544639 | 684.9465985 | 0.566450796 | 0.000198092 |
| CTPS1 | 2828.549406 | 4182.729557 | 0.564685975 | 0.001374126 |
| LTO1 | 792.1541943 | 1171.680224 | 0.564443188 | $1.32 \mathrm{E}-05$ |
| PQBP1 | 1346.84645 | 1990.745167 | 0.564209515 | $1.64 \mathrm{E}-05$ |
| SMAP2 | 400.9888561 | 592.6890343 | 0.564053492 | 0.006690987 |
| ZNF142 | 1340.372477 | 1981.053857 | 0.563996952 | 0.001072118 |
| NSRP1 | 1103.906938 | 1632.448258 | 0.56390739 | 0.000176641 |
| NCOA5 | 949.379337 | 1403.34151 | 0.562958891 | 0.000551049 |
| DHRS7B | 387.4099696 | 572.5122207 | 0.562911115 | 0.000371653 |
| LCMT2 | 650.9093971 | 961.0991397 | 0.562716086 | 0.002463389 |
| POLR3F | 435.1013686 | 642.0052936 | 0.56264225 | 0.000777328 |
| ODF2L | 854.8227656 | 1262.453325 | 0.562223852 | 3.89E-06 |
| OIP5 | 379.9502067 | 560.5456205 | 0.561456017 | 0.002132956 |
| MAP3K13 | 892.6421078 | 1317.591159 | 0.561054868 | 2.43E-05 |
| BCORL1 | 484.1969573 | 714.0217603 | 0.561025305 | 0.004592291 |
| ZNF17 | 138.2206838 | 204.5542029 | 0.560880354 | 0.025632262 |
| TRIM26 | 2213.936422 | 3265.778751 | 0.560838281 | 9.44E-05 |
| CARNS1 | 92.28470553 | 135.7930286 | 0.560442625 | 0.047020246 |
| UBXN2A | 855.4286187 | 1260.681404 | 0.560310041 | 0.000121623 |
| NUFIP1 | 390.5258515 | 575.3370815 | 0.559910925 | 0.001874263 |
| MRPS18C | 528.2650972 | 778.7591512 | 0.559553788 | 0.001731062 |
| ZNF174 | 391.588483 | 577.3285818 | 0.559500354 | 0.00025637 |
| LRRC37A | 144.8794306 | 213.0291119 | 0.558548866 | 0.017929111 |
| SYF2 | 1286.480094 | 874.0291541 | -0.558312725 | 0.001868987 |
| YPEL5 | 1246.10261 | 845.9292375 | -0.55879112 | 0.017629062 |
| PARM1 | 7002.293712 | 4753.047056 | -0.558994617 | 0.000347631 |
| FBXW4 | 1146.532641 | 778.5383024 | -0.559315599 | 0.000160496 |
| RGL2 | 2360.521494 | 1601.973716 | -0.559474923 | 0.002679373 |
| RNF141 | 1504.706774 | 1020.63124 | -0.559777985 | $4.07 \mathrm{E}-05$ |
| TMEM214 | 3470.929757 | 2354.959553 | -0.559961187 | 7.53E-07 |
| ALDH2 | 4258.973343 | 2888.492609 | -0.560024274 | 0.00055532 |
| CHMP4C | 787.7996404 | 534.6272943 | -0.560069575 | 0.002851003 |
| TMEM183A | 1637.901082 | 1110.432088 | -0.560278992 | 3.35E-05 |
| SIDT1 | 211.387477 | 143.2410539 | -0.560377302 | 0.020252517 |
| DERA | 1231.531146 | 835.2010137 | -0.560579622 | 2.73E-05 |
| ZBTB7C | 1260.084064 | 854.5381134 | -0.560648012 | 0.017491055 |
| RBM12 | 3307.295068 | 2241.222058 | -0.561054919 | 9.35E-05 |
| PIM1 | 1835.95624 | 1244.097807 | -0.561473094 | 0.000105953 |
| ZCRB1 | 1388.025979 | 940.0713424 | -0.561780764 | 0.000101789 |
| DARS | 3927.539423 | 2660.088656 | -0.562347233 | 8.13E-07 |
| TRDMT1 | 294.6105892 | 199.269769 | -0.562757517 | 0.004355645 |
| TMEM41B | 4396.802354 | 2975.233932 | -0.563191217 | 0.000491305 |
| PLEKHB2 | 6693.006817 | 4529.085443 | -0.563307451 | $1.41 \mathrm{E}-07$ |
| RNF13 | 1234.94639 | 836.1573134 | -0.563384452 | 0.000530074 |
| HAX1 | 2546.612355 | 1721.891285 | -0.564542265 | 4.01E-05 |
| AGA | 292.8643896 | 197.6588181 | -0.564809739 | 0.022667935 |


| VILL | 1970.930087 | 1332.139075 | -0.565135348 | 0.00720866 |
| :---: | :---: | :---: | :---: | :---: |
| RACK1 | 38693.03874 | 26149.30962 | -0.56532106 | 3.61E-08 |
| MAPK3 | 2819.704439 | 1905.377963 | -0.565337745 | 0.000443445 |
| WDSUB1 | 400.5386161 | 270.5412644 | -0.565825685 | 0.003755874 |
| PRDX1 | 11421.72633 | 7715.734622 | -0.565854241 | 0.000285664 |
| NIPSNAP3A | 795.6354329 | 537.9207077 | -0.565941274 | 8.61E-05 |
| DDOST | 8847.224705 | 5975.104928 | -0.566246347 | $2.48 \mathrm{E}-08$ |
| BRD3 | 1587.631289 | 1072.104208 | -0.566292474 | 3.32E-06 |
| BCLAF3 | 1004.434046 | 678.2563377 | -0.566459777 | 0.000963175 |
| PGK1 | 15184.68877 | 10250.17138 | -0.566894679 | $6.65 \mathrm{E}-08$ |
| TCF25 | 3989.202332 | 2692.752937 | -0.566932405 | 1.19E-06 |
| BRI3 | 1784.1815 | 1204.448681 | -0.566967643 | 0.002378139 |
| TXNDC15 | 653.904594 | 441.8747371 | -0.567122298 | 0.000151933 |
| ADAM10 | 8574.272992 | 5787.059642 | -0.567212971 | $1.80 \mathrm{E}-05$ |
| DOCK6 | 3358.758221 | 2266.035308 | -0.567702565 | 0.000188352 |
| TWF2 | 1214.462279 | 818.0014568 | -0.568653184 | $9.78 \mathrm{E}-05$ |
| ZNF407 | 533.6803372 | 360.5794503 | -0.568662 | 0.001427255 |
| MED28 | 2696.687968 | 1817.680843 | -0.568886834 | 4.82E-07 |
| CTTNBP2 | 323.1290188 | 217.6069375 | -0.568937027 | 0.007621695 |
| PTPN3 | 2384.911128 | 1607.408361 | -0.569003716 | 0.000163631 |
| ATP9A | 3074.594325 | 2071.883847 | -0.569275808 | 0.000232549 |
| FAHD2A | 893.9607974 | 602.3465781 | -0.56990415 | 5.41E-05 |
| KBTBD3 | 136.5772954 | 91.81777694 | -0.56992807 | 0.049729097 |
| GLI4 | 650.9260542 | 438.4045597 | -0.570435221 | 0.000214398 |
| RABGGTA | 875.2401024 | 589.4017434 | -0.570949866 | $6.24 \mathrm{E}-05$ |
| DCPS | 761.4301313 | 512.3429887 | -0.571018113 | 0.000133193 |
| RTEL1 | 131.7327958 | 88.44987784 | -0.571120929 | 0.042230339 |
| PRSS22 | 4001.017975 | 2690.19917 | -0.572341675 | 0.000111691 |
| PEX12 | 256.1451426 | 172.630782 | -0.572850538 | 0.01719239 |
| ABCA2 | 3445.200568 | 2315.842179 | -0.572883255 | $1.76 \mathrm{E}-05$ |
| CDC42EP1 | 1198.814525 | 804.7340991 | -0.574162653 | 0.00447448 |
| TTYH3 | 3798.599439 | 2550.421959 | -0.574304835 | 0.000134862 |
| ENTPD5 | 755.1881377 | 506.873129 | -0.57434504 | 0.000171875 |
| C16orf58 | 1243.039188 | 835.1430297 | -0.574430579 | 0.000110234 |
| NPHP3 | 306.371489 | 205.9582142 | -0.574726479 | 0.003798379 |
| KHNYN | 2793.741511 | 1875.429477 | -0.575159616 | 8.62E-06 |
| GRK2 | 5970.332825 | 4005.025538 | -0.575843418 | 2.13E-08 |
| HDAC5 | 1883.449553 | 1262.945281 | -0.576344027 | 0.000172438 |
| FAM69A | 307.2343424 | 205.9259583 | -0.576359594 | 0.025243224 |
| RNF149 | 1731.349001 | 1160.692201 | -0.576674569 | 6.35E-05 |
| GRB7 | 1223.900861 | 820.4904313 | -0.57668044 | 7.41E-06 |
| GCC2 | 9284.626185 | 6225.233791 | -0.576815532 | $1.85 \mathrm{E}-06$ |
| FARS2 | 154.2228285 | 103.7144687 | -0.576983854 | 0.035955507 |
| RPH3AL | 896.5919109 | 600.9281933 | -0.577199219 | 0.004879959 |
| RFX3 | 342.7241722 | 230.3214029 | -0.57720192 | 0.008242778 |
| ANKEF1 | 594.0962803 | 398.0825734 | -0.577518983 | 0.000190817 |
| PDSS2 | 1011.195553 | 678.0157823 | -0.577656007 | $4.06 \mathrm{E}-05$ |
| RNF139 | 1013.222316 | 678.8993559 | -0.57777676 | 6.58E-05 |
| FKBP7 | 201.7080245 | 134.6193442 | -0.578182481 | 0.043198568 |
| QARS | 7119.548321 | 4767.873753 | -0.578505156 | $3.84 \mathrm{E}-08$ |
| CCDC78 | 790.4714936 | 529.3624023 | -0.57894648 | 0.000318683 |
| ENTPD6 | 3148.404505 | 2107.240678 | -0.579125684 | $7.44 \mathrm{E}-08$ |
| UNC13B | 1954.830074 | 1308.727113 | -0.579358159 | 5.02E-06 |
| FGFR3 | 590.3739611 | 394.7712509 | -0.579718553 | 0.014858911 |
| ANXA9 | 1059.715626 | 708.258323 | -0.580635092 | 0.00031732 |
| SLC50A1 | 1767.741622 | 1181.848834 | -0.580683321 | 0.00046256 |
| MCRIP1 | 489.2175177 | 327.4618995 | -0.58103359 | 0.000859723 |
| HMGCL | 1376.268167 | 920.29986 | -0.581297445 | 0.000170544 |
| NRBP1 | 2887.255236 | 1929.674667 | -0.58152864 | $1.03 \mathrm{E}-07$ |
| LGMN | 2088.461887 | 1395.207447 | -0.581622439 | 0.005388616 |
| NIT2 | 1783.278487 | 1190.77899 | -0.581952756 | $6.01 \mathrm{E}-07$ |


| ZSCAN2 | 204.2569409 | 135.9904211 | -0.58309308 | 0.016543195 |
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| ZNF32 | 439.0741727 | 293.1636407 | -0.583417047 | 0.001008621 |
| CMYA5 | 180.6796382 | 120.6021336 | -0.583449326 | 0.029522861 |
| TGIF1 | 4189.485773 | 2795.119356 | -0.583990446 | $3.29 \mathrm{E}-07$ |
| TNFRSF10B | 6037.278191 | 4026.365018 | -0.584271975 | 5.57E-05 |
| CHP1 | 4568.353909 | 3046.487142 | -0.584630367 | $3.70 \mathrm{E}-06$ |
| MPIG6B | 170.8203643 | 113.9297819 | -0.584802925 | 0.039758079 |
| VPS39 | 2906.895645 | 1938.403275 | -0.584880186 | $2.40 \mathrm{E}-06$ |
| TMCO4 | 1064.506158 | 710.1982983 | -0.584900468 | 0.000440706 |
| XYLT2 | 1160.90832 | 773.4690324 | -0.585282848 | $1.16 \mathrm{E}-05$ |
| GSR | 8135.487951 | 5421.635865 | -0.585466601 | $2.38 \mathrm{E}-07$ |
| ERG28 | 2605.928128 | 1735.825693 | -0.585828949 | $1.92 \mathrm{E}-05$ |
| HELZ2 | 2151.776648 | 1433.235816 | -0.586167258 | $7.88 \mathrm{E}-06$ |
| DENND4C | 5802.868863 | 3864.931898 | -0.58649437 | $3.48 \mathrm{E}-06$ |
| KIAA1147 | 2233.596097 | 1487.462835 | -0.586515696 | 4.57E-07 |
| ESRRA | 2151.067048 | 1431.613264 | -0.586718544 | 3.67E-06 |
| GNPTAB | 1850.167891 | 1232.465573 | -0.586768707 | 6.82E-07 |
| ITFG1 | 1537.600837 | 1023.499173 | -0.587011327 | 6.27E-05 |
| RPL31 | 15448.92349 | 10282.9524 | -0.587176227 | $1.20 \mathrm{E}-06$ |
| SLC2A1 | 13888.63776 | 9244.480595 | -0.587237214 | 0.000362382 |
| RPS8 | 33192.29914 | 22078.38757 | -0.588209817 | 1.23E-07 |
| ABO | 1684.970038 | 1120.424617 | -0.588659554 | 0.000197233 |
| COQ8B | 1240.832287 | 825.0953473 | -0.589089888 | $1.09 \mathrm{E}-05$ |
| FOXK1 | 4389.908522 | 2917.62526 | -0.589179109 | $2.14 \mathrm{E}-07$ |
| KLF11 | 629.9910765 | 418.4643942 | -0.589436293 | 0.005807397 |
| NUDT4 | 6586.878238 | 4376.78623 | -0.589763616 | 3.60E-06 |
| NSDHL | 1054.294789 | 699.5071996 | -0.59018136 | 0.00026137 |
| RPS3A | 20918.95344 | 13892.99351 | -0.590397635 | 1.13E-06 |
| KLF7 | 1245.01348 | 827.3114021 | -0.590868925 | $3.26 \mathrm{E}-05$ |
| GPR157 | 2420.041315 | 1606.299923 | -0.591247391 | $1.00 \mathrm{E}-05$ |
| GPCPD1 | 867.1724874 | 575.5782941 | -0.591453102 | 0.000164833 |
| USO1 | 5371.126633 | 3562.67326 | -0.592412382 | 3.33E-07 |
| TRIM31 | 200.5228506 | 132.7251396 | -0.592581072 | 0.024400043 |
| SCNN1A | 11971.95282 | 7938.238088 | -0.592741472 | 0.000196701 |
| VSIG10L | 365.3011411 | 241.8538375 | -0.592871739 | 0.002682796 |
| CC2D1B | 1465.681787 | 971.3776826 | -0.59294069 | $4.12 \mathrm{E}-05$ |
| ANXA3 | 7345.460452 | 4869.833524 | -0.593109937 | 3.42E-05 |
| ARRDC1 | 2867.937961 | 1900.751512 | -0.593149976 | 2.81E-06 |
| CCPG1 | 235.0909827 | 155.7280652 | -0.593952653 | 0.037210323 |
| KLHL12 | 1768.574584 | 1171.94646 | -0.594091986 | $4.99 \mathrm{E}-06$ |
| SEL1L | 3508.437233 | 2323.921134 | -0.594253095 | $1.57 \mathrm{E}-05$ |
| CD81 | 8422.730714 | 5578.418293 | -0.594297311 | 5.76E-07 |
| RRAGB | 430.18289 | 284.9099915 | -0.59436399 | 0.010037952 |
| PROCR | 770.0845065 | 509.2191327 | -0.595590873 | 0.000589952 |
| FAM171B | 6881.790071 | 4552.476538 | -0.596027017 | $7.00 \mathrm{E}-06$ |
| EDF1 | 4016.228646 | 2654.866905 | -0.596749677 | $1.99 \mathrm{E}-05$ |
| PCMTD1 | 744.1905975 | 492.0827813 | -0.59711205 | 0.001756306 |
| DENND6A | 948.2806057 | 626.5376941 | -0.597197892 | 8.83E-06 |
| LAGE3 | 184.2522687 | 121.3329484 | -0.597655267 | 0.03198985 |
| TRAF1 | 604.8692977 | 399.463282 | -0.598014849 | 0.004927608 |
| SLC25A15 | 579.2662557 | 382.0528682 | -0.598275606 | 0.001000464 |
| SBSPON | 1581.019284 | 1043.836805 | -0.598541055 | 0.000257092 |
| IRF6 | 1926.44108 | 1271.575832 | -0.599215479 | 3.06E-05 |
| TRUB2 | 1612.193289 | 1064.124909 | -0.599784961 | $1.05 \mathrm{E}-05$ |
| HARS2 | 924.169282 | 608.9071072 | -0.600845065 | $1.30 \mathrm{E}-05$ |
| C1orf115 | 579.5898555 | 382.1264952 | -0.600866274 | 0.000639292 |
| SERINC3 | 5843.870063 | 3852.975199 | -0.600996815 | $5.69 \mathrm{E}-06$ |
| BNIP3L | 4071.560888 | 2684.055621 | -0.601104499 | 0.0016715 |
| RAB11FIP4 | 3311.593729 | 2183.174848 | -0.601184154 | 2.85E-07 |
| CTNND1 | 17168.4045 | 11314.52305 | -0.601603752 | 3.32E-07 |
| MAP3K8 | 198.8479446 | 130.9437753 | -0.602097566 | 0.007439889 |


| ZFP36L1 | 6856.289364 | 4513.784157 | -0.603223423 | 2.95E-05 |
| :---: | :---: | :---: | :---: | :---: |
| SULT1C3 | 215.3147586 | 141.6927626 | -0.60405054 | 0.01229108 |
| C12orf66 | 782.6311168 | 514.8784998 | -0.604155289 | 5.77E-05 |
| OVOL1 | 521.5660296 | 342.4363107 | -0.604649971 | 0.002135175 |
| NFE2L1 | 6297.637171 | 4141.551626 | -0.604717943 | 1.82E-06 |
| KLF3 | 3061.819242 | 2013.131031 | -0.604819643 | 2.97E-05 |
| MAP4 | 13123.87136 | 8623.834603 | -0.605821479 | 9.64E-09 |
| TMEM179B | 479.7333187 | 315.2802919 | -0.605854404 | 0.000484278 |
| TRIM27 | 3671.364124 | 2411.951978 | -0.606169355 | $1.97 \mathrm{E}-08$ |
| ALG6 | 411.7369822 | 271.0123083 | -0.606482848 | 0.000629831 |
| RPS18 | 37352.16706 | 24516.42195 | -0.607430219 | 8.90E-09 |
| APEX1 | 6243.288376 | 4097.079085 | -0.607649538 | $1.42 \mathrm{E}-08$ |
| UBE2E2 | 1797.717637 | 1179.721516 | -0.60802107 | $9.51 \mathrm{E}-06$ |
| KLHL9 | 2348.91701 | 1540.378845 | -0.608507477 | 5.55E-07 |
| SLPI | 496.5785309 | 325.5151175 | -0.608975198 | 0.022985867 |
| VPS51 | 2953.295934 | 1935.8265 | -0.609631081 | $2.26 \mathrm{E}-07$ |
| CAMKK2 | 2193.765713 | 1436.80018 | -0.609897967 | 2.04E-07 |
| ZNF581 | 586.355974 | 383.9137302 | -0.610363711 | 0.004398795 |
| IRS1 | 12198.2241 | 7989.41507 | -0.610555112 | 3.52E-06 |
| DENND4A | 679.1939382 | 444.5977996 | -0.610882538 | 0.000139702 |
| EGFL7 | 225.5757177 | 147.8359723 | -0.610911876 | 0.006346161 |
| GPR137B | 440.4033963 | 288.6169605 | -0.611018556 | 0.000340729 |
| BDH2 | 257.8586051 | 168.4968833 | -0.611394909 | 0.021713251 |
| GTF2E2 | 1386.23926 | 907.3111392 | -0.611455724 | 6.13E-06 |
| SLC9A3R2 | 1269.442337 | 830.6074338 | -0.611576384 | 0.000108022 |
| RPS24 | 19864.15508 | 12999.35268 | -0.611767819 | $1.24 \mathrm{E}-06$ |
| HSPA9 | 20388.33162 | 13335.34486 | -0.612493955 | $3.28 \mathrm{E}-10$ |
| CEP250 | 1747.886522 | 1142.674176 | -0.612904366 | 7.24E-08 |
| OAS1 | 1144.858933 | 748.5839083 | -0.61304077 | 0.000288598 |
| SRC | 2044.934021 | 1336.642004 | -0.613330513 | $3.73 \mathrm{E}-05$ |
| FBXL8 | 577.5612076 | 377.3355889 | -0.613671308 | 5.73E-05 |
| 08-Mar | 350.4002416 | 229.0765856 | -0.613790307 | 0.002076514 |
| CEBPG | 2780.970345 | 1817.344431 | -0.613953622 | 1.53E-06 |
| SLC1A1 | 2641.513374 | 1725.661057 | -0.614357474 | $1.52 \mathrm{E}-08$ |
| SLC27A1 | 608.3038002 | 396.896403 | -0.615000421 | 0.004294362 |
| MTMR4 | 3389.011194 | 2212.632224 | -0.615181891 | $1.15 \mathrm{E}-08$ |
| PTPN6 | 1415.52935 | 924.3995731 | -0.615537354 | $1.68 \mathrm{E}-05$ |
| RPL12 | 43695.38068 | 28513.47776 | -0.6158247 | 2.75E-09 |
| LYPD6 | 430.6290296 | 280.6339649 | -0.615857532 | 0.005945397 |
| GMDS | 710.5886386 | 463.4156409 | -0.616158707 | $4.24 \mathrm{E}-05$ |
| HAGHL | 902.9537528 | 588.9415851 | -0.616489653 | 7.48E-06 |
| CIAO3 | 845.9567506 | 551.6173515 | -0.616853328 | $2.54 \mathrm{E}-05$ |
| NBL1 | 3664.49572 | 2388.944904 | -0.616955706 | 2.89E-06 |
| PLD2 | 1008.431167 | 657.0525025 | -0.617645885 | 0.000101738 |
| ENOX2 | 568.3233545 | 370.4631281 | -0.618147099 | 0.000477593 |
| SECISBP2 | 2387.788503 | 1556.446961 | -0.618159288 | 3.03E-06 |
| EIF3F | 7195.001595 | 4688.019349 | -0.618260082 | $1.69 \mathrm{E}-07$ |
| ACPP | 470.445535 | 306.490252 | -0.618755677 | 0.002215951 |
| POF1B | 924.0610251 | 601.713117 | -0.619008504 | 0.000554814 |
| ITGA6 | 12347.51682 | 8039.408039 | -0.619090144 | $1.57 \mathrm{E}-05$ |
| ZNF449 | 339.6958045 | 220.7482707 | -0.619907924 | 0.005641894 |
| GALNT6 | 3674.142027 | 2390.649451 | -0.620382441 | 6.21E-09 |
| TMEM30B | 918.4807451 | 597.6107985 | -0.620504375 | 0.000524026 |
| DNPH1 | 1205.328771 | 783.1199314 | -0.620543399 | 8.76E-05 |
| NBR1 | 4430.128185 | 2881.906358 | -0.620560976 | 9.32E-05 |
| KDM5B | 870.0395395 | 565.5595333 | -0.621004551 | 0.010369875 |
| RNF170 | 1240.935203 | 807.0161872 | -0.621381218 | 8.14E-05 |
| EMP1 | 1230.732764 | 799.8691632 | -0.621381593 | 0.010518107 |
| HTATIP2 | 2438.68966 | 1584.448937 | -0.622110053 | $1.10 \mathrm{E}-07$ |
| RTN4R | 583.7118786 | 379.1089993 | -0.622658757 | $4.38 \mathrm{E}-05$ |
| ZNF524 | 551.7387697 | 358.4683509 | -0.622775453 | 0.000353256 |


| NCSTN | 4230.639513 | 2747.549907 | -0.622852674 | 7.36E-06 |
| :---: | :---: | :---: | :---: | :---: |
| HMGA1 | 27370.35121 | 17767.5679 | -0.623334777 | $1.07 \mathrm{E}-08$ |
| LRRC75A | 965.6115068 | 626.6292008 | -0.623388391 | 0.000212959 |
| CDPF1 | 289.8219086 | 187.9709002 | -0.623643312 | 0.002274093 |
| PHYH | 495.7909271 | 321.2719407 | -0.623781348 | 0.000549909 |
| RTEL1-TNFRSF6B | 250.7830751 | 162.4342817 | -0.624411222 | 0.002348973 |
| ARHGAP32 | 22189.35195 | 14391.33687 | -0.624700286 | 0.000163591 |
| MINK1 | 5852.732884 | 3795.316797 | -0.62476556 | $1.33 \mathrm{E}-08$ |
| TPP1 | 1918.816278 | 1244.656671 | -0.625024955 | $1.24 \mathrm{E}-05$ |
| PTPN18 | 1562.336674 | 1013.321311 | -0.625319984 | 2.52E-07 |
| PFKL | 8188.519862 | 5307.504723 | -0.625482132 | 1.03E-08 |
| SSH1 | 2180.578612 | 1412.950289 | -0.626237837 | 5.87E-06 |
| MBTPS1 | 4573.564334 | 2961.609017 | -0.627057478 | $1.90 \mathrm{E}-08$ |
| PTPRF | 21345.3223 | 13817.74299 | -0.627372494 | 7.51E-06 |
| PALD1 | 4350.125766 | 2813.467121 | -0.628213961 | $6.74 \mathrm{E}-07$ |
| SH3GLB2 | 6515.102514 | 4214.232238 | -0.628428279 | $1.51 \mathrm{E}-05$ |
| STK17B | 3180.539368 | 2057.069377 | -0.628668611 | 4.22E-06 |
| NAV2 | 203.5886186 | 131.443558 | -0.62873395 | 0.010988748 |
| CETN3 | 929.4339549 | 600.9468499 | -0.628793718 | 4.16E-05 |
| LTBP4 | 1119.179735 | 723.3814194 | -0.62905338 | 0.000573772 |
| IDI1 | 3585.044161 | 2316.378015 | -0.629425723 | 0.000215309 |
| ITGA9 | 447.9435412 | 289.1116916 | -0.629762056 | 0.01757602 |
| HECA | 919.4543481 | 593.9898342 | -0.629772016 | $4.10 \mathrm{E}-05$ |
| PGAP3 | 1354.939344 | 875.8482425 | -0.629895924 | $2.89 \mathrm{E}-05$ |
| ALCAM | 3616.209445 | 2336.474057 | -0.630001531 | $1.79 \mathrm{E}-05$ |
| BRWD3 | 1751.364105 | 1131.073259 | -0.630166411 | 7.54E-07 |
| ZNF160 | 797.8156447 | 516.0158704 | -0.630445545 | 0.000259474 |
| LRP5 | 6164.964725 | 3981.227267 | -0.630951821 | 6.97E-06 |
| CDK2AP2 | 1762.437286 | 1138.469351 | -0.631083488 | $6.78 \mathrm{E}-06$ |
| TOMM20 | 7087.714037 | 4574.731211 | -0.631473032 | $8.30 \mathrm{E}-08$ |
| ACOT11 | 836.4090433 | 539.528592 | -0.632076472 | 0.001569855 |
| DDX60L | 521.8335967 | 336.8563115 | -0.63233214 | 0.00211461 |
| HIBADH | 2286.202313 | 1474.501058 | -0.632663713 | 6.06E-06 |
| MAP1LC3A | 255.2774604 | 164.6390851 | -0.63306416 | 0.008953571 |
| KRT18 | 66763.92136 | 43043.82415 | -0.633268363 | $2.21 \mathrm{E}-09$ |
| FRK | 1200.616135 | 773.490138 | -0.633953878 | 5.79E-07 |
| SRPK3 | 247.5693226 | 159.5958187 | -0.63416852 | 0.004924233 |
| MT-ND3 | 20720.11552 | 13348.3014 | -0.634285747 | 5.19E-08 |
| ARHGAP27 | 6314.596909 | 4067.905602 | -0.634370532 | 4.67E-08 |
| SSR2 | 2996.442515 | 1930.092023 | -0.634578436 | $1.14 \mathrm{E}-07$ |
| DPH5 | 763.2046542 | 491.8430874 | -0.6346311 | $2.30 \mathrm{E}-05$ |
| LMTK3 | 505.1506089 | 325.1271364 | -0.634709716 | 0.003588756 |
| TRIQK | 418.3727464 | 269.4574834 | -0.634791539 | 0.002061517 |
| SUPT3H | 260.504784 | 167.8548587 | -0.635829175 | 0.003345251 |
| EFNB1 | 330.770632 | 212.4266399 | -0.636862063 | 0.000808401 |
| KRCC1 | 406.619448 | 262.1127357 | -0.636866347 | 0.016048039 |
| AGR2 | 14166.29978 | 9110.381287 | -0.636873967 | 5.59E-05 |
| PDIA3 | 14038.73902 | 9028.333758 | -0.636936458 | 2.25E-09 |
| FGGY | 273.6023134 | 175.9719989 | -0.637072614 | 0.011736968 |
| MTHFR | 1163.967795 | 748.3035569 | -0.63728878 | 8.52E-05 |
| FAM114A2 | 553.2254101 | 355.6005314 | -0.637596562 | 3.42E-05 |
| NR1D1 | 1797.408515 | 1155.317929 | -0.637765408 | 0.000136279 |
| PROM2 | 352.8286268 | 226.659155 | -0.638460048 | 0.037549307 |
| RHOQ | 1038.082308 | 666.9898388 | -0.638549362 | $1.51 \mathrm{E}-05$ |
| ZFP36 | 2617.691177 | 1680.862039 | -0.638724636 | $4.30 \mathrm{E}-05$ |
| PDIA5 | 707.2875855 | 453.6695294 | -0.639838313 | $5.38 \mathrm{E}-05$ |
| RPL5 | 30400.58798 | 19507.86297 | -0.640048008 | 3.81E-09 |
| SNUPN | 347.4096746 | 222.8505676 | -0.64027849 | 0.003635139 |
| CETN2 | 682.8587164 | 437.9391585 | -0.640519275 | 0.000440706 |
| NKD2 | 462.6316236 | 296.0069752 | -0.641015848 | 0.004349896 |
| MBNL2 | 2439.437488 | 1564.512493 | -0.641056984 | 0.000728556 |


| HOXB13 | 323.0445058 | 206.6131359 | -0.641712043 | 0.003180242 |
| :---: | :---: | :---: | :---: | :---: |
| GATD3B | 352.8792256 | 225.5211087 | -0.641886724 | 0.00123582 |
| NT5M | 119.6996621 | 76.77209226 | -0.641925727 | 0.033759629 |
| VDAC1 | 12795.54239 | 8195.408178 | -0.642721402 | $1.10 \mathrm{E}-08$ |
| CMTR2 | 1560.201819 | 999.2636784 | -0.643056235 | $9.50 \mathrm{E}-08$ |
| PTGR2 | 205.4879235 | 131.7605496 | -0.643548391 | 0.004898875 |
| PIGU | 867.1308819 | 555.1094271 | -0.643944549 | 7.67E-05 |
| RNF44 | 2369.413133 | 1516.557595 | -0.644225625 | 4.62E-07 |
| VGLL4 | 1125.426224 | 720.1502811 | -0.644615223 | 3.72E-06 |
| LRP8 | 2841.047528 | 1815.694745 | -0.645248786 | $1.87 \mathrm{E}-05$ |
| HNRNPA1 | 48025.80432 | 30695.24385 | -0.645802744 | $1.74 \mathrm{E}-08$ |
| VIPAS39 | 628.0934037 | 401.4408832 | -0.646076279 | $1.34 \mathrm{E}-05$ |
| G6PD | 9319.103793 | 5954.593371 | -0.646139266 | $1.85 \mathrm{E}-09$ |
| EIF4E2 | 1757.112426 | 1122.529888 | -0.646257681 | 4.13E-06 |
| POLM | 521.9366938 | 333.4333308 | -0.646361678 | $8.74 \mathrm{E}-05$ |
| GCAT | 1006.635841 | 642.6034558 | -0.646829169 | $1.86 \mathrm{E}-05$ |
| GMEB1 | 641.4998661 | 409.458491 | -0.647091071 | 0.002130086 |
| MBTD1 | 1077.179778 | 688.220311 | -0.647468091 | 5.86E-05 |
| LANCL3 | 111.3759802 | 70.7100552 | -0.64782674 | 0.045803745 |
| ICK | 2792.878004 | 1782.489498 | -0.647913047 | $1.19 \mathrm{E}-06$ |
| TMEM101 | 810.8548685 | 517.6220711 | -0.6480465 | 0.000184414 |
| KLC4 | 1072.370457 | 683.5832237 | -0.649209778 | 0.000133567 |
| TLCD1 | 329.2920663 | 209.9609976 | -0.649404689 | 0.000728556 |
| CRAT | 3881.340202 | 2473.782449 | -0.649501836 | $1.76 \mathrm{E}-05$ |
| WDR59 | 1981.415609 | 1263.083155 | -0.649933776 | $2.98 \mathrm{E}-07$ |
| PTPRG | 1982.022564 | 1263.217239 | -0.65034242 | $1.87 \mathrm{E}-06$ |
| SSB | 5470.35981 | 3483.887529 | -0.650900783 | $3.47 \mathrm{E}-07$ |
| RIMS3 | 949.6548011 | 604.0049006 | -0.651018859 | 0.000166129 |
| ARFRP1 | 1361.873495 | 866.2133416 | -0.651606309 | 8.02E-06 |
| ANKH | 693.0556613 | 441.1331536 | -0.651834983 | 5.23E-05 |
| FBXL2 | 296.4749291 | 188.7313683 | -0.652330603 | 0.001480037 |
| GLUD1 | 7263.80345 | 4621.378413 | -0.652375245 | $6.74 \mathrm{E}-07$ |
| COMMD8 | 881.2248042 | 560.3009862 | -0.65314816 | 2.03E-06 |
| SH2B3 | 489.0419384 | 310.8863282 | -0.653202618 | 0.000163207 |
| WDR19 | 423.452853 | 269.2287203 | -0.653333218 | 0.0001144 |
| SNX18 | 506.48399 | 321.7204293 | -0.654173036 | 0.000302702 |
| PLPP6 | 488.4196296 | 310.0477009 | -0.654878376 | $3.21 \mathrm{E}-05$ |
| RASSF3 | 5849.672262 | 3712.368892 | -0.655990982 | $1.20 \mathrm{E}-09$ |
| C17orf113 | 135.0099959 | 85.59019516 | -0.656035494 | 0.030264072 |
| FAR2 | 253.9716954 | 160.9690211 | -0.656211116 | 0.002493719 |
| CCDC191 | 236.7844973 | 150.248802 | -0.656347655 | 0.011052602 |
| GABARAPL1 | 2071.315194 | 1313.478901 | -0.656433261 | $1.65 \mathrm{E}-06$ |
| TPD52L1 | 1738.56654 | 1102.478939 | -0.656528034 | $3.98 \mathrm{E}-06$ |
| RPS4X | 24657.89346 | 15642.75971 | -0.656545436 | $6.57 \mathrm{E}-09$ |
| OGFRL1 | 3047.181206 | 1932.35943 | -0.656854822 | 4.69E-07 |
| MROH1 | 4624.471661 | 2932.232711 | -0.657232167 | 2.13E-07 |
| JMJD8 | 448.641292 | 284.2906786 | -0.657518355 | 0.00041801 |
| RPL15 | 37624.8423 | 23843.18974 | -0.65811201 | $1.06 \mathrm{E}-10$ |
| TCEAL8 | 555.0548758 | 351.4907491 | -0.658374712 | 0.000593458 |
| RPL7 | 36758.77668 | 23288.81837 | -0.658463233 | 9.43E-09 |
| AZIN2 | 95.06079951 | 60.18031345 | -0.658482904 | 0.046446117 |
| ORAI3 | 362.5221839 | 229.2390451 | -0.658783505 | 0.003159975 |
| TBC1D17 | 1301.132275 | 824.3167025 | -0.658975618 | $2.44 \mathrm{E}-05$ |
| PSD3 | 836.2826899 | 529.6639789 | -0.659568851 | 5.52E-06 |
| CDK7 | 1243.056147 | 787.1489435 | -0.659705972 | 6.55E-06 |
| NLRX1 | 876.9025297 | 555.0832643 | -0.660089722 | $1.55 \mathrm{E}-05$ |
| TBC1D14 | 2274.80867 | 1439.492121 | -0.660338455 | 3.93E-08 |
| HK2 | 5259.202025 | 3327.780081 | -0.660342781 | $3.92 \mathrm{E}-10$ |
| ARHGEF2 | 2401.951126 | 1517.483819 | -0.662291936 | 5.02E-05 |
| TOM1L1 | 2025.407569 | 1279.87534 | -0.662515578 | $1.47 \mathrm{E}-06$ |
| SHC1 | 2696.766847 | 1702.526533 | -0.663460345 | 1.49E-07 |


| HSD17B8 | 606.795102 | 382.6146053 | -0.663463386 | $1.46 \mathrm{E}-05$ |
| :---: | :---: | :---: | :---: | :---: |
| ZBTB5 | 1175.101561 | 741.4133671 | -0.66407162 | 7.47E-08 |
| IPP | 863.4075421 | 544.4902352 | -0.664126285 | 6.47E-06 |
| NPM3 | 1412.381945 | 891.0409237 | -0.664332236 | 0.000135552 |
| FDPS | 4352.923612 | 2745.493205 | -0.664439221 | $3.40 \mathrm{E}-07$ |
| 01-Mar | 270.5296091 | 171.0267039 | -0.664556766 | 0.001427255 |
| KATNBL1 | 992.732006 | 626.3618577 | -0.664580236 | $6.35 \mathrm{E}-07$ |
| ATF6B | 2382.495366 | 1503.039024 | -0.665172465 | 1.89E-07 |
| NMRK1 | 1001.825523 | 631.2077316 | -0.666010529 | 9.95E-07 |
| RPS25 | 12885.00104 | 8118.240637 | -0.666385416 | 1.59E-09 |
| KIFAP3 | 216.4135982 | 136.3558073 | -0.66725787 | 0.008066221 |
| CANT1 | 5093.228359 | 3207.136708 | -0.667289113 | $1.64 \mathrm{E}-07$ |
| C15orf61 | 178.6594168 | 112.1860672 | -0.667441606 | 0.006890721 |
| TXNDC12 | 416.6179188 | 261.9989384 | -0.66747042 | 0.000525232 |
| TIAF1 | 285.3867168 | 179.3741287 | -0.667771455 | 0.005242748 |
| SOCS7 | 2988.530521 | 1880.811039 | -0.667851777 | $1.02 \mathrm{E}-06$ |
| NUCB1 | 2734.229994 | 1720.68086 | -0.667874518 | 7.59E-05 |
| RABL2B | 505.7067424 | 318.1634603 | -0.668423622 | 6.19E-05 |
| FERMT1 | 2827.654182 | 1779.867463 | -0.668435161 | 3.48E-06 |
| FAM160B2 | 2240.444437 | 1409.358122 | -0.66903225 | 6.61E-09 |
| ZNF775 | 113.2096095 | 71.10101028 | -0.670297042 | 0.024270672 |
| MICAL2 | 6988.526596 | 4390.897608 | -0.67044009 | 0.000377418 |
| ACTR1B | 1667.237034 | 1046.912797 | -0.670504282 | 6.85E-08 |
| RPS3 | 36211.35746 | 22749.42173 | -0.670579444 | 1.12E-08 |
| SNX33 | 559.9495764 | 351.8556848 | -0.671177999 | 0.000197043 |
| OPN3 | 210.1404753 | 132.1483082 | -0.672406455 | 0.002938282 |
| METRN | 740.9754452 | 464.2487367 | -0.673071653 | 1.05E-05 |
| PIK3C2B | 4644.072631 | 2912.92603 | -0.673104513 | 5.46E-07 |
| KLK1 | 978.5040315 | 613.6440819 | -0.673154175 | 0.001616395 |
| IGSF3 | 2106.937871 | 1320.258321 | -0.674151351 | $2.90 \mathrm{E}-06$ |
| HOXB5 | 914.6126783 | 573.0415189 | -0.674460309 | 0.000331895 |
| LMBRD1 | 1242.121627 | 778.1812545 | -0.674511884 | $1.98 \mathrm{E}-05$ |
| EIF3L | 5850.151761 | 3665.082214 | -0.674802663 | 4.25E-09 |
| TDGF1 | 136.8224279 | 85.51935645 | -0.675002619 | 0.036788513 |
| NFE2L3 | 3706.839471 | 2321.379041 | -0.675159249 | $2.90 \mathrm{E}-07$ |
| ELK3 | 432.1436891 | 270.508261 | -0.675331959 | 0.000378546 |
| FBXO4 | 330.3270518 | 206.4610104 | -0.67697313 | 0.00067803 |
| POLRMT | 3252.108191 | 2032.953169 | -0.678098326 | $8.98 \mathrm{E}-11$ |
| BPHL | 277.6193881 | 173.1582195 | -0.678197395 | 0.001401565 |
| AJM1 | 985.5681725 | 615.7807501 | -0.678857912 | 4.57E-05 |
| CLIC1 | 12610.73277 | 7876.399401 | -0.679000745 | 5.01E-10 |
| SPTLC2 | 3507.331922 | 2190.69398 | -0.679045948 | 1.09E-07 |
| BBS2 | 1219.559114 | 761.6117341 | -0.679220678 | 0.0001653 |
| ICA1 | 1464.67097 | 914.2229697 | -0.679494417 | $1.90 \mathrm{E}-05$ |
| EPM2A | 296.2592068 | 185.2116407 | -0.679523513 | 0.002950391 |
| EPHX2 | 526.00888 | 328.508929 | -0.679628761 | 0.000755655 |
| PPP1R12B | 1856.932974 | 1159.697645 | -0.679742788 | 9.21E-05 |
| RAB43 | 172.9123668 | 107.8675168 | -0.679771509 | 0.020078356 |
| PRKCQ | 88.52349004 | 55.38045399 | -0.680287041 | 0.04873704 |
| VCP | 15161.49427 | 9461.001368 | -0.680336747 | $2.41 \mathrm{E}-07$ |
| AXIN2 | 16879.37989 | 10531.44436 | -0.680636401 | $1.90 \mathrm{E}-07$ |
| MCTP2 | 976.7888893 | 608.7643459 | -0.682758048 | 3.42E-05 |
| NAIF1 | 350.4847722 | 218.7425614 | -0.682942273 | 0.001787897 |
| GLT8D1 | 1492.192528 | 929.2084309 | -0.683380037 | 7.49E-09 |
| PUDP | 602.1826421 | 375.2406841 | -0.684142539 | 4.92E-05 |
| RXRB | 2209.600461 | 1374.081074 | -0.685507969 | $1.67 \mathrm{E}-08$ |
| RIMKLA | 534.9178134 | 332.2893421 | -0.685553635 | 0.000163631 |
| AKAP7 | 163.7002989 | 101.586009 | -0.686505845 | 0.023351896 |
| HAUS4 | 567.5106211 | 353.2342679 | -0.686736686 | $4.33 \mathrm{E}-05$ |
| TRAPPC9 | 999.7278281 | 620.5281333 | -0.6884008 | 1.85E-06 |
| DRAM2 | 1410.791132 | 875.8602092 | -0.688552688 | $3.34 \mathrm{E}-07$ |


| ADAP1 | 790.0416415 | 489.3366836 | -0.689201569 | 0.000108107 |
| :---: | :---: | :---: | :---: | :---: |
| RHOV | 684.4732631 | 424.0821836 | -0.689927221 | 8.62E-05 |
| KREMEN1 | 3427.767107 | 2124.307818 | -0.68993138 | $2.20 \mathrm{E}-06$ |
| MACROD1 | 806.6295496 | 499.8001482 | -0.690273588 | 8.03E-06 |
| SHANK2 | 360.1386051 | 223.3813422 | -0.690493613 | 0.000180667 |
| ARHGEF10L | 1307.152339 | 809.5515284 | -0.69080199 | $5.64 \mathrm{E}-05$ |
| VMP1 | 7215.991464 | 4470.253688 | -0.690815137 | $1.07 \mathrm{E}-05$ |
| ATXN3 | 1100.964052 | 681.9846799 | -0.690880701 | 1.72E-06 |
| PNPLA7 | 310.5112743 | 192.4389707 | -0.691055338 | 0.014406427 |
| SLC35B2 | 2637.268833 | 1633.195689 | -0.691133905 | $6.65 \mathrm{E}-09$ |
| HMGCR | 8315.639418 | 5148.434949 | -0.691415904 | $3.51 \mathrm{E}-06$ |
| KLHL36 | 2302.885545 | 1425.363424 | -0.691705324 | 3.54E-09 |
| ARL2 | 957.8427606 | 592.3560209 | -0.692922402 | $3.49 \mathrm{E}-06$ |
| ALDH9A1 | 2256.288139 | 1395.607589 | -0.693216216 | $1.05 \mathrm{E}-09$ |
| PTPRB | 418.7725981 | 258.9945676 | -0.693420572 | 0.000186496 |
| CCDC7 | 104.7472216 | 64.90167445 | -0.693599014 | 0.028387621 |
| ARSE | 136.8621644 | 84.43947708 | -0.695087903 | 0.011717727 |
| GALE | 3829.130253 | 2363.36353 | -0.69602562 | $3.77 \mathrm{E}-10$ |
| ANKZF1 | 1915.722514 | 1182.802257 | -0.696200972 | 1.33E-06 |
| KDELR1 | 8140.946953 | 5023.811127 | -0.696309203 | $4.42 \mathrm{E}-10$ |
| USPL1 | 472.8621702 | 291.6872296 | -0.696683639 | $5.90 \mathrm{E}-05$ |
| P4HB | 15724.82125 | 9701.628188 | -0.696802504 | 9.22E-12 |
| PHPT1 | 1823.105641 | 1124.731861 | -0.697252271 | $3.49 \mathrm{E}-08$ |
| SP100 | 1487.872397 | 917.7993987 | -0.697573063 | 2.33E-05 |
| ASMTL | 1524.138364 | 939.2783536 | -0.697766853 | $2.26 \mathrm{E}-07$ |
| SCRN2 | 920.156663 | 566.5747417 | -0.698142668 | $1.68 \mathrm{E}-05$ |
| DYNC2LI1 | 606.2680233 | 373.8041198 | -0.698162192 | $4.90 \mathrm{E}-05$ |
| WHRN | 387.4412882 | 238.5706046 | -0.69848746 | 0.004504049 |
| ATF3 | 611.2861877 | 375.8870579 | -0.699442982 | $5.00 \mathrm{E}-06$ |
| CD99L2 | 1143.545051 | 704.0586214 | -0.699730176 | 1.92E-07 |
| IKZF2 | 319.2080442 | 196.2369694 | -0.700266197 | 0.003338488 |
| MISP | 7357.246655 | 4527.833504 | -0.700421046 | 8.45E-10 |
| EIF3E | 13429.86334 | 8262.420954 | -0.70090789 | $6.71 \mathrm{E}-09$ |
| ACSL4 | 1482.148062 | 911.1798626 | -0.701212109 | $1.35 \mathrm{E}-08$ |
| CEBPA | 239.4361403 | 146.8600914 | -0.701418496 | 0.009535079 |
| EEF2 | 118619.2331 | 72928.25806 | -0.701800977 | $7.20 \mathrm{E}-10$ |
| ANO7 | 174.4190421 | 107.0660914 | -0.70233663 | 0.003558165 |
| EFCAB14 | 8436.122764 | 5184.207037 | -0.70255421 | $1.16 \mathrm{E}-08$ |
| SIL1 | 835.6187539 | 513.2228013 | -0.702606806 | 3.04E-06 |
| IGF1R | 1178.094771 | 723.7381438 | -0.70270791 | 3.84E-06 |
| EZH1 | 738.1364543 | 453.3247294 | -0.703039531 | 7.12E-07 |
| TMEM164 | 806.1923037 | 495.1108602 | -0.703057136 | 4.31E-06 |
| B3GALT6 | 607.8609758 | 373.240636 | -0.703517536 | 6.06E-06 |
| NUAK1 | 864.6813496 | 530.9094002 | -0.703850489 | 0.000346485 |
| FAM219B | 810.8197532 | 496.7669404 | -0.705829551 | 5.00E-06 |
| BCAT2 | 2043.753798 | 1253.130313 | -0.705913064 | $1.56 \mathrm{E}-07$ |
| CEP120 | 1148.302329 | 704.0693269 | -0.705983028 | $1.30 \mathrm{E}-06$ |
| KRT19 | 37851.23351 | 23191.63539 | -0.70675522 | 6.61E-07 |
| G2E3 | 1730.504558 | 1060.202077 | -0.70720432 | $6.40 \mathrm{E}-09$ |
| C6orf120 | 1119.404294 | 684.8956115 | -0.708752156 | 5.39E-08 |
| PPM1L | 518.6912821 | 317.5974851 | -0.708836028 | $6.19 \mathrm{E}-05$ |
| GATAD1 | 2538.505152 | 1552.620591 | -0.70926221 | 0.000133425 |
| CLK2 | 2585.657773 | 1581.296012 | -0.70960481 | 2.26E-09 |
| TRAF3IP2 | 1169.367504 | 715.0266713 | -0.709916628 | 3.97E-05 |
| SIRT5 | 598.6856036 | 366.1263293 | -0.710080638 | 0.001238027 |
| RNF187 | 4084.764107 | 2494.998931 | -0.711161623 | $5.38 \mathrm{E}-06$ |
| STAT5A | 226.1547975 | 138.0542521 | -0.712806436 | 0.014170726 |
| ZNF862 | 711.3149259 | 434.3757542 | -0.713515759 | 0.000508477 |
| SLC38A1 | 12463.16503 | 7600.300827 | -0.713584178 | $5.64 \mathrm{E}-11$ |
| ERLEC1 | 2377.96989 | 1450.306622 | -0.713905964 | 6.45E-06 |
| TMX4 | 3095.481787 | 1885.971153 | -0.71472013 | 1.27E-08 |


| PACS2 | 1763.93355 | 1073.961687 | -0.71579839 | 4.61E-06 |
| :---: | :---: | :---: | :---: | :---: |
| PDIA6 | 8397.497988 | 5112.530902 | -0.715802545 | $3.14 \mathrm{E}-11$ |
| ZDHHC24 | 736.2180595 | 448.3002308 | -0.716268106 | 5.40E-07 |
| ZNF784 | 229.1936632 | 139.4627957 | -0.716269663 | 0.001787563 |
| NEIL2 | 551.0051336 | 334.8102518 | -0.716679093 | 0.002404867 |
| CARF | 482.808675 | 293.6378545 | -0.716833908 | 0.002364879 |
| SERGEF | 272.9858965 | 166.2506694 | -0.717295036 | 0.000982322 |
| HNRNPA1P48 | 241.9664998 | 147.287318 | -0.717380975 | 0.001667208 |
| THEM4 | 669.6535648 | 406.835189 | -0.71786036 | $1.08 \mathrm{E}-06$ |
| C2orf68 | 1169.522765 | 711.0025865 | -0.718756535 | $1.26 \mathrm{E}-07$ |
| PEPD | 1066.765018 | 647.6469373 | -0.719694703 | $2.40 \mathrm{E}-07$ |
| PAN2 | 2273.459227 | 1380.361315 | -0.720218157 | $1.96 \mathrm{E}-05$ |
| MANSC1 | 1087.590194 | 660.062813 | -0.721417038 | 4.32E-07 |
| CRYZ | 4220.982144 | 2558.502009 | -0.722024699 | 3.59E-10 |
| GNPAT | 1363.9471 | 826.6927383 | -0.722412859 | $1.43 \mathrm{E}-07$ |
| TMEM17 | 166.8117251 | 101.0107414 | -0.722618297 | 0.007919428 |
| APOBEC3F | 951.2548762 | 576.4469536 | -0.72341019 | $2.55 \mathrm{E}-05$ |
| TMC4 | 2416.065264 | 1463.285693 | -0.723647694 | 0.001059265 |
| CTIF | 1448.21105 | 876.2978364 | -0.723679502 | 4.49E-05 |
| ATPAF1 | 3525.614628 | 2133.888984 | -0.724567495 | $1.96 \mathrm{E}-09$ |
| CCDC159 | 122.794491 | 74.14344167 | -0.725023699 | 0.032496897 |
| TIGD6 | 120.1985465 | 72.85565006 | -0.725128806 | 0.014452457 |
| MLYCD | 551.8968218 | 333.9915745 | -0.725510517 | 3.04E-06 |
| NLN | 2695.502337 | 1630.046137 | -0.725697797 | 1.92E-09 |
| SBF2 | 3479.093119 | 2103.825251 | -0.725839923 | $4.54 \mathrm{E}-06$ |
| WARS | 3918.013545 | 2368.368251 | -0.726669212 | $1.15 \mathrm{E}-08$ |
| ANP32B | 8998.207676 | 5436.423166 | -0.727036517 | $5.80 \mathrm{E}-12$ |
| CRELD1 | 1099.966885 | 664.4575958 | -0.727143868 | $6.49 \mathrm{E}-07$ |
| FOXQ1 | 8134.745408 | 4914.364606 | -0.727189319 | 2.89E-05 |
| RPL7A | 36709.14764 | 22140.827 | -0.72942722 | $4.84 \mathrm{E}-11$ |
| LZTS2 | 2344.353588 | 1413.357022 | -0.729564706 | 2.79E-07 |
| PLA2G4F | 213.2490445 | 128.6629648 | -0.730284725 | 0.002929892 |
| CTSC | 348.9562343 | 210.1067301 | -0.731370312 | 0.001059337 |
| SNAI1 | 95.8337331 | 57.55329554 | -0.731532623 | 0.026874609 |
| CRELD2 | 1631.210329 | 981.7708674 | -0.731816273 | 4.43E-09 |
| PRKX | 444.5214335 | 268.0820839 | -0.732646563 | $2.04 \mathrm{E}-05$ |
| PDK1 | 1173.846108 | 706.1587692 | -0.732799758 | $9.35 \mathrm{E}-06$ |
| MPI | 1289.469129 | 775.8943057 | -0.732957826 | $1.85 \mathrm{E}-09$ |
| RPL29 | 26353.36743 | 15853.99179 | -0.733135124 | $1.45 \mathrm{E}-11$ |
| CALCOCO2 | 3235.787407 | 1945.97382 | -0.733692299 | 5.87E-06 |
| SEC23A | 3480.136854 | 2093.009867 | -0.733845804 | 2.43E-11 |
| CFAP97 | 4544.069209 | 2732.137948 | -0.733941583 | $1.33 \mathrm{E}-08$ |
| GPX8 | 988.7354573 | 593.684881 | -0.735206913 | $9.20 \mathrm{E}-08$ |
| ME2 | 4694.004649 | 2818.588622 | -0.735845607 | $6.68 \mathrm{E}-10$ |
| GTPBP2 | 4173.60124 | 2504.430661 | -0.736846652 | $4.68 \mathrm{E}-05$ |
| ZNF165 | 484.3294795 | 290.7967143 | -0.737281424 | 0.000102763 |
| MED18 | 734.1961073 | 440.0760943 | -0.737748175 | 7.83E-06 |
| FUCA1 | 3590.220033 | 2152.248477 | -0.738032376 | $8.41 \mathrm{E}-10$ |
| PITPNM2 | 820.8443434 | 492.2178377 | -0.738533114 | $4.10 \mathrm{E}-06$ |
| CHMP6 | 366.9316022 | 220.0211718 | -0.739663226 | 3.06E-05 |
| EBLN2 | 101.6498216 | 61.12300809 | -0.73970441 | 0.024101375 |
| G6PC3 | 1851.880608 | 1108.701594 | -0.740413875 | $1.41 \mathrm{E}-07$ |
| CPLANE2 | 146.4651214 | 87.45942203 | -0.740713278 | 0.005282371 |
| TMEM231 | 257.6665367 | 153.8984627 | -0.740817157 | 0.000578419 |
| CADPS2 | 110.2844893 | 66.12345649 | -0.741915047 | 0.018813592 |
| NIPSNAP1 | 3627.005885 | 2168.356501 | -0.741997794 | 1.92E-08 |
| TMEM102 | 485.3037178 | 289.7197345 | -0.742984363 | $1.97 \mathrm{E}-05$ |
| GLB1 | 3227.735989 | 1928.03656 | -0.743394913 | 4.65E-09 |
| TMPRSS13 | 1574.051162 | 940.5421187 | -0.743505818 | $2.77 \mathrm{E}-06$ |
| ATP6V1E2 | 414.1152114 | 247.2294416 | -0.743625306 | $1.78 \mathrm{E}-05$ |
| DNASE1L1 | 468.651585 | 279.5882022 | -0.744642484 | $9.58 \mathrm{E}-05$ |


| ACER2 | 290.3218586 | 173.3168068 | -0.744726445 | 0.00016508 |
| :---: | :---: | :---: | :---: | :---: |
| TSPAN31 | 484.6270348 | 288.730209 | -0.747644615 | 0.000332468 |
| MFSD14A | 79.68695463 | 47.28375937 | -0.747713975 | 0.039888572 |
| HYOU1 | 9516.511357 | 5664.28797 | -0.748542852 | $1.88 \mathrm{E}-11$ |
| EDEM1 | 2925.285508 | 1740.159126 | -0.749431592 | $1.78 \mathrm{E}-10$ |
| EIF2S2 | 8153.624069 | 4844.1191 | -0.751183379 | $1.30 \mathrm{E}-12$ |
| PCP4 | 516.3772114 | 306.5348562 | -0.751227245 | 0.00187934 |
| FASN | 37422.29083 | 22213.26099 | -0.752431149 | $1.47 \mathrm{E}-09$ |
| MTMR10 | 971.4125606 | 577.046412 | -0.752435267 | 6.82E-07 |
| ZNF517 | 212.321786 | 126.2130078 | -0.752529081 | 0.005007701 |
| CLIC4 | 8831.274487 | 5239.468999 | -0.753210994 | 6.39E-07 |
| TMEM42 | 494.9678734 | 293.4141457 | -0.754258964 | $3.16 \mathrm{E}-05$ |
| TJP3 | 2903.445369 | 1719.57979 | -0.755394318 | 1.51E-07 |
| ERCC5 | 219.0064781 | 129.66301 | -0.755840227 | 0.000430382 |
| ALDH3A2 | 6604.873648 | 3909.127084 | -0.756577524 | 5.04E-11 |
| MAFF | 756.57259 | 446.8825218 | -0.756875204 | $2.52 \mathrm{E}-05$ |
| NT5E | 5031.812637 | 2977.293081 | -0.75716296 | 0.000111368 |
| VMAC | 147.7560234 | 87.59615627 | -0.757178013 | 0.006354695 |
| SMIM19 | 554.0790899 | 327.7978576 | -0.757196987 | 0.000102927 |
| STEAP4 | 453.6395111 | 268.3455282 | -0.757789919 | 0.000158089 |
| TNFSF9 | 173.9675923 | 102.3879566 | -0.758088509 | 0.008069004 |
| IGSF8 | 1490.294728 | 880.0905074 | -0.758734782 | $9.08 \mathrm{E}-08$ |
| MYDGF | 2058.917092 | 1215.052566 | -0.76052272 | $1.76 \mathrm{E}-09$ |
| CD9 | 12650.66999 | 7460.230108 | -0.761903203 | 7.47E-08 |
| ERN2 | 3815.969853 | 2249.795222 | -0.762122666 | $2.52 \mathrm{E}-05$ |
| GMPPA | 1492.651092 | 879.7445518 | -0.762251299 | 1.17E-09 |
| MT-ATP8 | 1931.993482 | 1137.795089 | -0.763056883 | 6.96E-09 |
| CPLX1 | 236.6764148 | 139.4428723 | -0.763482692 | 0.000468764 |
| PLEKHH1 | 954.8741433 | 562.5318807 | -0.764085849 | 4.86E-07 |
| VSNL1 | 464.4447031 | 273.2480053 | -0.764189324 | $1.14 \mathrm{E}-05$ |
| SLC38A10 | 4622.207961 | 2719.719229 | -0.765265112 | 3.06E-12 |
| UHRF1BP1 | 3751.103787 | 2207.027467 | -0.765363005 | $4.42 \mathrm{E}-11$ |
| PIKFYVE | 2734.343478 | 1607.556034 | -0.766868139 | 1.25E-11 |
| CFTR | 1102.855897 | 647.6043941 | -0.767741096 | 0.001734412 |
| PTPRU | 3066.670872 | 1800.323234 | -0.767783399 | $2.80 \mathrm{E}-07$ |
| SUMF1 | 475.8424469 | 280.2078358 | -0.767847846 | 0.00015345 |
| FECH | 1817.664485 | 1067.028272 | -0.768512963 | 7.49E-09 |
| BDKRB2 | 560.4310656 | 328.6637344 | -0.768636635 | 0.000722835 |
| TBC1D22A | 965.0135207 | 565.6658244 | -0.769708979 | 7.37E-08 |
| ALKBH7 | 1225.445961 | 717.9502804 | -0.770411879 | 1.72E-09 |
| MED20 | 631.3955407 | 370.1552037 | -0.770648937 | 1.16E-06 |
| PHB2 | 8337.655672 | 4886.701957 | -0.770755178 | 8.39E-11 |
| DCBLD1 | 5359.38658 | 3138.522441 | -0.772083779 | $6.81 \mathrm{E}-08$ |
| ERVW-1 | 160.1142202 | 93.51837666 | -0.773599564 | 0.004484519 |
| WBP2 | 2792.639733 | 1631.895576 | -0.774930763 | 5.07E-09 |
| CLIP2 | 426.0249325 | 248.7167117 | -0.775060358 | 0.013936939 |
| SNX9 | 3852.506339 | 2249.935392 | -0.7758438 | $1.90 \mathrm{E}-10$ |
| MMAB | 911.8800303 | 531.851729 | -0.776051165 | 1.07E-07 |
| CCNG1 | 4566.033524 | 2665.389888 | -0.776355105 | 5.89E-09 |
| ALDH3A1 | 3452.432571 | 2014.889269 | -0.776873413 | $1.75 \mathrm{E}-06$ |
| TKT | 21833.40015 | 12741.78145 | -0.77696453 | $3.45 \mathrm{E}-14$ |
| NARS | 10098.43498 | 5892.042178 | -0.777428021 | $1.73 \mathrm{E}-11$ |
| PPA2 | 3154.046938 | 1839.476376 | -0.777504031 | $1.70 \mathrm{E}-11$ |
| MTIF3 | 967.8974172 | 565.2970431 | -0.777825883 | 4.39E-06 |
| FAM189B | 1372.393397 | 800.2092561 | -0.777905753 | $1.39 \mathrm{E}-10$ |
| KDM7A | 4188.633357 | 2441.359186 | -0.778454225 | $1.71 \mathrm{E}-07$ |
| MDM4 | 1654.456183 | 963.8948198 | -0.779933328 | $1.27 \mathrm{E}-08$ |
| B4GALT5 | 3997.921799 | 2327.111291 | -0.780744488 | $1.39 \mathrm{E}-13$ |
| TRPM4 | 2485.035524 | 1445.969988 | -0.781014381 | $2.46 \mathrm{E}-09$ |
| DNAL4 | 325.9831375 | 189.978608 | -0.781536446 | 0.000175698 |
| ADPRM | 138.9074036 | 80.73228283 | -0.781567117 | 0.008798664 |


| AKR1A1 | 2606.390178 | 1515.48291 | -0.781727495 | $1.14 \mathrm{E}-10$ |
| :---: | :---: | :---: | :---: | :---: |
| SLC30A10 | 826.8906625 | 480.0970447 | -0.783165028 | 0.000106015 |
| ADGRF4 | 758.4217026 | 440.2288532 | -0.784928735 | $4.60 \mathrm{E}-05$ |
| SPR | 1459.404687 | 846.5648478 | -0.785326173 | $2.14 \mathrm{E}-06$ |
| HDHD5 | 1988.759116 | 1153.760033 | -0.785436071 | 2.76E-09 |
| KAZALD1 | 527.2890764 | 305.2820004 | -0.787092711 | 1.32E-06 |
| MUC20 | 626.4557048 | 363.1181286 | -0.787571255 | 0.00486127 |
| ITGB5 | 5973.41266 | 3456.313544 | -0.789231247 | $3.68 \mathrm{E}-10$ |
| ST6GALNAC4 | 122.5533505 | 70.4583257 | -0.789977981 | 0.019150763 |
| SLC6A8 | 246.1393953 | 142.0899276 | -0.790456494 | 0.010347152 |
| MVK | 1022.229662 | 590.1033186 | -0.791062825 | $1.10 \mathrm{E}-05$ |
| STAT6 | 7101.926256 | 4099.844871 | -0.792622247 | $1.38 \mathrm{E}-09$ |
| PRSS23 | 20628.88608 | 11906.25356 | -0.792977121 | $1.69 \mathrm{E}-10$ |
| NECTIN4 | 818.9935114 | 472.4403626 | -0.793171113 | 0.001462287 |
| DGKG | 159.9599076 | 92.37457088 | -0.793196333 | 0.005388616 |
| PRR15 | 1000.562349 | 576.9847968 | -0.793851405 | $4.80 \mathrm{E}-07$ |
| KCTD17 | 758.2874735 | 437.163005 | -0.794176344 | 1.26E-07 |
| RPL4 | 57388.65573 | 33085.8873 | -0.794558971 | 5.32E-12 |
| ALDH5A1 | 1702.858567 | 980.4838204 | -0.796368077 | 7.17E-09 |
| ZNF277 | 1192.918949 | 685.8822797 | -0.798548898 | 8.76E-05 |
| SMPD2 | 328.0603341 | 188.1633523 | -0.799165722 | $6.32 \mathrm{E}-05$ |
| RPL10A | 18005.26187 | 10346.07036 | -0.79938965 | $1.95 \mathrm{E}-13$ |
| TYSND1 | 1934.518431 | 1111.166826 | -0.800205765 | 3.58E-09 |
| TPRG1 | 118.3663954 | 68.04352696 | -0.801252553 | 0.013302563 |
| TARS | 10978.91961 | 6298.419239 | -0.801725061 | $1.71 \mathrm{E}-14$ |
| NTHL1 | 616.3329615 | 353.3161881 | -0.803160569 | $1.18 \mathrm{E}-07$ |
| SNX22 | 76.96387374 | 44.23348531 | -0.804203025 | 0.026875743 |
| FAM234B | 185.7949234 | 106.28808 | -0.804203556 | 0.000391045 |
| KDM1B | 1659.614312 | 950.6617266 | -0.804248099 | $2.04 \mathrm{E}-11$ |
| NT5DC1 | 2073.89698 | 1187.419326 | -0.805306598 | $2.21 \mathrm{E}-11$ |
| P2RX4 | 1368.492069 | 782.7621654 | -0.805582299 | $3.80 \mathrm{E}-08$ |
| MRPL24 | 1453.275617 | 831.7352839 | -0.805601339 | $2.47 \mathrm{E}-10$ |
| BET1 | 679.7552408 | 388.9527162 | -0.806354533 | $1.55 \mathrm{E}-07$ |
| TAZ | 974.6435968 | 556.8221075 | -0.807841002 | $1.40 \mathrm{E}-08$ |
| EXD3 | 252.1417387 | 143.886752 | -0.808812422 | 0.008309114 |
| SMAD6 | 186.8197031 | 106.428053 | -0.809476761 | 0.011444228 |
| CBWD6 | 262.9175716 | 149.8210108 | -0.810234122 | $6.45 \mathrm{E}-05$ |
| DYRK2 | 1181.696219 | 672.7078628 | -0.812200723 | $3.85 \mathrm{E}-11$ |
| HNRNPH2 | 2484.630658 | 1414.525193 | -0.812614765 | 1.18E-07 |
| TESC | 282.1766764 | 160.2730015 | -0.813784453 | 0.000280065 |
| BBS4 | 353.0260028 | 200.5398345 | -0.814231059 | 0.000405135 |
| COG7 | 669.3026137 | 380.6314965 | -0.814784382 | 7.49E-09 |
| C6orf141 | 101.9471243 | 57.5707276 | -0.818236936 | 0.013389617 |
| SLC41A3 | 1485.568712 | 841.9156669 | -0.819404088 | 1.13E-10 |
| IL1R1 | 173.3348428 | 98.06795637 | -0.82083912 | 0.019322937 |
| H1F0 | 5973.692479 | 3379.879438 | -0.821522418 | 3.52E-10 |
| ARMC2 | 94.70227082 | 53.53464393 | -0.823885365 | 0.013994921 |
| CTSB | 7158.850728 | 4039.803218 | -0.825486884 | 2.47E-10 |
| RASSF9 | 586.5456429 | 330.6194136 | -0.825737053 | 0.000801387 |
| ISG20 | 149.9780553 | 84.36997691 | -0.825995475 | 0.007366182 |
| PACRGL | 431.9183329 | 243.3215472 | -0.827216096 | $4.50 \mathrm{E}-07$ |
| UFSP1 | 95.39008959 | 53.65736783 | -0.827695176 | 0.013692146 |
| CNNM4 | 979.6609903 | 551.1928443 | -0.828924474 | 2.01E-07 |
| AIG1 | 2756.144303 | 1550.589617 | -0.829799056 | 8.93E-08 |
| CCDC107 | 117.8715602 | 66.31713313 | -0.830728243 | 0.008757187 |
| PRR5 | 680.8521325 | 382.9497313 | -0.831395331 | $1.37 \mathrm{E}-08$ |
| PANX2 | 199.7858392 | 111.9270173 | -0.832139046 | 0.002595477 |
| TACC2 | 3817.643829 | 2144.1937 | -0.832274843 | 8.35E-08 |
| TMEM187 | 208.0728254 | 116.8955728 | -0.832561907 | 0.000267939 |
| GOLPH3L | 1299.650169 | 730.1394337 | -0.832640517 | 6.61E-09 |
| GCNA | 146.5798181 | 82.16041332 | -0.833154979 | 0.002564599 |


| ZNF575 | 97.44114214 | 54.88171291 | -0.833332862 | 0.016925893 |
| :---: | :---: | :---: | :---: | :---: |
| GALNT11 | 1057.113748 | 592.8915952 | -0.834017158 | 7.32E-10 |
| CEBPB | 2376.338802 | 1330.129398 | -0.836929582 | 3.05E-06 |
| LIG3 | 1734.068006 | 970.9585053 | -0.837006345 | $2.88 \mathrm{E}-12$ |
| ECHDC2 | 709.39881 | 396.7514179 | -0.837146141 | 7.13E-05 |
| EML2 | 2246.894687 | 1256.545555 | -0.837724883 | 4.57E-07 |
| TNFRSF11B | 70.0440895 | 39.17922209 | -0.838603645 | 0.036479448 |
| ENTPD2 | 368.8056271 | 206.0232246 | -0.838785656 | 0.000260241 |
| NIPAL2 | 833.0937441 | 464.9028235 | -0.842843421 | 2.37E-05 |
| EFNA1 | 1524.605636 | 849.4870523 | -0.843680989 | 0.000428502 |
| HS1BP3 | 1031.241298 | 574.0146962 | -0.84451374 | $1.52 \mathrm{E}-07$ |
| LGALS3BP | 4430.602248 | 2467.266299 | -0.844599417 | 2.19E-06 |
| GALNT3 | 2777.52496 | 1546.07337 | -0.845476182 | $2.20 \mathrm{E}-11$ |
| ATP8A1 | 1649.760652 | 917.8622835 | -0.846304408 | 4.65E-07 |
| TFF1 | 215.4142666 | 119.5864454 | -0.847659166 | 0.039866712 |
| C7orf50 | 1582.113452 | 877.823254 | -0.848843624 | $5.27 \mathrm{E}-11$ |
| WFS1 | 6920.210219 | 3842.326897 | -0.848872108 | $4.32 \mathrm{E}-11$ |
| ACAP1 | 231.8767154 | 128.5970693 | -0.849022439 | 0.000829955 |
| USF3 | 1995.843069 | 1107.964729 | -0.849655073 | 4.45E-12 |
| C1GALT1C1 | 440.6002064 | 244.5694203 | -0.849741835 | 8.27E-06 |
| UGDH | 9598.179309 | 5324.57266 | -0.849991359 | $1.06 \mathrm{E}-15$ |
| LSM2 | 1101.680471 | 610.3885726 | -0.850704697 | 4.75E-09 |
| LDLR | 5825.793483 | 3228.196086 | -0.851240436 | $8.50 \mathrm{E}-06$ |
| CALR | 26861.14338 | 14867.17924 | -0.853334097 | 8.82E-15 |
| ENOSF1 | 1962.582484 | 1086.302519 | -0.853523689 | 3.97E-10 |
| LARS | 4072.247585 | 2253.65517 | -0.85377117 | $1.15 \mathrm{E}-11$ |
| MID1IP1 | 4570.914793 | 2527.849067 | -0.854535719 | 2.32E-18 |
| MT-CO3 | 97680.30786 | 53932.06872 | -0.856932738 | 5.31E-07 |
| MIA2 | 1793.121879 | 989.3287884 | -0.858171936 | $1.48 \mathrm{E}-05$ |
| RHOF | 599.288919 | 329.778475 | -0.858814698 | 8.60E-08 |
| DHRS12 | 85.45749319 | 46.99118383 | -0.858947613 | 0.028255195 |
| TTC21A | 162.7831952 | 90.02938634 | -0.858956615 | 0.007075643 |
| STK40 | 2846.705049 | 1568.834021 | -0.859033165 | $3.36 \mathrm{E}-12$ |
| CLDN12 | 1654.717013 | 910.3950501 | -0.862133386 | 3.28E-10 |
| DPYSL2 | 8396.60988 | 4615.331718 | -0.863438679 | 8.21E-14 |
| PHF11 | 431.806788 | 237.0634534 | -0.865373308 | $9.80 \mathrm{E}-05$ |
| SRD5A3 | 472.9891017 | 259.4318341 | -0.86589381 | 4.37E-07 |
| SLC22A18 | 4583.790744 | 2514.530131 | -0.866192575 | 0.029388863 |
| KYAT3 | 1349.719358 | 739.2479335 | -0.867765059 | 3.43E-08 |
| RORA | 6000.290965 | 3285.213134 | -0.868976026 | $1.49 \mathrm{E}-13$ |
| CLDN3 | 828.1452235 | 452.8087815 | -0.871095836 | $5.20 \mathrm{E}-07$ |
| RNF145 | 4594.384528 | 2511.025026 | -0.871720849 | $4.58 \mathrm{E}-16$ |
| ZNF18 | 420.1237747 | 229.4511531 | -0.872663251 | $5.28 \mathrm{E}-06$ |
| HID1 | 2406.13321 | 1313.840646 | -0.872726029 | 2.03E-06 |
| HOXB6 | 4710.396527 | 2566.490168 | -0.876318274 | $5.08 \mathrm{E}-10$ |
| RCN1 | 3659.753812 | 1993.39601 | -0.876572562 | $1.36 \mathrm{E}-12$ |
| NOA1 | 2003.379719 | 1091.384659 | -0.876656289 | $3.99 \mathrm{E}-11$ |
| IER3 | 3864.945864 | 2104.054555 | -0.876682233 | 5.07E-07 |
| CLDN4 | 10455.02061 | 5692.578132 | -0.876895603 | 1.47E-13 |
| ARHGEF4 | 126.9832736 | 69.3149998 | -0.878136678 | 0.006266967 |
| ADAM21 | 84.14880788 | 45.98225437 | -0.878481829 | 0.018150803 |
| GAS6 | 3021.651067 | 1643.225879 | -0.878509102 | 6.96E-17 |
| POLD4 | 249.538617 | 135.6611235 | -0.879030449 | 5.77E-05 |
| GPT | 292.4861868 | 159.0290272 | -0.87929863 | 0.000275166 |
| SDF2L1 | 1032.87372 | 561.1211851 | -0.879507204 | 8.66E-08 |
| PLPP5 | 892.7183262 | 485.2388578 | -0.879815345 | $7.71 \mathrm{E}-11$ |
| MTHFD1L | 3099.832385 | 1684.102485 | -0.880606136 | 1.14E-14 |
| COX18 | 1028.365919 | 558.4323956 | -0.88069586 | 3.10E-12 |
| ANKRD37 | 177.0607142 | 96.29781417 | -0.880938833 | 0.000240141 |
| OSGEPL1 | 360.1365488 | 195.2032874 | -0.881212382 | $1.21 \mathrm{E}-05$ |
| MPST | 3121.955218 | 1694.598903 | -0.881505871 | $4.89 \mathrm{E}-15$ |


| THSD1 | 120.33314 | 65.63512114 | -0.88216744 | 0.006095852 |
| :---: | :---: | :---: | :---: | :---: |
| SEMA4B | 1894.359088 | 1027.567147 | -0.882278301 | $5.26 \mathrm{E}-09$ |
| KIF27 | 263.1686319 | 142.6267982 | -0.883178811 | $1.38 \mathrm{E}-05$ |
| NFS1 | 1131.676509 | 613.4777502 | -0.883561168 | $2.89 \mathrm{E}-10$ |
| IZUMO1 | 291.6537914 | 158.2878067 | -0.884616748 | 0.003881863 |
| CRYL1 | 617.7879092 | 334.1544873 | -0.885101327 | $1.26 \mathrm{E}-05$ |
| GXYLT2 | 643.8823399 | 348.1816108 | -0.885242993 | 5.94E-09 |
| MVD | 1975.22531 | 1067.913385 | -0.885807338 | $7.38 \mathrm{E}-08$ |
| SREBF2 | 11872.80422 | 6423.414843 | -0.88605631 | $2.60 \mathrm{E}-10$ |
| MAGED1 | 160.4111287 | 86.6338747 | -0.888247008 | 0.005672854 |
| PPP1R32 | 84.31897423 | 45.36287257 | -0.888480673 | 0.011272528 |
| DLX3 | 130.1952619 | 70.12861995 | -0.889151179 | 0.020371337 |
| TKFC | 2550.195974 | 1375.963951 | -0.889843691 | $1.39 \mathrm{E}-13$ |
| CHMP2A | 2402.485049 | 1295.450593 | -0.890489704 | $2.44 \mathrm{E}-10$ |
| PTPRJ | 1559.041966 | 840.095057 | -0.891537426 | 8.57E-11 |
| SLC4A8 | 841.2888509 | 453.4281661 | -0.891760675 | 9.91E-09 |
| MMP15 | 3938.302362 | 2121.140858 | -0.892365992 | $4.86 \mathrm{E}-17$ |
| IL1RAP | 292.6474301 | 157.8901646 | -0.892916651 | 1.32E-05 |
| EEF1A1 | 314345.8993 | 169253.2765 | -0.893173168 | 1.93E-15 |
| DTD1 | 548.892629 | 295.1470436 | -0.893258493 | 7.41E-09 |
| RPL13A | 44562.42212 | 23991.30415 | -0.893312184 | $1.50 \mathrm{E}-14$ |
| PHLDA1 | 11244.51789 | 6051.701934 | -0.893806274 | 4.53E-16 |
| LYPD6B | 580.0602177 | 311.9487066 | -0.894406289 | $6.01 \mathrm{E}-06$ |
| ETFDH | 599.3475167 | 322.0178368 | -0.896348125 | $4.30 \mathrm{E}-09$ |
| KLHL31 | 126.3811416 | 68.11012762 | -0.897519099 | 0.01061446 |
| HIC1 | 84.40966756 | 45.22591308 | -0.897618731 | 0.047282792 |
| FAM72D | 198.5200456 | 106.3517095 | -0.900541892 | 0.002123784 |
| ACOT13 | 765.4211076 | 410.1670683 | -0.901315735 | $6.30 \mathrm{E}-10$ |
| FBXL4 | 562.4075135 | 300.974672 | -0.902410034 | 5.37E-08 |
| ERP29 | 5461.521265 | 2916.216483 | -0.90510877 | $1.78 \mathrm{E}-17$ |
| SLC33A1 | 614.1713426 | 327.4846535 | -0.905401767 | 3.43E-09 |
| NUDT12 | 976.4336363 | 521.2394788 | -0.905469605 | $2.30 \mathrm{E}-08$ |
| FZD4 | 429.0471136 | 228.8796013 | -0.905824684 | $1.96 \mathrm{E}-06$ |
| FAM160B1 | 1502.513695 | 801.0000929 | -0.907217691 | 8.03E-11 |
| LIPH | 2433.067533 | 1296.183629 | -0.908463888 | 3.03E-06 |
| KAZN | 145.8038198 | 77.91032145 | -0.909708554 | 0.001867659 |
| DIAPH2 | 308.5179316 | 164.3867222 | -0.910024728 | 2.52E-05 |
| FTL | 30613.04621 | 16281.60239 | -0.910898622 | 4.27E-10 |
| PRSS27 | 309.5823211 | 164.6577417 | -0.912263561 | 0.000403402 |
| TMEM268 | 746.4795694 | 396.0511547 | -0.912886193 | $5.26 \mathrm{E}-09$ |
| EGLN3 | 359.7829061 | 191.3116666 | -0.912921457 | 1.53E-05 |
| NATD1 | 321.6555917 | 170.5033638 | -0.912953322 | 0.000246387 |
| CCDC171 | 157.7119878 | 83.50770754 | -0.913636949 | 0.000712496 |
| CD55 | 3544.354196 | 1880.182614 | -0.914836815 | $2.75 \mathrm{E}-09$ |
| ERO1B | 816.4808937 | 432.6188613 | -0.914985931 | 6.16E-07 |
| KLHL35 | 207.0855271 | 109.7846878 | -0.915791488 | 0.000712216 |
| LITAF | 2526.971233 | 1338.752003 | -0.916286809 | 2.15E-09 |
| PLCB1 | 230.669107 | 122.0805166 | -0.91701213 | 2.34E-05 |
| ERN1 | 1314.588486 | 695.7350244 | -0.917921994 | 4.23E-07 |
| PEX7 | 406.8636171 | 215.1396625 | -0.918585364 | 3.07E-05 |
| SND1 | 9044.438165 | 4784.629057 | -0.918792369 | 3.12E-14 |
| COX20 | 115.1703119 | 60.63646177 | -0.918916748 | 0.003290095 |
| VAMP4 | 377.9912984 | 199.7362514 | -0.91910855 | 2.02E-05 |
| ALS2CL | 4365.952968 | 2306.329715 | -0.920694715 | 0.020266848 |
| AGO4 | 845.5635912 | 446.1313754 | -0.922017571 | 3.09E-08 |
| RMDN2 | 160.6012491 | 84.67935111 | -0.923778131 | 0.001687046 |
| RBM43 | 287.9549703 | 152.1629566 | -0.925892199 | 7.65E-05 |
| IKBKB | 2113.34967 | 1112.662559 | -0.9262407 | 5.93E-12 |
| AUH | 722.2108623 | 380.0303631 | -0.926306563 | $4.26 \mathrm{E}-09$ |
| HSD17B7 | 1071.192858 | 562.8268815 | -0.92696558 | 6.59E-12 |
| GNPDA1 | 1661.055585 | 873.1681572 | -0.92748725 | 5.03E-15 |


| IARS | 14872.2973 | 7815.61334 | -0.92825782 | $3.76 \mathrm{E}-20$ |
| :---: | :---: | :---: | :---: | :---: |
| DHCR7 | 5603.56759 | 2941.550419 | -0.929206125 | $6.54 \mathrm{E}-11$ |
| CASP4 | 1352.809894 | 710.5320592 | -0.929575136 | 9.05E-07 |
| MAGED2 | 2376.533939 | 1246.62097 | -0.931300111 | $1.70 \mathrm{E}-14$ |
| FER1L6 | 251.2184723 | 131.6426971 | -0.93148655 | 0.008529819 |
| KLF9 | 1319.042344 | 689.4889847 | -0.934634172 | $1.27 \mathrm{E}-08$ |
| PRSS8 | 1868.361958 | 977.3317214 | -0.934643905 | $6.85 \mathrm{E}-08$ |
| BCL2L14 | 308.89008 | 161.9042812 | -0.934862494 | 1.19E-05 |
| RPIA | 857.6918353 | 448.4697883 | -0.935032119 | 8.03E-08 |
| MMP24OS | 887.61101 | 463.8408718 | -0.935843984 | 7.19E-09 |
| SNHG28 | 98.82137971 | 51.55053585 | -0.938037536 | 0.009458476 |
| DDIT3 | 559.3499699 | 291.1996389 | -0.941335006 | 0.00074486 |
| SLC35D2 | 229.9079146 | 119.8777541 | -0.942705926 | 0.000461541 |
| GABARAP | 60.37192248 | 31.2230916 | -0.943672831 | 0.038302634 |
| BICRAL | 963.1726719 | 500.9449956 | -0.943888221 | $7.44 \mathrm{E}-08$ |
| VPS28 | 1377.697854 | 715.450776 | -0.945914152 | $5.63 \mathrm{E}-11$ |
| ANK3 | 1269.151423 | 658.7369636 | -0.947072858 | $1.57 \mathrm{E}-08$ |
| HDDC3 | 290.5653986 | 150.626563 | -0.947115248 | $1.97 \mathrm{E}-06$ |
| CUTC | 514.2393248 | 266.7297776 | -0.947134293 | 2.25E-09 |
| LCP1 | 54.48581712 | 28.14910658 | -0.947196922 | 0.025804949 |
| PLCH1 | 135.7470135 | 70.10293704 | -0.947545411 | 0.002212226 |
| NR4A2 | 221.2820439 | 114.7795596 | -0.948271544 | 2.33E-05 |
| TSKU | 2981.291795 | 1543.803344 | -0.94947411 | 7.76E-13 |
| KLK3 | 119.3898623 | 61.58257811 | -0.950167888 | 0.023512053 |
| ZNF337 | 109.1796585 | 56.33935618 | -0.950379395 | 0.00165759 |
| SRI | 1107.882969 | 572.5461996 | -0.951568813 | $4.86 \mathrm{E}-11$ |
| TSEN15 | 2235.673393 | 1156.087077 | -0.951868979 | $9.94 \mathrm{E}-12$ |
| CTSD | 7333.974734 | 3784.927969 | -0.954139411 | $1.85 \mathrm{E}-17$ |
| ITGA2 | 3519.579983 | 1816.575082 | -0.954544244 | $6.38 \mathrm{E}-14$ |
| PBX1 | 488.8479885 | 252.2308204 | -0.95533754 | 8.57E-06 |
| ST3GAL5 | 306.3918855 | 157.5335937 | -0.957649819 | 0.000948774 |
| SH3RF3 | 522.4984206 | 269.0634008 | -0.957766541 | 4.05E-05 |
| ING4 | 431.2968671 | 222.0293301 | -0.958825814 | $1.82 \mathrm{E}-06$ |
| RAPGEFL1 | 2181.870483 | 1121.75101 | -0.959233363 | $2.08 \mathrm{E}-07$ |
| ADAMTS19 | 185.0228028 | 94.97683626 | -0.960362643 | 0.000122941 |
| ATP6AP1L | 300.7653905 | 154.1231708 | -0.964150658 | 0.000688352 |
| ZBTB41 | 991.7910012 | 508.5233199 | -0.965012129 | $3.72 \mathrm{E}-12$ |
| BCO2 | 62.27293432 | 31.81876245 | -0.965525927 | 0.01666487 |
| TIMP4 | 271.3045656 | 138.891358 | -0.96617261 | 0.000456402 |
| PYGB | 5455.314802 | 2792.219644 | -0.966270457 | 2.59E-08 |
| HELB | 263.2722859 | 134.7955465 | -0.966811006 | 6.93E-06 |
| FAAH2 | 353.2408489 | 180.5762098 | -0.967964187 | 0.000549806 |
| LBHD1 | 395.0796353 | 201.6339043 | -0.970599973 | $3.79 \mathrm{E}-07$ |
| UVSSA | 3417.08617 | 1742.633984 | -0.971526365 | 7.22E-08 |
| STX8 | 424.0377164 | 215.5062015 | -0.973180281 | 4.39E-08 |
| LRRC27 | 192.9434206 | 98.42992088 | -0.973210062 | 0.000263478 |
| SCG5 | 196.8682394 | 99.77413268 | -0.977453839 | 0.002184616 |
| MKNK2 | 7741.997361 | 3930.382949 | -0.97778648 | 1.49E-09 |
| B4GALNT3 | 662.1339874 | 335.8266158 | -0.978459423 | 5.73E-05 |
| PRKAG1 | 1247.282203 | 632.9411095 | -0.978995766 | 5.69E-13 |
| FRAT2 | 300.6719246 | 152.3716134 | -0.980856099 | $4.34 \mathrm{E}-07$ |
| S100A14 | 7585.347838 | 3841.475934 | -0.981461103 | $1.45 \mathrm{E}-15$ |
| MT-ATP6 | 62621.81546 | 31699.03349 | -0.982223289 | $4.59 \mathrm{E}-15$ |
| GSS | 3539.35299 | 1790.449403 | -0.982743066 | $5.38 \mathrm{E}-13$ |
| ULK2 | 443.834617 | 224.3677852 | -0.983531341 | $4.44 \mathrm{E}-06$ |
| FAM117B | 887.9226999 | 448.5711125 | -0.984069645 | $2.41 \mathrm{E}-07$ |
| C14orf28 | 146.9362394 | 74.14384984 | -0.985115598 | 0.000294651 |
| IMMP2L | 135.1073157 | 68.14469478 | -0.98778223 | 0.00018458 |
| PSD | 130.3752848 | 65.630292 | -0.990124693 | 0.012271971 |
| PCCA | 2072.275277 | 1042.948477 | -0.990331037 | 4.53E-16 |
| RBL2 | 3383.497453 | 1702.898204 | -0.990442916 | 3.23E-13 |


| ENDOD1 | 3281.68398 | 1648.642371 | -0.993205025 | 1.21E-10 |
| :---: | :---: | :---: | :---: | :---: |
| IMPACT | 1683.630473 | 845.3910522 | -0.993988349 | $3.98 \mathrm{E}-08$ |
| NOS2 | 50.88120541 | 25.56003522 | -0.997509514 | 0.030130333 |
| TPT1 | 22514.32256 | 11264.15446 | -0.999131114 | $7.24 \mathrm{E}-15$ |
| MCF2L | 230.5175608 | 115.0469744 | -1.003331855 | 0.000824861 |
| LEPR | 302.4316083 | 151.0967217 | -1.003410363 | 3.37E-05 |
| CCDC115 | 948.9581042 | 473.0598133 | -1.00347781 | 5.22E-13 |
| MB | 274.2957679 | 136.4275047 | -1.003833543 | $3.28 \mathrm{E}-05$ |
| ELMO3 | 1554.470074 | 772.520467 | -1.00824314 | 6.54E-11 |
| NOP53 | 4939.647861 | 2455.078708 | -1.008743599 | 1.15E-14 |
| PPIB | 4270.595267 | 2118.217357 | -1.011190823 | 2.07E-19 |
| MXI1 | 1320.070221 | 654.3416771 | -1.011702937 | 8.66E-08 |
| SDHAF4 | 486.9730812 | 240.356798 | -1.017714503 | 6.62E-09 |
| R3HDM2 | 968.5075687 | 478.3334332 | -1.018203493 | 8.09E-06 |
| DBP | 1567.811055 | 773.8224677 | -1.018510602 | 0.037131475 |
| MANF | 2530.252976 | 1246.181186 | -1.021258586 | $7.12 \mathrm{E}-21$ |
| MT-CYB | 67861.51102 | 33422.23196 | -1.021804099 | 3.29E-11 |
| PLCG2 | 203.7031437 | 100.1704391 | -1.024082262 | 8.12E-05 |
| EPHB2 | 2089.314945 | 1024.84853 | -1.026489627 | 2.39E-10 |
| NQO1 | 21497.35386 | 10546.51926 | -1.027300288 | $1.68 \mathrm{E}-13$ |
| GRID2IP | 65.46719035 | 32.143822 | -1.027620839 | 0.013936939 |
| POLR3GL | 194.5106567 | 95.00861513 | -1.028307611 | $2.40 \mathrm{E}-05$ |
| MT-CO2 | 121565.0023 | 59577.37216 | -1.028894431 | 5.67E-14 |
| SMPDL3A | 526.1274543 | 257.3417291 | -1.03069032 | 1.42E-07 |
| TNKS1BP1 | 4454.08012 | 2178.599623 | -1.03113161 | $3.48 \mathrm{E}-15$ |
| PTPN22 | 42.59326799 | 20.69892643 | -1.031704769 | 0.036436885 |
| RHBDD1 | 1711.691442 | 837.4041026 | -1.03245105 | 3.17E-16 |
| SLIT1 | 124.0101979 | 60.52466297 | -1.034156564 | 0.006209484 |
| PARPBP | 499.1319065 | 243.2734202 | -1.03483131 | 7.10E-06 |
| CLMN | 197.9816262 | 96.23957838 | -1.035358218 | 0.000478793 |
| PAM | 2520.933903 | 1228.945047 | -1.036593475 | 1.87E-14 |
| MVP | 3524.049858 | 1714.544433 | -1.039380245 | $1.69 \mathrm{E}-09$ |
| DUSP5 | 2292.010034 | 1114.139455 | -1.039985154 | 5.86E-08 |
| ERRFI1 | 16694.59323 | 8113.52595 | -1.040975036 | $2.51 \mathrm{E}-12$ |
| TARBP1 | 1834.022347 | 891.5928784 | -1.041346428 | 7.29E-13 |
| PTCHD1 | 50.5822529 | 24.67580161 | -1.041460378 | 0.022365792 |
| FAM114A1 | 880.3234003 | 427.855528 | -1.041569332 | 2.32E-12 |
| HLA-DMA | 354.6273397 | 171.896519 | -1.043360116 | 5.89E-09 |
| ZBTB22 | 786.8288585 | 381.3004285 | -1.043923961 | $4.86 \mathrm{E}-11$ |
| ASS1 | 4581.176511 | 2221.695128 | -1.043943391 | 5.81E-08 |
| SLC1A4 | 7162.77291 | 3470.714596 | -1.045202417 | $5.06 \mathrm{E}-25$ |
| FPGT | 675.1928827 | 326.5848486 | -1.045882023 | 7.86E-13 |
| IL20RB | 41.51779634 | 20.20018535 | -1.046131399 | 0.0355947 |
| TNFRSF1B | 176.5812691 | 85.20150617 | -1.049285888 | 0.000151817 |
| BNIPL | 74.69383529 | 36.02469777 | -1.049415126 | 0.022115616 |
| PDCD4 | 2596.285458 | 1254.072992 | -1.049641954 | 2.19E-09 |
| CLCN5 | 1110.851143 | 535.3185327 | -1.051551544 | 1.89E-12 |
| ZSCAN32 | 54.79486106 | 26.43322969 | -1.051656531 | 0.021995505 |
| HOXB4 | 3426.915719 | 1651.113281 | -1.053365186 | 3.43E-08 |
| TNS4 | 16654.00608 | 8021.763569 | -1.053755781 | $1.53 \mathrm{E}-09$ |
| PGLYRP1 | 65.8794246 | 31.76234226 | -1.054868374 | 0.01279505 |
| SLC7A1 | 9221.670892 | 4433.484797 | -1.056699404 | 1.17E-16 |
| NIPSNAP2 | 2128.998648 | 1022.867486 | -1.057501053 | $2.34 \mathrm{E}-16$ |
| HGSNAT | 1361.650149 | 653.8796158 | -1.058148911 | 3.02E-08 |
| ARTN | 127.6093455 | 61.0151532 | -1.058481722 | 0.000257092 |
| PIP5KL1 | 158.8241612 | 76.05845776 | -1.059615409 | 0.002149178 |
| ZC3H6 | 1046.604112 | 502.0378466 | -1.060165955 | 1.85E-08 |
| SMIM29 | 394.2462949 | 188.6321724 | -1.062569056 | $1.98 \mathrm{E}-08$ |
| BCAS1 | 247.5630182 | 118.4250963 | -1.062892979 | 0.000453372 |
| ABHD14B | 1334.930473 | 639.2807418 | -1.06344515 | $4.30 \mathrm{E}-14$ |
| ARHGAP30 | 121.4633889 | 57.86887973 | -1.066038539 | 0.007626959 |


| TSPAN1 | 3914.249589 | 1867.540514 | -1.067300407 | $1.18 \mathrm{E}-07$ |
| :---: | :---: | :---: | :---: | :---: |
| PDE3A | 149.6748247 | 71.27788828 | -1.067369725 | 0.000899693 |
| FBXL20 | 1089.223966 | 519.4978078 | -1.067981817 | $8.45 \mathrm{E}-11$ |
| IARS2 | 6663.070924 | 3176.259096 | -1.068759691 | $1.96 \mathrm{E}-22$ |
| MT1X | 153.9785899 | 72.94477949 | -1.06987546 | 0.000782363 |
| VIL1 | 578.5337177 | 275.2342711 | -1.070302569 | $1.21 \mathrm{E}-06$ |
| CPPED1 | 1063.091296 | 505.4539122 | -1.073052539 | $5.51 \mathrm{E}-18$ |
| MMAA | 121.4165385 | 57.79439407 | -1.078832304 | 0.00053378 |
| KIAA1257 | 80.26444192 | 38.04901849 | -1.079619602 | 0.028015891 |
| BCAS3 | 451.2236528 | 213.3332488 | -1.079972766 | $4.40 \mathrm{E}-08$ |
| TMEM143 | 341.088539 | 161.035847 | -1.080897542 | 4.60E-09 |
| MANEA | 713.463416 | 336.7181275 | -1.083355739 | $1.22 \mathrm{E}-13$ |
| IL33 | 611.8516449 | 288.619314 | -1.083559827 | 0.029435447 |
| MKX | 60.03476272 | 28.08826543 | -1.083966843 | 0.027861459 |
| KCTD18 | 585.3405544 | 275.4092855 | -1.087729182 | 3.58E-09 |
| TLR5 | 65.16225283 | 30.68175776 | -1.088096351 | 0.004695011 |
| SLC9B2 | 161.2576586 | 75.73584723 | -1.091180002 | $2.35 \mathrm{E}-05$ |
| FHIT | 117.0734372 | 54.95783125 | -1.091661715 | 0.000275302 |
| ZBTB45 | 1603.078986 | 751.4083932 | -1.092244795 | $4.60 \mathrm{E}-19$ |
| FURIN | 4936.098319 | 2314.522251 | -1.092379061 | $1.97 \mathrm{E}-14$ |
| IDH2 | 3277.397881 | 1536.063676 | -1.092639633 | $1.31 \mathrm{E}-09$ |
| DUSP18 | 242.0127149 | 113.4017533 | -1.093855968 | 1.79E-06 |
| HECW2 | 104.4441054 | 48.9678574 | -1.095134382 | 0.000954561 |
| ACSM3 | 157.9470861 | 73.636675 | -1.096017917 | 0.001155062 |
| MAPT | 136.4479883 | 63.92720095 | -1.09648062 | 0.003317108 |
| PRPF40B | 443.0897481 | 207.1734204 | -1.096837942 | $9.56 \mathrm{E}-08$ |
| C8orf82 | 1452.497089 | 678.3631482 | -1.098436247 | $1.69 \mathrm{E}-16$ |
| SLC16A5 | 2083.686913 | 971.4315233 | -1.100696032 | 0.005779232 |
| RNF135 | 729.5109628 | 340.2172983 | -1.101710924 | $1.36 \mathrm{E}-13$ |
| SWT1 | 222.4264907 | 103.4024203 | -1.103336748 | $2.10 \mathrm{E}-06$ |
| TTC39B | 1216.227113 | 565.6512919 | -1.103567471 | 1.12E-15 |
| MPND | 223.6926036 | 103.6322968 | -1.105671261 | 3.98E-06 |
| NT5C | 651.1721652 | 301.857273 | -1.106796577 | 8.72E-14 |
| DNAJB9 | 493.1558718 | 229.1147151 | -1.107141252 | $1.48 \mathrm{E}-05$ |
| RASIP1 | 347.5535404 | 161.4735905 | -1.108782209 | $1.71 \mathrm{E}-05$ |
| FAM107B | 398.0373508 | 183.9483498 | -1.111104268 | 5.22E-08 |
| METTL26 | 1491.875605 | 689.3606391 | -1.112424308 | $9.65 \mathrm{E}-16$ |
| FDFT1 | 11595.74482 | 5354.901976 | -1.114380096 | 1.13E-12 |
| FDXACB1 | 82.61002465 | 37.93878348 | -1.115172142 | 0.001369636 |
| LRRC23 | 282.624312 | 130.0308876 | -1.116897642 | 9.43E-08 |
| DUOX1 | 99.83556823 | 45.74795693 | -1.120088499 | 0.001446131 |
| BTBD8 | 513.8432602 | 236.0467236 | -1.12013294 | 4.49E-09 |
| HSP90B1 | 39653.33816 | 18238.05198 | -1.12046744 | 9.33E-30 |
| MAPRE3 | 1573.373305 | 723.4478372 | -1.120697936 | 8.89E-07 |
| D2HGDH | 1899.411397 | 872.097048 | -1.122770442 | 8.77E-12 |
| SARS | 7739.332147 | 3552.02335 | -1.123550206 | $2.44 \mathrm{E}-13$ |
| AL117339.5 | 147.8889671 | 67.62822752 | -1.124467968 | 0.000721504 |
| CCDC28A | 377.2420188 | 172.8104483 | -1.126904846 | 5.43E-07 |
| CCDC167 | 256.790389 | 117.7315258 | -1.126986904 | $7.20 \mathrm{E}-06$ |
| LONP1 | 6511.553859 | 2980.416013 | -1.127458361 | $1.84 \mathrm{E}-16$ |
| HFE | 1074.100071 | 491.2619914 | -1.128429804 | $3.29 \mathrm{E}-12$ |
| SULT1C2 | 1411.125976 | 645.2683835 | -1.128903055 | 0.010571347 |
| HBP1 | 912.6336777 | 416.7326519 | -1.130387432 | 5.80E-09 |
| ENPP5 | 314.8094732 | 143.4976549 | -1.130760215 | 1.33E-06 |
| MT-CO1 | 367081.6105 | 167473.8829 | -1.13216663 | $2.31 \mathrm{E}-15$ |
| N6AMT1 | 437.7529904 | 199.5947146 | -1.135708039 | $1.48 \mathrm{E}-09$ |
| ADGRL2 | 149.2211409 | 67.78848979 | -1.13673358 | 0.000861951 |
| NTRK2 | 82.70740156 | 37.76551012 | -1.138085263 | 0.002780387 |
| TBC1D5 | 2945.405514 | 1338.018321 | -1.138395373 | $3.30 \mathrm{E}-17$ |
| MYC | 4589.592358 | 2083.983847 | -1.139772774 | $1.28 \mathrm{E}-15$ |
| GNA14 | 163.1700684 | 73.96295905 | -1.140514315 | 9.96E-06 |


| NEK3 | 369.3077812 | 166.6884976 | -1.143898511 | 9.26E-09 |
| :---: | :---: | :---: | :---: | :---: |
| PHYKPL | 2704.670502 | 1222.533156 | -1.145581272 | 8.62E-10 |
| ZNF516 | 534.5366964 | 240.9036395 | -1.146212641 | 7.18E-06 |
| DEPDC7 | 171.7541225 | 77.54464111 | -1.146372727 | $1.51 \mathrm{E}-05$ |
| ZFP14 | 318.2801778 | 143.9967618 | -1.146674206 | 3.61E-10 |
| FTCDNL1 | 82.00002913 | 37.08145729 | -1.146984382 | 0.000807331 |
| ATF4 | 24697.5708 | 11152.44997 | -1.147006488 | 2.52E-17 |
| ZNF169 | 740.8594507 | 334.843621 | -1.147052137 | $3.14 \mathrm{E}-10$ |
| RHOBTB1 | 220.4485197 | 99.29085171 | -1.147716642 | 8.66E-08 |
| BEST1 | 104.780681 | 46.97375177 | -1.153796199 | 0.001106164 |
| CCDC149 | 318.9981353 | 143.6235329 | -1.15519589 | 3.23E-08 |
| FAM78A | 55.67575659 | 24.87917885 | -1.156486428 | 0.014102819 |
| TGFB2 | 2522.575545 | 1128.897923 | -1.160293059 | 3.43E-09 |
| TMEM141 | 1786.48736 | 797.6902229 | -1.161727136 | $4.41 \mathrm{E}-16$ |
| PSPH | 2758.272812 | 1231.359576 | -1.163511977 | 3.57E-29 |
| TXNRD3 | 713.5375904 | 317.7881188 | -1.164074868 | $4.88 \mathrm{E}-13$ |
| RNF125 | 369.5790816 | 164.4899732 | -1.164691308 | $3.11 \mathrm{E}-09$ |
| RAP1GAP | 267.0865444 | 119.1160615 | -1.164753885 | $1.16 \mathrm{E}-05$ |
| FRAT1 | 224.6842098 | 100.1462059 | -1.164759192 | 1.52E-07 |
| KBTBD7 | 439.691767 | 195.688087 | -1.16555428 | $7.78 \mathrm{E}-12$ |
| SUMF2 | 2936.553647 | 1307.94898 | -1.166179392 | $1.48 \mathrm{E}-17$ |
| ACVR2B | 722.0167438 | 321.1901374 | -1.167397714 | 3.22E-10 |
| BTD | 495.0001529 | 219.9335372 | -1.169194572 | $5.71 \mathrm{E}-12$ |
| ACCS | 807.056975 | 358.7706299 | -1.169621249 | 7.08E-10 |
| APBB3 | 1314.941449 | 584.2458353 | -1.170099912 | $2.28 \mathrm{E}-13$ |
| SREBF1 | 10359.30497 | 4599.715328 | -1.171027327 | 3.52E-15 |
| PLA2G4A | 302.6850954 | 133.8920652 | -1.17217167 | 5.73E-07 |
| PTPRD | 111.3614963 | 49.16907976 | -1.176142694 | 0.001755774 |
| ASB13 | 807.9511172 | 356.9948817 | -1.176857197 | $4.65 \mathrm{E}-11$ |
| PITPNM3 | 333.228313 | 146.4980846 | -1.186170362 | $1.51 \mathrm{E}-05$ |
| CTBS | 278.7415386 | 122.145821 | -1.186485504 | 6.97E-06 |
| SHMT2 | 7774.215632 | 3414.948955 | -1.186748619 | $3.84 \mathrm{E}-29$ |
| RSL24D1 | 5208.401334 | 2282.008793 | -1.190293901 | 8.35E-20 |
| GCLC | 5952.662531 | 2607.701553 | -1.190657443 | 7.99E-16 |
| TTC34 | 104.2238763 | 45.82065356 | -1.190847635 | 0.000983748 |
| AC099489.1 | 79.83465307 | 35.11054322 | -1.190867163 | 0.029911565 |
| ETV5 | 2555.320859 | 1118.446696 | -1.191259359 | 2.42E-17 |
| NUDT3 | 184.475969 | 80.5728369 | -1.192710464 | $1.98 \mathrm{E}-07$ |
| PQLC3 | 475.4080069 | 207.9105858 | -1.193494334 | $1.76 \mathrm{E}-10$ |
| SUCLG2 | 2238.75825 | 977.7247173 | -1.194901086 | 2.69E-20 |
| ZNF397 | 1423.274827 | 621.501637 | -1.1958471 | 4.42E-17 |
| CYP2J2 | 2234.174416 | 974.0639852 | -1.197137745 | 5.45E-17 |
| BHLHE40 | 1462.202037 | 637.0803092 | -1.198330108 | 0.008268901 |
| IGBP1 | 1670.208206 | 726.8965274 | -1.20071666 | $2.09 \mathrm{E}-17$ |
| BTN3A1 | 676.7391079 | 293.7346013 | -1.203066195 | 3.33E-09 |
| NDUFV2 | 200.9968889 | 87.31305607 | -1.205850907 | $8.98 \mathrm{E}-07$ |
| PNRC1 | 1030.602786 | 446.203892 | -1.206649543 | $3.41 \mathrm{E}-11$ |
| ULK1 | 2834.460554 | 1225.376085 | -1.209518545 | 1.95E-13 |
| GGACT | 85.02976061 | 36.6648193 | -1.215638185 | 0.00159632 |
| ZNF333 | 387.8622562 | 166.9696976 | -1.21647747 | $3.71 \mathrm{E}-11$ |
| EPRS | 16348.02907 | 7034.922814 | -1.216677079 | $1.05 \mathrm{E}-26$ |
| FRMD3 | 559.4010083 | 239.8821043 | -1.220912714 | $1.81 \mathrm{E}-06$ |
| GRAMD4 | 733.5307318 | 313.9692398 | -1.223240933 | 2.69E-08 |
| SLC24A1 | 681.7421709 | 291.9576552 | -1.22363551 | 7.21E-08 |
| PCSK9 | 587.4786549 | 250.4915001 | -1.225393929 | 7.12E-08 |
| VGF | 963.63278 | 412.1493213 | -1.225542802 | $8.03 \mathrm{E}-11$ |
| DDR2 | 74.32619366 | 31.72759218 | -1.225744773 | 0.003703594 |
| MT-ND2 | 84985.41522 | 36210.55445 | -1.230801037 | $2.10 \mathrm{E}-17$ |
| SLC39A11 | 491.2795952 | 208.6797129 | -1.235638526 | 5.52E-13 |
| EDEM2 | 797.8614295 | 338.4530003 | -1.236020775 | $1.36 \mathrm{E}-14$ |
| ACSS2 | 3983.106757 | 1689.353102 | -1.236941237 | 4.51E-18 |


| HSD17B4 | 4728.004035 | 2004.561771 | -1.237509997 | $4.40 \mathrm{E}-26$ |
| :---: | :---: | :---: | :---: | :---: |
| SLC38A2 | 11929.55717 | 5052.577752 | -1.239295234 | $3.06 \mathrm{E}-22$ |
| PLA2R1 | 173.5886458 | 73.43586082 | -1.24122354 | 5.87E-06 |
| FUT1 | 1306.259765 | 551.8544796 | -1.242960283 | $4.84 \mathrm{E}-10$ |
| RBCK1 | 13260.40056 | 5593.265647 | -1.245332974 | 2.92E-13 |
| BEND6 | 143.761296 | 60.27148372 | -1.250365022 | 0.000204808 |
| CTH | 483.5952679 | 202.7099989 | -1.251284669 | $9.66 \mathrm{E}-11$ |
| BTN3A2 | 549.3809072 | 230.4651369 | -1.251813297 | 7.91E-12 |
| GALC | 1509.921237 | 634.0592323 | -1.252124407 | 4.86E-17 |
| LZTFL1 | 531.8370018 | 223.2053229 | -1.252554544 | $1.26 \mathrm{E}-10$ |
| RPL3 | 53278.13659 | 22351.03646 | -1.253226684 | $5.34 \mathrm{E}-27$ |
| SPINK4 | 120.8088913 | 50.75602276 | -1.253463934 | 0.000583394 |
| EDAR | 171.6769073 | 71.79725787 | -1.253758271 | 0.001837519 |
| CPQ | 106.6837491 | 44.6027014 | -1.255501858 | 0.000224546 |
| MYO15A | 39.4895909 | 16.46463395 | -1.256657818 | 0.048390857 |
| NOL4 | 42.9219228 | 17.87131958 | -1.258110851 | 0.011052602 |
| ACY1 | 47.26103207 | 19.57615734 | -1.258290778 | 0.012049483 |
| GDF15 | 9188.052631 | 3836.971081 | -1.259530685 | 2.87E-17 |
| PDIA4 | 12035.39333 | 5013.202781 | -1.263353251 | 3.02E-37 |
| RSAD1 | 801.4587496 | 332.5115588 | -1.270537769 | 8.25E-20 |
| GDPD1 | 95.08075356 | 38.98885595 | -1.272851081 | 0.000797193 |
| EIF4EBP1 | 2948.884191 | 1218.972067 | -1.274001168 | $1.26 \mathrm{E}-24$ |
| CLDN7 | 8526.905266 | 3521.251827 | -1.275698983 | 3.32E-19 |
| FOXO4 | 192.6326125 | 79.37458289 | -1.278317041 | 7.33E-06 |
| HOXD8 | 53.20225787 | 21.99195534 | -1.278693877 | 0.014481134 |
| SELENON | 1974.036345 | 812.7002243 | -1.279280756 | 1.12E-15 |
| ATP2C2 | 1496.148782 | 616.0276928 | -1.279955463 | 7.20E-12 |
| IDH1 | 10067.26958 | 4143.289256 | -1.280507594 | 7.17E-23 |
| TDRD3 | 706.5195379 | 290.640873 | -1.28294903 | 3.05E-15 |
| SYTL1 | 719.2175942 | 295.3830878 | -1.283901294 | 0.028483957 |
| GABRR2 | 236.0074212 | 96.69486804 | -1.284786384 | 4.02E-06 |
| MT-ND4L | 58260.67298 | 23846.71704 | -1.288721801 | 3.67E-23 |
| MFSD3 | 1280.935995 | 522.6497691 | -1.29186894 | $1.84 \mathrm{E}-25$ |
| H1FX | 2776.680369 | 1131.54491 | -1.294540755 | 1.13E-26 |
| EIF4B | 20787.84777 | 8472.229495 | -1.295023091 | 6.03E-27 |
| SGSM1 | 32.22553303 | 13.12003763 | -1.295609987 | 0.030946333 |
| CXCL8 | 52.96294482 | 21.37216537 | -1.296897823 | 0.044930381 |
| ST6GALNAC2 | 59.3673045 | 24.10116745 | -1.298100621 | 0.003461218 |
| HBEGF | 381.7817464 | 154.8574761 | -1.298235849 | 4.01E-09 |
| CCDC146 | 91.99321619 | 37.21574252 | -1.299695379 | 0.000479667 |
| NAGLU | 1812.155608 | 735.8326391 | -1.299873156 | $1.90 \mathrm{E}-25$ |
| PEMT | 485.2939994 | 196.3139758 | -1.304834241 | $1.30 \mathrm{E}-11$ |
| LHPP | 245.9357695 | 99.61486967 | -1.305916564 | 3.05E-07 |
| AMN1 | 115.8434691 | 46.53700747 | -1.306524437 | 0.000163886 |
| C9orf50 | 61.24277768 | 24.71333999 | -1.30956856 | 0.007062551 |
| LRRC75B | 527.5734246 | 212.530596 | -1.310153311 | 5.57E-13 |
| S1PR4 | 42.16130848 | 16.91520568 | -1.310704585 | 0.016246798 |
| TMEM8B | 639.5454611 | 257.4874616 | -1.311090185 | $1.24 \mathrm{E}-08$ |
| GRB10 | 3056.056841 | 1228.141647 | -1.31508703 | $1.76 \mathrm{E}-21$ |
| PPP1R14D | 162.3788245 | 64.9378054 | -1.315767305 | 0.001512978 |
| AP1S1 | 8298.416482 | 3329.137436 | -1.317310402 | $1.96 \mathrm{E}-28$ |
| ACADS | 562.097741 | 224.4848636 | -1.320660864 | 8.80E-16 |
| MT-ND4 | 214875.7271 | 86003.97901 | -1.321024529 | $1.32 \mathrm{E}-24$ |
| PLA2G6 | 659.4866108 | 263.9684744 | -1.323371209 | 8.95E-14 |
| AOAH | 135.9936753 | 54.21468397 | -1.325895957 | 0.000363681 |
| BEAN1 | 61.94962923 | 24.54308017 | -1.330326279 | 0.006370028 |
| FGD2 | 484.5326354 | 192.3972366 | -1.330357105 | 3.91E-12 |
| THBS3 | 411.1819594 | 163.3768652 | -1.332563317 | 1.82E-06 |
| TMCC3 | 212.4540373 | 83.99994449 | -1.335827931 | 5.86E-05 |
| ARSD | 1354.639238 | 536.4239386 | -1.336541433 | $1.26 \mathrm{E}-09$ |
| PDK4 | 70.21801909 | 27.5543661 | -1.341544348 | 0.008276876 |


| DDX60 | 199.4651112 | 78.62492865 | -1.342703054 | 7.06E-07 |
| :---: | :---: | :---: | :---: | :---: |
| CNTD2 | 32.34063613 | 12.59119268 | -1.343029412 | 0.026916577 |
| PPARG | 1455.750135 | 573.1038521 | -1.344483135 | $7.20 \mathrm{E}-13$ |
| HSPA13 | 2341.327228 | 920.4585347 | -1.346777774 | $7.38 \mathrm{E}-18$ |
| ITGA5 | 1334.546666 | 523.0130004 | -1.351053312 | $1.65 \mathrm{E}-10$ |
| C11orf71 | 89.37878971 | 34.89739368 | -1.351064655 | 0.000814569 |
| C17orf49 | 24.2148871 | 9.540510447 | -1.353140765 | 0.046897457 |
| TBL1X | 2304.809777 | 897.9131677 | -1.35973771 | $4.17 \mathrm{E}-22$ |
| ISL2 | 277.2595529 | 107.5758716 | -1.360189758 | $2.49 \mathrm{E}-10$ |
| CAMK4 | 45.38590208 | 17.46653707 | -1.363364426 | 0.017303412 |
| ADA | 225.5479573 | 87.50881588 | -1.365137867 | $1.76 \mathrm{E}-09$ |
| BDKRB1 | 58.06830412 | 22.27784384 | -1.367056109 | 0.00514776 |
| GCNT3 | 94.75357694 | 36.71700145 | -1.368936551 | 0.000436763 |
| PBXIP1 | 1230.299715 | 475.8829275 | -1.369611762 | $9.99 \mathrm{E}-15$ |
| ABCC3 | 6879.50576 | 2659.650605 | -1.37104611 | 0.001488446 |
| GPRC5C | 364.1642385 | 140.4100677 | -1.372334581 | $1.37 \mathrm{E}-05$ |
| LENG9 | 345.2408785 | 132.9150975 | -1.376865874 | $1.22 \mathrm{E}-11$ |
| FAM151B | 37.93313868 | 14.65398215 | -1.37744526 | 0.025983048 |
| DAPK2 | 168.4787103 | 64.51733754 | -1.379302983 | 0.000244849 |
| ZSWIM4 | 317.0891966 | 121.178782 | -1.381427145 | $2.48 \mathrm{E}-08$ |
| TMEM63C | 58.19457033 | 22.13129496 | -1.38716885 | 0.023488667 |
| FBXO6 | 90.64649523 | 34.30666599 | -1.391902032 | 6.43E-05 |
| LMBR1L | 854.695572 | 324.9526385 | -1.392422453 | 2.99E-18 |
| STAC3 | 100.1226652 | 38.04861032 | -1.395104734 | 3.26E-05 |
| ALPK1 | 428.0545772 | 162.3343808 | -1.398288659 | 0.012430796 |
| C6orf222 | 59.08197785 | 22.20235891 | -1.401612256 | 0.030024115 |
| PYROXD1 | 1325.779528 | 501.5142361 | -1.403795153 | $1.37 \mathrm{E}-22$ |
| ZNF25 | 254.1608373 | 95.88861069 | -1.40462479 | $1.27 \mathrm{E}-09$ |
| CEMIP | 18352.94957 | 6920.392522 | -1.407009992 | $1.23 \mathrm{E}-14$ |
| ZNF624 | 120.4044634 | 45.4909478 | -1.409932311 | $1.21 \mathrm{E}-05$ |
| CREBRF | 492.7048284 | 185.1660767 | -1.412664063 | 6.64E-10 |
| ABCC2 | 116.7208935 | 43.73311156 | -1.413435386 | $2.95 \mathrm{E}-06$ |
| HOXD9 | 109.3197794 | 41.06112076 | -1.417048722 | 2.16E-05 |
| EREG | 33056.62868 | 12344.01725 | -1.421138282 | $2.40 \mathrm{E}-42$ |
| FADS2 | 388.4695936 | 144.5713271 | -1.422239543 | 2.12E-11 |
| AREG | 8866.488329 | 3294.963284 | -1.427941048 | 3.37E-28 |
| AARS | 9955.368319 | 3692.283962 | -1.430941839 | 8.80E-29 |
| KCNAB2 | 196.0486209 | 72.6925995 | -1.431912844 | 2.52E-06 |
| SNTB1 | 5642.978412 | 2090.387191 | -1.432363604 | $6.96 \mathrm{E}-30$ |
| TBC1D16 | 2267.397027 | 834.3916502 | -1.441599318 | 1.32E-16 |
| CTSO | 115.3143104 | 42.25094101 | -1.443474915 | $9.40 \mathrm{E}-05$ |
| CCNG2 | 1350.316016 | 494.5263188 | -1.447814506 | 8.53E-12 |
| CCDC114 | 56.89768341 | 20.89208086 | -1.452119081 | 0.001605096 |
| ABTB1 | 564.0414124 | 205.7776627 | -1.454578244 | $6.21 \mathrm{E}-10$ |
| FBXO36 | 198.3983161 | 72.36753996 | -1.455312457 | $2.74 \mathrm{E}-10$ |
| ZFP2 | 24.69598207 | 8.954428977 | -1.45756473 | 0.032918086 |
| LDLRAD1 | 170.3578323 | 61.95837005 | -1.458860193 | 0.000213698 |
| MAPK10 | 44.89818684 | 16.29519046 | -1.459134894 | 0.006762672 |
| ERMARD | 965.6008944 | 349.7991082 | -1.463747171 | 5.07E-16 |
| FGFBP1 | 1030.907185 | 372.369978 | -1.466749783 | 2.59E-16 |
| SCART1 | 74.97546201 | 27.04778235 | -1.46736982 | 0.000776691 |
| OR2A7 | 45.11841602 | 16.3102424 | -1.469550165 | 0.003173078 |
| BTBD3 | 582.4904155 | 209.493516 | -1.474391343 | $1.73 \mathrm{E}-21$ |
| MAP7D2 | 354.1019558 | 126.5740871 | -1.48222825 | 6.17E-06 |
| PF4 | 55.70363751 | 19.8407839 | -1.485529371 | 0.000672366 |
| DCHS1 | 55.33160346 | 19.67773333 | -1.492700198 | 0.002439252 |
| UNC5B | 341.3976129 | 121.2384676 | -1.493097138 | 3.93E-08 |
| MAML3 | 54.48171069 | 19.569131 | -1.493957865 | 0.001148612 |
| RBM44 | 34.92524593 | 12.31088077 | -1.502027958 | 0.010610834 |
| FREM1 | 23.69992623 | 8.31151915 | -1.505889767 | 0.042230339 |
| KLK10 | 2260.498819 | 795.0077547 | -1.50692634 | $9.94 \mathrm{E}-12$ |


| DHFR2 | 251.1292845 | 88.45790344 | -1.508993849 | $4.98 \mathrm{E}-13$ |
| :---: | :---: | :---: | :---: | :---: |
| CFAP69 | 101.3684237 | 35.64362621 | -1.510748023 | 2.12E-05 |
| SLC7A5 | 28862.63414 | 10121.80616 | -1.511832671 | 9.67E-52 |
| MSMO1 | 6431.8114 | 2236.579724 | -1.523306429 | 9.95E-16 |
| SGK2 | 91.95347968 | 31.99686495 | -1.525797895 | 1.13E-05 |
| LGALS4 | 81.09021701 | 28.07722629 | -1.528555513 | 0.001870239 |
| PLEKHM1 | 7257.177464 | 2505.001629 | -1.534389849 | 1.83E-31 |
| MARS | 10822.32628 | 3735.914941 | -1.534691808 | $1.59 \mathrm{E}-48$ |
| FBN1 | 107.1681137 | 36.96698424 | -1.535589362 | 2.52E-05 |
| YARS | 10366.65619 | 3572.33587 | -1.537050194 | $1.10 \mathrm{E}-60$ |
| SSPO | 79.81093578 | 27.37388348 | -1.537952908 | 0.002907064 |
| C1S | 34.06766119 | 11.66477449 | -1.542477821 | 0.008104935 |
| SQLE | 4771.27484 | 1636.510603 | -1.54279546 | $5.46 \mathrm{E}-22$ |
| GTDC1 | 227.69051 | 78.20260287 | -1.543863268 | $1.73 \mathrm{E}-11$ |
| CD177 | 39.21241381 | 13.55131938 | -1.5443166 | 0.009842132 |
| LFNG | 738.7113705 | 251.9969311 | -1.549813962 | $9.52 \mathrm{E}-20$ |
| SYCP2 | 45.73833137 | 15.50892822 | -1.55829477 | 0.001070083 |
| NUDT18 | 460.6728631 | 156.2363957 | -1.559308455 | $7.10 \mathrm{E}-19$ |
| SAMD13 | 24.31584955 | 8.104129118 | -1.563188893 | 0.030437264 |
| NOXA1 | 1141.306699 | 382.8142373 | -1.574094355 | 3.09E-11 |
| HIST3H2A | 110.7499082 | 37.21522032 | -1.5746707 | 7.01E-06 |
| ST3GAL1 | 303.7843081 | 101.6524267 | -1.574674849 | $3.91 \mathrm{E}-11$ |
| TSC22D3 | 1631.724081 | 547.3311473 | -1.575408952 | 7.88E-13 |
| APOBEC3H | 26.55555043 | 8.784577322 | -1.577095069 | 0.029016851 |
| METTL27 | 221.9687637 | 73.79507935 | -1.581334222 | 5.94E-09 |
| C19orf73 | 40.15927699 | 13.53987207 | -1.582292122 | 0.00239131 |
| SLC25A6 | 17067.29874 | 5688.475232 | -1.585089749 | 1.11E-57 |
| AC073111.5 | 344.5700064 | 114.3678648 | -1.591219864 | 6.33E-16 |
| CARS | 5835.289125 | 1927.832778 | -1.597619039 | $1.61 \mathrm{E}-45$ |
| CACNG4 | 276.239346 | 90.68489909 | -1.605375977 | 5.22E-06 |
| FAM129A | 137.4491079 | 44.84948773 | -1.616877978 | 4.54E-05 |
| NDUFA4L2 | 87.24163776 | 28.30710277 | -1.618117469 | 0.000197043 |
| BANK1 | 81.01126488 | 26.55409566 | -1.620505021 | 0.000176711 |
| ADGRD1 | 43.64884279 | 14.09904613 | -1.623199154 | 0.000946796 |
| BBC3 | 1051.449861 | 340.796144 | -1.623313134 | $2.46 \mathrm{E}-15$ |
| PRSS12 | 129.6410793 | 42.06261571 | -1.624752234 | 7.32E-08 |
| MTHFD2 | 11165.26564 | 3609.16586 | -1.629299347 | $3.26 \mathrm{E}-45$ |
| APOL6 | 1808.129425 | 582.8585481 | -1.633257147 | $1.84 \mathrm{E}-16$ |
| AGXT | 151.360343 | 48.57916841 | -1.636739255 | $1.41 \mathrm{E}-07$ |
| TG | 66.83328727 | 21.31533702 | -1.637212547 | 0.002129093 |
| SEC24D | 2253.95362 | 723.4206594 | -1.639877307 | 1.02E-34 |
| SLC1A5 | 12522.91824 | 4012.440981 | -1.641848911 | 4.99E-53 |
| HMGCS1 | 12732.92282 | 4073.551819 | -1.643824097 | 7.12E-21 |
| CXCL3 | 122.6167471 | 39.12198556 | -1.644860195 | $3.88 \mathrm{E}-08$ |
| AKR1B10 | 43.74347096 | 14.0161267 | -1.647781869 | 0.007723968 |
| PHGR1 | 23.78292759 | 7.48091744 | -1.648099939 | 0.04827286 |
| VAV3 | 54.89154549 | 17.3685657 | -1.649114195 | 0.000579371 |
| HLF | 47.26695987 | 14.92284675 | -1.650735915 | 0.001728352 |
| PLB1 | 75.5120839 | 24.01319364 | -1.652476034 | $7.91 \mathrm{E}-05$ |
| GPT2 | 3505.654679 | 1112.507841 | -1.656051214 | 1.26E-36 |
| POU2F2 | 35.29123778 | 11.1276787 | -1.658731548 | 0.005444229 |
| LGR6 | 148.5339063 | 46.59104753 | -1.667695195 | 3.05E-06 |
| DNASE2 | 1593.188215 | 500.720738 | -1.668819921 | $1.63 \mathrm{E}-25$ |
| BBS9 | 205.7414977 | 64.70026918 | -1.669054494 | 5.13E-12 |
| TCEANC | 79.68906809 | 25.07552974 | -1.672409564 | 1.15E-05 |
| MMP11 | 107.2342257 | 33.66776897 | -1.673735553 | $1.64 \mathrm{E}-06$ |
| TMTC4 | 962.9019347 | 299.7404434 | -1.680816052 | 4.44E-33 |
| TSNARE1 | 281.4351521 | 87.85160161 | -1.684970324 | 3.72E-12 |
| SLC2A12 | 544.2728468 | 167.3319297 | -1.701078453 | 0.005652079 |
| OAF | 913.3499555 | 280.2648628 | -1.701620531 | 8.54E-22 |
| FAM84B | 1617.300833 | 493.4365373 | -1.712959346 | 2.11E-32 |


| TRIB3 | 9849.587466 | 2999.60443 | -1.71507671 | 3.67E-35 |
| :---: | :---: | :---: | :---: | :---: |
| CYP4F12 | 511.491081 | 153.0539647 | -1.73981859 | 0.006929524 |
| CDK18 | 247.8517016 | 74.01833766 | -1.74281154 | 7.18E-07 |
| PDE2A | 125.1466034 | 37.20150692 | -1.747838474 | 0.000231713 |
| ADAMTS14 | 114.2683061 | 33.83081953 | -1.755974759 | 2.73E-05 |
| NAT16 | 131.4334367 | 38.8105282 | -1.760327258 | $7.00 \mathrm{E}-07$ |
| PAQR8 | 118.3975125 | 34.72248764 | -1.762753543 | 3.86E-05 |
| CAPN5 | 1598.165245 | 467.3341425 | -1.773618616 | 0.00064924 |
| XYLT1 | 68.38186982 | 20.03393833 | -1.777194415 | 0.001589832 |
| CLDN2 | 1174.68237 | 341.3875316 | -1.782242124 | $2.76 \mathrm{E}-16$ |
| LMF1 | 211.7237605 | 61.28896098 | -1.7840011 | 7.48E-08 |
| H6PD | 2910.395646 | 843.0296363 | -1.78727513 | $3.14 \mathrm{E}-18$ |
| SESN2 | 1706.298509 | 492.5397883 | -1.790982568 | $2.10 \mathrm{E}-26$ |
| OPLAH | 381.6166315 | 109.9099058 | -1.791934734 | $2.61 \mathrm{E}-10$ |
| APOBR | 23.09568691 | 6.588432991 | -1.793886928 | 0.022115616 |
| LONRF1 | 779.6454475 | 223.3665155 | -1.801261644 | $2.62 \mathrm{E}-23$ |
| SPRYD3 | 1101.532288 | 315.7889165 | -1.802581068 | 6.68E-40 |
| MAP2K6 | 22.18086827 | 6.244083468 | -1.804378485 | 0.020167985 |
| LVRN | 27.30225288 | 7.748740458 | -1.814043977 | 0.006398583 |
| PDE9A | 110.4896504 | 31.17648604 | -1.814434609 | 0.00016796 |
| TMEM154 | 340.8054068 | 96.51669383 | -1.814830386 | 7.49E-09 |
| CCDC121 | 96.70277304 | 27.42327733 | -1.819898213 | 5.51E-07 |
| KNDC1 | 107.7194271 | 30.03762343 | -1.829374836 | $1.66 \mathrm{E}-05$ |
| CUBN | 16.02961911 | 4.464168953 | -1.834494504 | 0.038156399 |
| XBP1 | 5285.333367 | 1478.909062 | -1.837476424 | 3.58E-39 |
| FOXN1 | 310.5213446 | 86.40050763 | -1.844482369 | 0.02622395 |
| SYTL5 | 252.7856002 | 69.82756831 | -1.854327768 | 6.27E-09 |
| KCNN4 | 81.88047031 | 22.51957578 | -1.855791806 | 0.000462633 |
| FBXO32 | 312.8353403 | 85.79688289 | -1.864987642 | 0.004812996 |
| LTF | 55.58049315 | 15.176026 | -1.875489523 | 0.00057328 |
| NR3C2 | 28.85688373 | 7.941486724 | -1.880196942 | 0.004004872 |
| SLC43A1 | 517.2666807 | 140.6087564 | -1.880647889 | $1.51 \mathrm{E}-20$ |
| SLC16A13 | 550.1374029 | 146.244089 | -1.906948529 | $1.08 \mathrm{E}-27$ |
| LRMDA | 87.56676423 | 23.24302491 | -1.913698873 | $1.48 \mathrm{E}-07$ |
| FSBP | 53.48331261 | 14.02675767 | -1.915159111 | 0.000710973 |
| DPEP1 | 395.290586 | 104.0551448 | -1.917893657 | 1.03E-16 |
| GEMIN8 | 203.6757264 | 53.88218992 | -1.917999854 | $1.44 \mathrm{E}-14$ |
| MLXIPL | 895.0961216 | 235.1982156 | -1.926691843 | 9.33E-06 |
| DUSP13 | 17.20599601 | 4.524601939 | -1.930057362 | 0.023313238 |
| HSPA5 | 38865.13706 | 10174.1928 | -1.933574252 | $6.18 \mathrm{E}-57$ |
| PYCR1 | 4790.188943 | 1250.962229 | -1.936989057 | $4.98 \mathrm{E}-81$ |
| B3GALT4 | 199.4765031 | 52.11372271 | -1.937702301 | $1.44 \mathrm{E}-10$ |
| KPNA7 | 20.20226197 | 5.325916116 | -1.944981023 | 0.024273919 |
| GARS | 12655.04982 | 3255.621945 | -1.958825975 | 2.15E-67 |
| KRT81 | 49.67859737 | 12.73495326 | -1.960450487 | 0.007949679 |
| SLC22A11 | 72.44615036 | 18.241352 | -1.974071349 | $5.90 \mathrm{E}-06$ |
| DPH6 | 217.0157813 | 54.83707931 | -1.976177461 | $2.29 \mathrm{E}-11$ |
| PTPRM | 202.8147577 | 51.22268801 | -1.985224864 | 2.26E-07 |
| NAALADL2 | 481.8269675 | 121.4225548 | -1.987810964 | $3.04 \mathrm{E}-12$ |
| HOPX | 37.38243333 | 9.215042735 | -1.998331428 | 0.005440602 |
| VEGFA | 5803.708198 | 1431.187604 | -2.019703709 | 8.27E-07 |
| NFASC | 14.23144828 | 3.424727459 | -2.023013468 | 0.043298868 |
| NLRP6 | 276.8887621 | 68.34784677 | -2.023964786 | 5.27E-18 |
| LDHD | 57.71547444 | 14.18876665 | -2.026362273 | 0.000777328 |
| INSIG1 | 5938.861885 | 1452.897178 | -2.031046987 | 0.000203829 |
| RGS6 | 206.2495462 | 50.74579996 | -2.031582287 | $1.64 \mathrm{E}-10$ |
| HERPUD1 | 3812.581364 | 931.4538973 | -2.033085228 | 1.83E-31 |
| PIR | 428.0514704 | 104.6444916 | -2.037389546 | $4.54 \mathrm{E}-29$ |
| SEMA5A | 662.5670642 | 160.5893992 | -2.044190849 | $1.29 \mathrm{E}-23$ |
| MYO16 | 18.3486786 | 4.346499441 | -2.049174477 | 0.034646332 |
| CXCL5 | 12799.39775 | 3082.233407 | -2.053831191 | 2.20E-36 |


| CYP4F11 | 241.8152185 | 57.51133619 | -2.067056318 | 5.87E-08 |
| :---: | :---: | :---: | :---: | :---: |
| ST6GALNAC3 | 13.49871488 | 3.175152837 | -2.070823116 | 0.037344709 |
| CPS1 | 21.58461301 | 5.147813618 | -2.072982645 | 0.025774451 |
| XPOT | 8837.819327 | 2096.725228 | -2.075814309 | 5.04E-50 |
| ULBP1 | 511.330633 | 119.2378578 | -2.09926615 | 2.69E-20 |
| LURAP1L | 425.5355674 | 99.17021098 | -2.099497021 | $8.30 \mathrm{E}-05$ |
| JDP2 | 970.2771301 | 225.3005246 | -2.104359623 | $3.18 \mathrm{E}-22$ |
| LYRM9 | 61.73755571 | 14.07934798 | -2.130597497 | 0.00036782 |
| ANG | 21.41244759 | 4.895042534 | -2.14061083 | 0.005793463 |
| TEX19 | 15.56425737 | 3.424727459 | -2.157530096 | 0.02451933 |
| HMCN2 | 66.19141879 | 14.65822019 | -2.160771023 | 0.001254242 |
| PPIL6 | 22.93344132 | 5.075933326 | -2.161815131 | 0.009821944 |
| PSAT1 | 17663.65792 | 3923.437487 | -2.170572291 | 3.11E-64 |
| CYP4F3 | 586.3689823 | 127.406772 | -2.201357968 | 0.00053378 |
| SCD | 49466.1121 | 10746.60344 | -2.202432548 | $2.11 \mathrm{E}-32$ |
| CDX1 | 16.58015286 | 3.628921029 | -2.209669026 | 0.015964885 |
| YPEL2 | 317.2289743 | 67.94566963 | -2.217458304 | 1.02E-14 |
| TUBE1 | 1308.057839 | 281.4888263 | -2.218126705 | 2.32E-32 |
| NDRG1 | 2672.336385 | 571.2571992 | -2.225693219 | 0.000533506 |
| OMA1 | 567.3415503 | 120.0887911 | -2.236326192 | $1.57 \mathrm{E}-24$ |
| TCAF2 | 19.63998702 | 4.093728358 | -2.242165921 | 0.006370028 |
| PHGDH | 11590.08204 | 2438.880407 | -2.248437859 | 4.23E-36 |
| HES2 | 235.9696504 | 48.78295381 | -2.271296357 | $3.74 \mathrm{E}-12$ |
| TACSTD2 | 5839.612363 | 1197.685223 | -2.28549153 | 3.63E-08 |
| SLC16A4 | 1229.905874 | 247.4088855 | -2.313548963 | 0.00017263 |
| GRIP1 | 19.144923 | 3.809811821 | -2.314812201 | 0.00907921 |
| PCED1B | 358.8244733 | 71.45012006 | -2.319119855 | 7.17E-19 |
| C1orf127 | 16.14055858 | 3.031392254 | -2.361214063 | 0.017360691 |
| GRIK1 | 10.11016873 | 1.958017014 | -2.373966282 | 0.049519303 |
| FANK1 | 35.83766511 | 6.709298965 | -2.414354817 | 0.000420176 |
| RAB44 | 13.44911574 | 2.411377037 | -2.424323883 | 0.032121451 |
| RPL22L1 | 3897.675561 | 724.9326368 | -2.426614891 | $1.01 \mathrm{E}-52$ |
| KLHL24 | 860.3341358 | 158.2647743 | -2.439071873 | 3.33E-25 |
| CLYBL | 184.9169781 | 33.92054005 | -2.445915359 | $1.54 \mathrm{E}-17$ |
| ESPN | 463.0152572 | 82.56315499 | -2.485179677 | 2.75E-06 |
| KIAA1024 | 46.77189585 | 8.236442397 | -2.487220715 | $1.28 \mathrm{E}-05$ |
| GLDN | 167.4170361 | 29.32283331 | -2.500495854 | $1.01 \mathrm{E}-08$ |
| AKR1C2 | 16.46339999 | 2.902683606 | -2.501530354 | 0.012588522 |
| KCTD16 | 23.87214885 | 4.119819429 | -2.520911424 | 0.001391827 |
| KIF21B | 1167.75718 | 202.7449054 | -2.524580642 | 7.12E-07 |
| C6orf223 | 412.2607939 | 70.49527299 | -2.545842815 | 0.009458476 |
| AKAP6 | 121.9509386 | 20.94426301 | -2.552995782 | $1.63 \mathrm{E}-11$ |
| DEPTOR | 126.5354665 | 21.39082194 | -2.5579294 | $1.46 \mathrm{E}-12$ |
| PRR9 | 80.60935084 | 13.34671764 | -2.582604312 | 4.86E-09 |
| ADRA2C | 402.9748799 | 67.13454082 | -2.583804029 | $3.42 \mathrm{E}-29$ |
| CADPS | 1796.313224 | 297.6854249 | -2.592510033 | 1.89E-09 |
| CKMT1B | 22.76697491 | 3.639960166 | -2.598447567 | 0.003013252 |
| SLCO2B1 | 32.36400413 | 5.201445513 | -2.603989763 | 0.001785529 |
| PHOSPHO1 | 125.4068673 | 20.09314681 | -2.624398698 | 5.96E-12 |
| PADI1 | 927.1805124 | 149.3424635 | -2.633264503 | 0.001668567 |
| CKMT1A | 22.17494047 | 3.485160446 | -2.654333759 | 0.0010587 |
| ANK2 | 182.0704669 | 28.579572 | -2.662462494 | 4.43E-15 |
| KCNQ1 | 1125.274015 | 177.0942487 | -2.666261773 | $1.02 \mathrm{E}-38$ |
| UPK1A | 12.40340357 | 1.81425643 | -2.722315126 | 0.02409664 |
| SLC7A11 | 4467.889244 | 668.056755 | -2.740925664 | 3.12E-50 |
| DMGDH | 92.88373335 | 13.69786825 | -2.764781478 | $1.38 \mathrm{E}-06$ |
| CPNE5 | 23.75721734 | 3.103272546 | -2.899745699 | 0.000542906 |
| CST1 | 26.78130702 | 3.606026419 | -2.91065423 | 0.000213698 |
| SLC6A9 | 984.1540594 | 130.4151556 | -2.914530482 | $8.48 \mathrm{E}-11$ |
| DNAH5 | 19.35688212 | 2.494704634 | -2.918250681 | 0.001477857 |
| GPR182 | 10.09032907 | 1.289016115 | -2.963485105 | 0.024101492 |


| FPGT-TNNI3K | 27.5835936 | 3.473713141 | -2.96525466 | 7.29E-05 |
| :---: | :---: | :---: | :---: | :---: |
| VLDLR | 551.723238 | 70.7477765 | -2.967316655 | 2.53E-31 |
| PRSS2 | 895.9723925 | 113.3098779 | -2.98245513 | 2.97E-08 |
| HRASLS | 9.918049259 | 1.194241214 | -2.987321063 | 0.042003463 |
| PRDM16 | 17.81376368 | 2.233682707 | -2.991824119 | 0.01898791 |
| ASNS | 544.2433013 | 66.15233585 | -3.038407742 | $1.94 \mathrm{E}-42$ |
| PDE7B | 16.01969928 | 1.958017014 | -3.041887871 | 0.003022435 |
| TCP11L2 | 298.7745221 | 34.74114421 | -3.102106776 | $3.76 \mathrm{E}-20$ |
| SERPINE1 | 1072.142722 | 122.0957249 | -3.132930917 | 3.06E-06 |
| TGM3 | 14.06503907 | 1.504248822 | -3.156210565 | 0.006938409 |
| PCK2 | 6301.428949 | 693.4835144 | -3.183509434 | 1.23E-14 |
| GSTA4 | 149.1572867 | 16.28734779 | -3.20096729 | 5.96E-13 |
| SLC8A1 | 67.21975407 | 7.177302755 | -3.201050488 | $2.54 \mathrm{E}-08$ |
| ADM2 | 81.88634091 | 9.015270132 | -3.20517307 | $2.09 \mathrm{E}-08$ |
| TTLL1 | 128.2782247 | 13.56235851 | -3.242479139 | 5.22E-17 |
| FGD5 | 113.7379041 | 11.46098908 | -3.324012017 | $1.89 \mathrm{E}-15$ |
| SPARC | 9.803060553 | 0.967561202 | -3.344364823 | 0.027637989 |
| PDGFRB | 63.07863486 | 5.874051041 | -3.435261803 | $2.00 \mathrm{E}-10$ |
| PTP4A3 | 38.81426301 | 3.329952557 | -3.486893679 | $1.54 \mathrm{E}-05$ |
| FUT3 | 112.3331996 | 9.960978307 | -3.487654674 | 0.002557411 |
| ZNF114 | 15.59983026 | 1.48176238 | -3.525709199 | 0.005007701 |
| KRT16 | 37.94664405 | 3.296018811 | -3.541482484 | 8.53E-05 |
| ST6GALNAC1 | 123.4539713 | 10.16836834 | -3.587843564 | $1.37 \mathrm{E}-17$ |
| CHAC1 | 1900.79547 | 150.8598189 | -3.65797242 | 3.99E-90 |
| CDK14 | 8.539633055 | 0.597120607 | -3.757218514 | 0.029646694 |
| CFAP47 | 8.222662251 | 0.298560303 | -4.561137613 | 0.019991057 |
| S100P | 2692.618194 | 110.3648296 | -4.60784584 | $2.16 \mathrm{E}-07$ |
| RORC | 15.98589057 | 0.597120607 | -4.654482228 | 0.003096858 |
| PRSS1 | 147.4540872 | 5.84795997 | -4.659939868 | $1.10 \mathrm{E}-16$ |
| MEGF10 | 9.03076224 | 0.298560303 | -4.686471828 | 0.014557183 |
| AC009119.2 | 9.702098103 | 0.370440595 | -4.796628456 | 0.006841227 |
| IL2RB | 10.27834211 | 0.370440595 | -4.881572049 | 0.007424211 |
| DDIT4 | 5147.138653 | 155.6840679 | -5.045999148 | 5.24E-23 |
| FGF21 | 43.54553809 | 1.30046342 | -5.07229892 | $1.64 \mathrm{E}-07$ |
| NUPR1 | 537.2601925 | 15.69847803 | -5.100942832 | $3.79 \mathrm{E}-17$ |
| PSD2 | 8.652451099 | 0 | -5.588083263 | 0.004607638 |
| ENOX1 | 10.84290212 | 0 | -5.915918393 | 0.000459791 |

Table 8. HCT15 RNA-seq data

| Gene symbols <br> (Protein coding) | Ctrl (FPKM) | Oxaliplatin (FPKM) | log2 FoldChange | p-adj |
| :---: | :---: | :---: | :---: | :---: |
| KRTAP2-3 | 0 | 125.2869734 | 9.346411215 | 0.000822836 |
| CYP24A1 | 0.645985892 | 73.91566603 | 6.735820341 | $2.60 \mathrm{E}-08$ |
| VSTM1 | 0.322992946 | 38.76174837 | 6.697601482 | $3.47 \mathrm{E}-05$ |
| RFPL4A | 0 | 13.31136649 | 6.101070502 | 0.00062468 |
| NPPB | 1.982261228 | 122.4772137 | 5.923907619 | 0.000154238 |
| LCK | 0.345144722 | 22.4735449 | 5.901918684 | 0.0001421 |
| BIRC7 | 0 | 11.39585598 | 5.880086644 | 0.001313292 |
| PRR35 | 0.345144722 | 21.92623207 | 5.86539495 | 0.000187016 |
| KRT9 | 0 | 10.86855432 | 5.814285504 | 0.001184268 |
| HS3ST6 | 0 | 9.642396919 | 5.640915916 | 0.002780822 |
| SSTR3 | 1.013282389 | 45.82666816 | 5.456949584 | $7.27 \mathrm{E}-07$ |
| TMPRSS7 | 0 | 7.836157053 | 5.353880062 | 0.006101127 |
| ADAMTS2 | 0.38081625 | 15.21411853 | 5.33938626 | 0.001615086 |
| SRRM4 | 0 | 7.34284595 | 5.257292063 | 0.012565035 |
| EIF4E1B | 0 | 7.230008502 | 5.22289714 | 0.017273012 |
| LCN10 | 0.322992946 | 12.19816562 | 5.027935484 | 0.004747616 |
| HSPB8 | 0.725960971 | 21.13577096 | 4.908199231 | 0.000947597 |
| FLT4 | 0.345144722 | 9.85969415 | 4.711884638 | 0.009902761 |


| CHRNA6 | 0.322992946 | 9.405088523 | 4.634463318 | 0.018943818 |
| :---: | :---: | :---: | :---: | :---: |
| XAF1 | 0.690289443 | 16.50837613 | 4.568367934 | 0.010104646 |
| MATK | 2.040084531 | 46.98371948 | 4.496302136 | $2.01 \mathrm{E}-08$ |
| PHF21B | 0.322992946 | 8.392757488 | 4.476010289 | 0.020318371 |
| NXPH3 | 0.322992946 | 8.072125448 | 4.420445965 | 0.025793578 |
| ATP1A4 | 0.38081625 | 8.029853169 | 4.413252593 | 0.023099204 |
| RTP4 | 0.38081625 | 7.798576551 | 4.387449964 | 0.027914431 |
| HCAR3 | 0.345144722 | 7.740984883 | 4.369117289 | 0.02452052 |
| FAM92B | 0.322992946 | 7.754964271 | 4.355803974 | 0.04006894 |
| C4orf54 | 0.690289443 | 14.08672325 | 4.343227528 | 0.009454433 |
| PRSS42 | 0.38081625 | 7.582404294 | 4.334104743 | 0.028220147 |
| DRGX | 0.322992946 | 7.452116596 | 4.322380286 | 0.034623455 |
| APOL3 | 10.50305893 | 208.2544095 | 4.314170911 | $6.98 \mathrm{E}-22$ |
| DYDC2 | 0.645985892 | 13.04497435 | 4.256247912 | 0.007933229 |
| SLC15A3 | 2.514395612 | 46.94254903 | 4.254588477 | $1.82 \mathrm{E}-07$ |
| CACNG8 | 1.832738192 | 33.40182175 | 4.231699872 | $5.38 \mathrm{E}-05$ |
| IGFL1 | 2.155731138 | 38.27056813 | 4.185045954 | $1.39 \mathrm{E}-05$ |
| KRT17 | 3.850670948 | 68.95377886 | 4.172827901 | $3.03 \mathrm{E}-11$ |
| EBI3 | 14.83487788 | 266.0035139 | 4.15521294 | 4.57E-37 |
| C16orf90 | 0.703809196 | 11.90929734 | 4.101257861 | 0.017437336 |
| IGF2 | 0.703809196 | 11.95379642 | 4.09722856 | 0.014115672 |
| COL24A1 | 0.725960971 | 11.99965864 | 4.096047544 | 0.011797236 |
| EDN2 | 6.955024248 | 113.4347255 | 4.072292564 | $2.95 \mathrm{E}-13$ |
| NYAP2 | 1.084625445 | 17.74741109 | 4.066588654 | 0.001891278 |
| GCNT4 | 1.523264998 | 23.60117836 | 4.050536826 | 0.000364396 |
| REN | 4.231487197 | 68.31979062 | 4.030919015 | 2.42E-09 |
| ITGAM | 1.048953917 | 16.93258115 | 4.027097243 | 0.002851174 |
| HBA1 | 0.645985892 | 11.00846375 | 4.020184502 | 0.021304122 |
| IL2RG | 1.832738192 | 28.61641862 | 4.019125292 | 0.000344523 |
| LRRC36 | 0.703809196 | 10.80983768 | 3.94970852 | 0.026958678 |
| FAM71E2 | 0.690289443 | 10.38587083 | 3.900474734 | 0.037724297 |
| WFDC1 | 2.169250891 | 31.24933696 | 3.891210709 | $1.48 \mathrm{E}-05$ |
| MYL9 | 29.9329762 | 436.3212348 | 3.86698279 | 3.81E-27 |
| ELF5 | 0.725960971 | 10.26139989 | 3.866506692 | 0.02582918 |
| ZFR2 | 0.690289443 | 9.980694236 | 3.844324484 | 0.035209322 |
| HOXD1 | 0.761632499 | 9.872667651 | 3.795635882 | 0.026157866 |
| TMEM40 | 10.85683567 | 147.2144137 | 3.764734464 | $9.07 \mathrm{E}-15$ |
| AZU1 | 1.465441695 | 19.09803945 | 3.748475391 | 0.001746411 |
| ZFP28 | 0.725960971 | 9.157486628 | 3.710785603 | 0.041477085 |
| CREB3L3 | 1.336275335 | 17.89904996 | 3.701912394 | 0.001550174 |
| GNAO1 | 0.703809196 | 9.099775873 | 3.695245462 | 0.039404822 |
| LRRC15 | 1.013282389 | 12.81001184 | 3.626272077 | 0.009022534 |
| ANO2 | 1.810586416 | 20.1612586 | 3.518297597 | 0.004383479 |
| RNF113B | 1.013282389 | 11.87272272 | 3.511094279 | 0.014796324 |
| SCN2B | 1.071105693 | 11.91387003 | 3.498138024 | 0.024626459 |
| TXNIP | 899.8830436 | 10036.04559 | 3.479143186 | 4.63E-06 |
| PTPN7 | 17.09648016 | 188.901704 | 3.467242815 | $1.52 \mathrm{E}-19$ |
| TPSD1 | 1.048953917 | 11.02478902 | 3.395584352 | 0.017021385 |
| GZMM | 4.182295917 | 43.14589896 | 3.372146633 | $5.79 \mathrm{E}-05$ |
| HRC | 1.659268282 | 16.78685498 | 3.296420599 | 0.003711629 |
| SCUBE1 | 4.36928558 | 41.52237034 | 3.287034387 | $4.63 \mathrm{E}-06$ |
| C13orf46 | 2.097907835 | 19.82406311 | 3.250468261 | 0.001187576 |
| LHX2 | 2.964759819 | 28.86277645 | 3.239629366 | 0.000644174 |
| VGLL1 | 26.8051736 | 246.1089317 | 3.207428689 | $1.18 \mathrm{E}-16$ |
| CEACAM6 | 5.855083951 | 54.1772493 | 3.199711511 | 2.97E-06 |
| CDHR4 | 8.930602647 | 82.10587339 | 3.190183791 | $4.05 \mathrm{E}-06$ |
| S100A3 | 4.643087245 | 41.78071894 | 3.188558103 | $6.59 \mathrm{E}-06$ |
| MMP19 | 5.222617811 | 47.54513078 | 3.185793212 | $1.21 \mathrm{E}-07$ |
| GPR17 | 4.24500695 | 38.08814825 | 3.176743059 | $1.50 \mathrm{E}-05$ |
| ANKRD1 | 64.25265034 | 580.2346946 | 3.173307719 | 0.000160831 |
| IL1R2 | 1.752763113 | 15.63238772 | 3.172450673 | 0.006490111 |


| LBX1 | 1.106777221 | 9.618914892 | 3.16860988 | 0.040110054 |
| :---: | :---: | :---: | :---: | :---: |
| DCLK1 | 5.079931699 | 45.7135162 | 3.159245943 | 0.000697116 |
| GBP1 | 7.738808522 | 66.6366817 | 3.143431289 | 9.04E-06 |
| DIRAS1 | 3.075518696 | 26.90535092 | 3.12587463 | 0.0143173 |
| MILR1 | 2.385229253 | 21.05235137 | 3.112814563 | 0.001615086 |
| DDO | 1.371946863 | 11.94328789 | 3.112391452 | 0.016382018 |
| PDE4C | 1.394098639 | 11.91734089 | 3.089205739 | 0.026461864 |
| ANXA8L1 | 10.10872292 | 85.89033726 | 3.08655477 | $1.00 \mathrm{E}-05$ |
| THEG | 7.975143561 | 68.02767004 | 3.085037208 | $9.35 \mathrm{E}-08$ |
| OTOF | 4.792610281 | 40.19632584 | 3.055734913 | 0.000558872 |
| CPA4 | 20.3177776 | 168.9733429 | 3.054153821 | $9.58 \mathrm{E}-08$ |
| UNC13A | 21.8120539 | 180.1873513 | 3.052635168 | $1.27 \mathrm{E}-08$ |
| CRYAB | 7.815193403 | 65.62724924 | 3.047183088 | $1.54 \mathrm{E}-08$ |
| ATP6V0A4 | 20.97044632 | 171.0269002 | 3.033721222 | $1.62 \mathrm{E}-15$ |
| RBP4 | 10.28039773 | 83.82321103 | 3.014208343 | 5.02E-08 |
| KCND3 | 5.026996125 | 40.95806047 | 3.012894703 | 0.002270591 |
| CRLF2 | 4.576631919 | 36.47325861 | 3.000539642 | $1.25 \mathrm{E}-05$ |
| FBLL1 | 1.407618391 | 10.9896735 | 2.986068246 | 0.040737209 |
| ACVRL1 | 9.134856355 | 71.78700092 | 2.974877945 | $6.94 \mathrm{E}-06$ |
| IL12RB1 | 2.004413003 | 16.12311476 | 2.964920427 | 0.011891189 |
| TBXA2R | 11.6523446 | 91.50494974 | 2.964081034 | $8.86 \mathrm{E}-11$ |
| MUC2 | 1.672788034 | 13.40888455 | 2.961997246 | 0.031449498 |
| FST | 9.714386921 | 74.89424469 | 2.94625714 | 2.92E-08 |
| IL12B | 4.347133804 | 32.35348839 | 2.933203479 | 0.000289491 |
| CLDN1 | 12.82183285 | 97.65521838 | 2.931360437 | $6.66 \mathrm{E}-06$ |
| CNGB1 | 3.806367397 | 28.84968386 | 2.915803968 | 0.005137731 |
| IL36RN | 31.5484385 | 232.3447563 | 2.893649086 | $3.43 \mathrm{E}-12$ |
| JPH2 | 20.28015688 | 149.2585805 | 2.88491473 | $4.81 \mathrm{E}-17$ |
| GFAP | 2.420900781 | 17.87556793 | 2.881487896 | 0.003159536 |
| TTLL6 | 20.81049617 | 152.0661897 | 2.864814607 | $5.10 \mathrm{E}-16$ |
| RUBCNL | 31.55966559 | 230.2962481 | 2.863960489 | $2.32 \mathrm{E}-11$ |
| GPR20 | 5.68340914 | 40.72240659 | 2.850811658 | 0.000280015 |
| ZYG11A | 1.99578098 | 14.70795301 | 2.845434803 | 0.025461129 |
| PLET1 | 1.394098639 | 10.01592885 | 2.844311279 | 0.037296555 |
| ATP2A3 | 20.50102297 | 145.7013997 | 2.827196303 | $4.38 \mathrm{E}-08$ |
| MX2 | 12.09652354 | 85.16086589 | 2.823026953 | $2.22 \mathrm{E}-05$ |
| OMP | 2.398749005 | 17.0592789 | 2.818782402 | 0.009363973 |
| IGF2BP1 | 6.61182872 | 46.30980485 | 2.811627054 | $1.51 \mathrm{E}-05$ |
| LIMS2 | 26.33754535 | 183.5888374 | 2.810763803 | $5.88 \mathrm{E}-12$ |
| RHBDL3 | 60.00894671 | 422.2563067 | 2.807333175 | $1.71 \mathrm{E}-17$ |
| KCNQ5 | 1.982261228 | 13.90353566 | 2.774169407 | 0.030634705 |
| ATAD3C | 10.90602695 | 73.36500143 | 2.761209154 | $3.31 \mathrm{E}-09$ |
| DMKN | 17.46801273 | 119.0021889 | 2.758818682 | $1.02 \mathrm{E}-07$ |
| CALHM3 | 6.797023284 | 46.27780292 | 2.748140992 | $4.40 \mathrm{E}-05$ |
| CLDN6 | 19.9542254 | 134.5270495 | 2.746478416 | $1.34 \mathrm{E}-10$ |
| HTR3A | 2.062236307 | 13.88697221 | 2.738555674 | 0.028946978 |
| ANXA8 | 22.81361164 | 151.1064741 | 2.73524126 | $4.88 \mathrm{E}-07$ |
| ADRA2B | 6.208860695 | 41.03722187 | 2.714956592 | 0.000301962 |
| MDGA1 | 101.3978459 | 663.1472065 | 2.709220887 | $5.47 \mathrm{E}-33$ |
| UPK2 | 21.91418076 | 138.7580096 | 2.66714404 | $1.40 \mathrm{E}-06$ |
| CIB2 | 10.0422676 | 63.93808539 | 2.664230971 | 7.61E-05 |
| MRGPRG | 2.434420533 | 15.38914348 | 2.658423838 | 0.016579453 |
| SFTA2 | 8.024334841 | 49.83292916 | 2.633873185 | $2.20 \mathrm{E}-06$ |
| MCAM | 88.63887814 | 547.1473611 | 2.625449642 | $1.39 \mathrm{E}-17$ |
| ALPL | 4.833169539 | 29.84358191 | 2.625117521 | 0.001808261 |
| MT3 | 6.208860695 | 38.14684174 | 2.61218483 | 0.004606724 |
| GIMAP2 | 4.231487197 | 25.3969097 | 2.598755102 | 0.000748433 |
| ITGAX | 117.9623515 | 706.8325541 | 2.583046465 | $3.43 \mathrm{E}-12$ |
| SBK2 | 2.572218916 | 15.01326566 | 2.582278646 | 0.027137881 |
| ARRDC4 | 261.8367972 | 1549.862991 | 2.565112606 | $2.18 \mathrm{E}-12$ |
| ALPP | 96.92921787 | 570.055246 | 2.559326459 | $5.00 \mathrm{E}-20$ |


| ERP27 | 4.993119696 | 29.00134588 | 2.558792635 | 0.000440686 |
| :---: | :---: | :---: | :---: | :---: |
| HLA-DPA1 | 11.16142113 | 64.9941478 | 2.54003726 | $1.61 \mathrm{E}-05$ |
| ANK1 | 7.386980972 | 42.48919641 | 2.535252698 | 8.89E-05 |
| ADGRB2 | 208.937943 | 1201.812548 | 2.524295853 | 5.43E-21 |
| RARRES3 | 24.39779257 | 137.3959859 | 2.500645553 | $3.42 \mathrm{E}-08$ |
| PSG4 | 4.222855174 | 23.75729397 | 2.500222646 | 0.006648295 |
| ANKRD2 | 21.58759761 | 122.8549415 | 2.497368366 | $6.40 \mathrm{E}-12$ |
| LAPTM5 | 3.952797802 | 22.08234769 | 2.496210297 | 0.009585571 |
| IFI44 | 19.39310231 | 109.3174966 | 2.491687586 | $4.70 \mathrm{E}-05$ |
| RSAD2 | 42.9276331 | 238.4719569 | 2.480117863 | $1.31 \mathrm{E}-07$ |
| FAM3B | 4.814762056 | 26.83083854 | 2.469763897 | 0.015850422 |
| GNAT1 | 2.443052556 | 13.56511925 | 2.465260509 | 0.029048695 |
| ETS1 | 57.97554501 | 317.6918564 | 2.45379726 | 0.023011409 |
| ECM1 | 65.48761037 | 358.5621837 | 2.446202861 | $7.49 \mathrm{E}-16$ |
| APOBEC3A | 4.093688815 | 22.31149345 | 2.428721335 | 0.005004955 |
| HOXC10 | 15.02186754 | 80.40229656 | 2.423013134 | 9.05E-08 |
| CST6 | 308.581178 | 1645.621996 | 2.414066153 | $2.20 \mathrm{E}-09$ |
| GPR55 | 3.571981552 | 18.79038091 | 2.409474354 | 0.01206045 |
| TGM2 | 39.45907593 | 208.5924653 | 2.407045409 | 1.13E-14 |
| RNF151 | 3.456334945 | 18.34293203 | 2.397620204 | 0.012477706 |
| KRT74 | 3.102558201 | 16.48836496 | 2.396786405 | 0.038012663 |
| SPINK2 | 6.61182872 | 34.72805813 | 2.391912833 | 0.002023582 |
| NES | 226.7150797 | 1178.400063 | 2.376241298 | 1.11E-14 |
| SLC19A3 | 4.993119696 | 25.09741379 | 2.3510939 | 0.002315531 |
| ITGB3 | 5.311224913 | 26.89068016 | 2.345834781 | 0.00771852 |
| APOE | 80.5202485 | 407.5220726 | 2.342287044 | $1.27 \mathrm{E}-12$ |
| NGFR | 13.44077924 | 68.06175653 | 2.334189923 | 0.000973775 |
| IFI44L | 7.759165199 | 38.99252549 | 2.333647687 | 0.029332254 |
| IL1A | 7.409132747 | 37.10746188 | 2.329804178 | 0.000883533 |
| KLK5 | 5.821207522 | 28.61024461 | 2.322288392 | 0.013013735 |
| CACNG6 | 8.015702819 | 39.80177686 | 2.312572898 | 0.002464713 |
| SYNPO2L | 5.253401609 | 26.05215316 | 2.309246838 | 0.003094289 |
| C22orf31 | 6.966748901 | 34.46145095 | 2.30656431 | 0.001315539 |
| OBSL1 | 5.12423525 | 25.2442418 | 2.291078473 | 0.01708731 |
| VWF | 10.56397486 | 52.12889018 | 2.289531267 | 0.001124412 |
| AXL | 52.60650259 | 256.5849686 | 2.289285209 | $3.21 \mathrm{E}-10$ |
| HIST1H2BJ | 28.87733946 | 141.1375983 | 2.286751458 | 5.03E-08 |
| GAL3ST3 | 5.576394556 | 27.17497576 | 2.281567514 | 0.002249745 |
| ABCG4 | 16.99060902 | 82.89197684 | 2.280606818 | 7.87E-08 |
| S100A2 | 56.78944437 | 276.5635032 | 2.278057803 | 8.11E-12 |
| OR4C6 | 3.340688339 | 16.47551055 | 2.267187248 | 0.032342054 |
| SCN4B | 37.60403187 | 179.7164077 | 2.262627186 | $2.40 \mathrm{E}-05$ |
| APLP1 | 305.0846446 | 1464.824855 | 2.262448229 | $6.84 \mathrm{E}-29$ |
| LY6G6C | 35.64098388 | 169.7459075 | 2.261987761 | 6.05E-09 |
| SUN3 | 60.28015331 | 288.5349117 | 2.259605058 | $4.30 \mathrm{E}-20$ |
| UCN2 | 3.779327892 | 18.35691142 | 2.25859046 | 0.025002076 |
| CX3CL1 | 92.01164781 | 441.5470596 | 2.257408959 | $2.81 \mathrm{E}-16$ |
| LYPD3 | 39.15090027 | 187.5420562 | 2.257014706 | $6.38 \mathrm{E}-08$ |
| PLA2G4D | 7.67430239 | 36.64826041 | 2.254699228 | 0.003184047 |
| RASGRP3 | 27.46174071 | 130.0397791 | 2.245717063 | 2.17E-08 |
| CARD6 | 37.85778505 | 179.2002332 | 2.240042244 | $3.64 \mathrm{E}-14$ |
| C1QTNF2 | 90.19082365 | 423.9483656 | 2.235901504 | 1.15E-17 |
| MDK | 684.3124147 | 3205.818858 | 2.227791908 | 5.61E-16 |
| PLA2G4C | 15.17009305 | 70.08490633 | 2.224006969 | 0.001358529 |
| DMBX1 | 120.441751 | 561.4390208 | 2.223552064 | $3.14 \mathrm{E}-16$ |
| SHD | 4.204447692 | 19.66761338 | 2.218832359 | 0.026303863 |
| APOD | 4.195815669 | 19.54905512 | 2.218465366 | 0.049378211 |
| CRYM | 12.99041503 | 60.44291986 | 2.217962211 | 0.000105085 |
| KRT13 | 8.427302866 | 38.90678317 | 2.209586826 | 0.000188746 |
| CALD1 | 77.13036309 | 356.0343331 | 2.208113315 | 5.74E-06 |
| LTB | 11.38717496 | 52.53600221 | 2.207538656 | 0.002796859 |


| COL9A2 | 31.31046246 | 144.2518174 | 2.204715398 | $9.64 \mathrm{E}-06$ |
| :---: | :---: | :---: | :---: | :---: |
| TNFRSF9 | 13.97291362 | 64.08897969 | 2.202149082 | $7.84 \mathrm{E}-06$ |
| PINLYP | 19.53578843 | 89.86253492 | 2.200321778 | 2.05E-08 |
| SLC26A8 | 9.08860361 | 41.09021771 | 2.195149605 | 0.014414037 |
| TNFSF10 | 9.139744085 | 41.46353461 | 2.183504703 | 0.002545121 |
| CRIP2 | 62.53915474 | 283.6978864 | 2.180642003 | $1.89 \mathrm{E}-08$ |
| SERPINE1 | 68.34878591 | 310.350695 | 2.179844021 | 7.29E-08 |
| PI16 | 3.930646027 | 17.38819267 | 2.17145219 | 0.021718341 |
| VANGL2 | 56.04442426 | 253.4918498 | 2.170275541 | $4.01 \mathrm{E}-11$ |
| KIF25 | 7.068875756 | 31.54871377 | 2.166401242 | 0.002229283 |
| ATG9B | 20.15164218 | 90.05352789 | 2.161553134 | 0.001452312 |
| RPP25 | 24.30918547 | 107.8096508 | 2.153214798 | 8.75E-06 |
| C2CD4C | 65.20811522 | 289.0068786 | 2.144529104 | $5.08 \mathrm{E}-08$ |
| ASTL | 7.307005893 | 32.45883497 | 2.142983474 | 0.001586565 |
| ARHGDIB | 18.95251357 | 83.23755 | 2.141740758 | 5.44E-08 |
| UBA7 | 181.5724932 | 798.2774735 | 2.138053439 | 2.03E-06 |
| LY6D | 18.88980253 | 83.09730646 | 2.13505072 | $7.66 \mathrm{E}-06$ |
| SPTSSB | 31.38489815 | 137.6553404 | 2.132578882 | $1.01 \mathrm{E}-06$ |
| APOL1 | 188.9459133 | 828.3981411 | 2.132370838 | $4.98 \mathrm{E}-15$ |
| RIPPLY3 | 12.88649308 | 56.63169497 | 2.120712615 | 0.00316497 |
| EPSTI1 | 30.39816349 | 131.7429756 | 2.119593353 | 8.65E-06 |
| TENT5C | 24.66670651 | 106.2009351 | 2.115044952 | 4.59E-09 |
| CIDEC | 15.72078901 | 67.96313665 | 2.110180413 | $6.84 \mathrm{E}-05$ |
| AVPR1B | 4.634455222 | 19.69131044 | 2.107278997 | 0.024703789 |
| FBXO17 | 17.78791304 | 76.37264947 | 2.103509693 | 7.83E-05 |
| RAB3B | 247.9875164 | 1065.116174 | 2.102714038 | $3.72 \mathrm{E}-13$ |
| ZNF512B | 5.754752196 | 24.2986941 | 2.098249261 | 0.009438695 |
| SELL | 8.466067025 | 36.48264216 | 2.090991925 | 0.008742058 |
| IL15 | 18.16384156 | 77.29342143 | 2.090520255 | $2.49 \mathrm{E}-07$ |
| TRIML2 | 6.130680715 | 25.64707251 | 2.086207225 | 0.023828971 |
| GPRC5B | 60.90154067 | 258.8424692 | 2.082711647 | $1.32 \mathrm{E}-10$ |
| GPR137C | 158.0426549 | 669.1066972 | 2.081515143 | $7.88 \mathrm{E}-28$ |
| PDE6G | 24.2741656 | 101.4668769 | 2.07580343 | 3.02E-05 |
| CYP1A2 | 6.846214565 | 28.97908476 | 2.072331941 | 0.003124132 |
| RASGEF1B | 11.29547522 | 47.08358343 | 2.069545413 | 8.40E-05 |
| PTH1R | 10.3787803 | 43.73031594 | 2.069479761 | 0.002588761 |
| COL5A3 | 24.35543821 | 101.9553308 | 2.067914353 | 5.75E-08 |
| SPHK1 | 130.7944458 | 547.1965092 | 2.063102836 | 1.97E-15 |
| HSPA2 | 40.52464223 | 168.720292 | 2.058190451 | $4.72 \mathrm{E}-11$ |
| LINGO1 | 14.51677266 | 60.56044908 | 2.054450037 | 0.000768749 |
| DISP2 | 26.08604955 | 107.5212588 | 2.045914896 | $1.31 \mathrm{E}-08$ |
| SPIB | 7.12490396 | 29.62975554 | 2.041979643 | 0.009141265 |
| THPO | 7.184522362 | 29.15265063 | 2.030809493 | 0.028663936 |
| ADGRB1 | 4.527440638 | 18.32301681 | 2.017965623 | 0.025583001 |
| FGF22 | 15.77177539 | 63.04488491 | 2.017760202 | 0.000146168 |
| SCNN1B | 17.04045196 | 68.40376289 | 2.012767461 | 0.0006329 |
| MSANTD1 | 24.59356835 | 99.34323765 | 2.01227228 | $2.30 \mathrm{E}-07$ |
| CLCN1 | 16.93587834 | 68.94403805 | 2.010861886 | 0.000200027 |
| ZNF488 | 136.0673984 | 548.8536549 | 2.01056387 | $2.50 \mathrm{E}-11$ |
| APOBEC3G | 16.71012452 | 67.75993789 | 2.005076171 | 0.00022229 |
| RELB | 277.0425381 | 1111.002425 | 2.003771871 | $2.26 \mathrm{E}-06$ |
| C3 | 8.513960774 | 33.42822195 | 2.001378708 | 0.04776639 |
| PSMB9 | 264.1448417 | 1055.398833 | 1.998205094 | 2.47E-19 |
| COL1A1 | 171.0099525 | 683.4444077 | 1.997962519 | 3.63E-08 |
| TTLL10 | 21.97884098 | 87.83296605 | 1.996003555 | $7.16 \mathrm{E}-07$ |
| RUNX3 | 8.598977678 | 34.3652729 | 1.994621544 | 0.001826782 |
| ZNF541 | 5.093451452 | 20.46867896 | 1.984234989 | 0.0321252 |
| MYH15 | 14.26577443 | 55.76803144 | 1.978515117 | 0.009856342 |
| BEST3 | 12.00612134 | 47.30245883 | 1.977636288 | 0.006162473 |
| DES | 6.745882809 | 26.350405 | 1.971616005 | 0.027073613 |
| OAS2 | 22.60821449 | 88.35452375 | 1.97110769 | 0.000345485 |


| PTAFR | 52.68532844 | 207.0713615 | 1.966302053 | $1.07 \mathrm{E}-08$ |
| :---: | :---: | :---: | :---: | :---: |
| DPF1 | 101.3323446 | 397.3209144 | 1.966044208 | 1.93E-09 |
| PGF | 21.02956716 | 82.88850598 | 1.964768286 | 7.54E-05 |
| NRIP3 | 7.254070319 | 28.52079325 | 1.962697337 | 0.014108772 |
| OLFML2A | 286.3893441 | 1114.174116 | 1.959433125 | 8.09E-11 |
| LHX1 | 49.88166221 | 194.6065887 | 1.957036727 | 8.68E-09 |
| SH2D3C | 7.155687758 | 28.12265431 | 1.955702324 | 0.021941862 |
| ADAMTS15 | 50.97980741 | 198.0287437 | 1.953846273 | $7.04 \mathrm{E}-11$ |
| OPRL1 | 25.12570273 | 97.17438483 | 1.949013774 | 0.000771704 |
| DMC1 | 69.94778992 | 269.7219125 | 1.942018901 | $6.44 \mathrm{E}-14$ |
| ART5 | 16.28679982 | 62.65579541 | 1.937563531 | 5.87E-05 |
| GFY | 5.855083951 | 22.54164509 | 1.934487152 | 0.031442323 |
| OLFML3 | 9.892744561 | 37.57023014 | 1.931579204 | 0.005542442 |
| INAFM2 | 79.64376936 | 303.2709622 | 1.927756989 | $1.16 \mathrm{E}-09$ |
| CFAP74 | 33.04791072 | 125.7926961 | 1.92520302 | 0.000140842 |
| DLG4 | 172.6423528 | 655.1002476 | 1.924896935 | $2.71 \mathrm{E}-06$ |
| TNNT1 | 295.3053009 | 1114.164838 | 1.915993233 | $1.38 \mathrm{E}-06$ |
| CCNE2 | 516.2977097 | 1942.583379 | 1.912080372 | $4.70 \mathrm{E}-30$ |
| VSIG2 | 16.92106106 | 63.18096621 | 1.908875711 | $7.80 \mathrm{E}-05$ |
| PDZD4 | 14.62753154 | 54.66486274 | 1.903345877 | 5.85E-05 |
| TMPRSS6 | 106.4707923 | 397.3301129 | 1.902981562 | $5.48 \mathrm{E}-07$ |
| CALY | 41.34589313 | 154.2374416 | 1.902131698 | $1.12 \mathrm{E}-05$ |
| CDKN1A | 1606.133744 | 6004.065309 | 1.901981588 | $3.00 \mathrm{E}-25$ |
| C15orf48 | 43.57556818 | 162.3697196 | 1.901543324 | $2.40 \mathrm{E}-05$ |
| HTR1D | 167.5425093 | 626.7486985 | 1.900155786 | $2.47 \mathrm{E}-11$ |
| IRF8 | 31.33734787 | 116.1003175 | 1.899285734 | 0.000375767 |
| SCN3B | 7.883443828 | 28.90282193 | 1.897196007 | 0.013020014 |
| DACT3 | 18.22345997 | 67.27277765 | 1.896535671 | 0.000418239 |
| USH1G | 61.37195916 | 226.2225655 | 1.886839203 | $4.06 \mathrm{E}-05$ |
| IL10RA | 22.96263711 | 85.62657547 | 1.886673297 | 0.000140584 |
| FXYD6 | 21.05840176 | 77.55385459 | 1.876420855 | 0.004747616 |
| C1QL1 | 119.4351514 | 437.6698224 | 1.875001219 | 5.06E-05 |
| HOXC8 | 43.50062914 | 159.9407377 | 1.871741307 | 0.000199574 |
| SLC25A45 | 102.5341151 | 374.1455955 | 1.871051064 | 8.64E-07 |
| CTSS | 10.72392502 | 39.51147263 | 1.870828704 | 0.005974837 |
| PNCK | 5.186946283 | 18.99827144 | 1.865171089 | 0.049872685 |
| GCNT2 | 7.873016707 | 28.8439862 | 1.863593002 | 0.008839209 |
| CGB7 | 50.36884718 | 182.9382394 | 1.862562962 | 0.000114258 |
| VSIR | 159.9400534 | 580.0573413 | 1.85723526 | $2.71 \mathrm{E}-22$ |
| CALHM1 | 11.95677597 | 42.77548063 | 1.856708258 | 0.005927393 |
| KLF1 | 12.4735955 | 44.61247837 | 1.853662197 | 0.000924296 |
| RPGRIP1 | 9.316306626 | 33.70165176 | 1.851253763 | 0.002941102 |
| RIMKLB | 104.0085265 | 373.3229671 | 1.847601682 | 2.25E-06 |
| STX11 | 93.28684732 | 335.3011154 | 1.842827142 | 2.82E-07 |
| SOWAHA | 87.95966169 | 316.0094331 | 1.841025324 | $6.23 \mathrm{E}-11$ |
| CEACAM1 | 32.7063562 | 116.6581157 | 1.840017626 | 0.000615557 |
| ARAP3 | 158.0734387 | 566.2374206 | 1.839350927 | 8.90E-16 |
| DEPP1 | 16.50946101 | 58.85629996 | 1.835221258 | 0.008591571 |
| CIART | 4.92177664 | 17.45507195 | 1.833509414 | 0.037021542 |
| RASGRF1 | 66.05346709 | 234.9254628 | 1.829971 | 2.82E-07 |
| GABRD | 6.307243256 | 22.44412703 | 1.829583059 | 0.046174435 |
| SLC4A9 | 23.45780243 | 83.24657629 | 1.827474945 | 0.001980462 |
| TUBB2A | 316.0049386 | 1116.492323 | 1.820472854 | 0.015347675 |
| NPTX1 | 16.47558458 | 57.69927179 | 1.814073394 | 0.011749272 |
| FBLN5 | 108.3031813 | 378.4558094 | 1.80353624 | 2.87E-08 |
| PRDM1 | 10.56397486 | 37.0817299 | 1.802996955 | 0.027423082 |
| YPEL4 | 19.0749971 | 66.6675159 | 1.801440858 | 0.024217546 |
| KCNG2 | 11.50282156 | 39.86420254 | 1.79834175 | 0.001513147 |
| RAB9B | 36.88865211 | 127.2945529 | 1.797103 | $4.16 \mathrm{E}-07$ |
| HCAR2 | 12.08918905 | 42.5559566 | 1.79538533 | 0.006112757 |
| IGFN1 | 22.03162246 | 76.06913356 | 1.793265858 | 0.034799208 |


| MYBL1 | 494.2304041 | 1707.424776 | 1.788441855 | $3.06 \mathrm{E}-12$ |
| :---: | :---: | :---: | :---: | :---: |
| MDFI | 119.1225503 | 412.0016532 | 1.78722436 | 1.74E-15 |
| ACP7 | 170.2021977 | 586.6094579 | 1.783413545 | 5.40E-15 |
| TAS1R1 | 8.825383162 | 30.17237659 | 1.783357777 | 0.019725965 |
| CYTH4 | 7.444804275 | 25.42855436 | 1.782316014 | 0.018032472 |
| GPR3 | 135.3979337 | 466.1127077 | 1.78178468 | $1.54 \mathrm{E}-07$ |
| FOXL2NB | 17.891835 | 60.81444002 | 1.781475052 | 0.000432922 |
| ANKRD63 | 10.43351097 | 35.54300716 | 1.780269148 | 0.017375724 |
| HPN | 36.6917329 | 125.5052638 | 1.780250273 | 0.003278366 |
| CYGB | 5.289073137 | 18.0880543 | 1.777379393 | 0.047594327 |
| CCDC151 | 37.42208403 | 128.1292749 | 1.776344711 | $2.39 \mathrm{E}-07$ |
| IL11 | 61.20548026 | 209.1354204 | 1.774029775 | $1.74 \mathrm{E}-09$ |
| CRYBA2 | 19.27730161 | 64.90043471 | 1.766308648 | 0.000281281 |
| FCMR | 27.41189776 | 93.14928039 | 1.761236424 | 0.000682955 |
| PPP1R14C | 237.2444969 | 803.9040792 | 1.758972528 | $7.71 \mathrm{E}-08$ |
| ITPKA | 233.4993889 | 790.5928583 | 1.758192861 | $1.06 \mathrm{E}-10$ |
| CSPG5 | 220.6353853 | 746.0249693 | 1.755717458 | $3.36 \mathrm{E}-08$ |
| TRIM72 | 7.378348949 | 24.60668675 | 1.753638512 | 0.044020577 |
| TMEM92 | 21.27991952 | 71.81663381 | 1.75215068 | 0.000158456 |
| TMEM217 | 19.65143503 | 65.85318546 | 1.75092852 | 0.002529365 |
| ZG16 | 34.13807556 | 114.8044817 | 1.750264747 | 0.000279951 |
| TMEM191B | 46.74018576 | 156.0407829 | 1.742886019 | $1.69 \mathrm{E}-07$ |
| NOCT | 197.0148483 | 656.5797623 | 1.736447377 | 0.03178158 |
| RFPL2 | 7.019684475 | 23.15248542 | 1.729722295 | 0.037115355 |
| CAV1 | 462.2110496 | 1531.453691 | 1.72719695 | $1.26 \mathrm{E}-10$ |
| SLC12A4 | 1769.976953 | 5854.080311 | 1.725794628 | $3.10 \mathrm{E}-23$ |
| KCNN4 | 29.14300667 | 95.31112558 | 1.720586003 | $1.64 \mathrm{E}-05$ |
| GFI1 | 302.2579856 | 996.7006264 | 1.719820983 | $2.24 \mathrm{E}-15$ |
| ADPRH | 50.59589853 | 167.0209769 | 1.719402653 | $2.08 \mathrm{E}-09$ |
| KCNG3 | 14.15322046 | 46.35911479 | 1.712068545 | 0.001474081 |
| CHRD | 75.21016703 | 245.585538 | 1.708676317 | 0.000204105 |
| KCNA7 | 10.74298416 | 34.79493741 | 1.706623323 | 0.027354523 |
| CABP1 | 40.66927754 | 132.9041695 | 1.704549074 | 0.000154823 |
| PROC | 30.89217958 | 101.0304661 | 1.704445336 | $1.74 \mathrm{E}-05$ |
| EGR2 | 34.57621755 | 112.9203014 | 1.701520802 | 6.19E-06 |
| GNG13 | 19.29765829 | 62.58300344 | 1.698592164 | 0.000151979 |
| HOXA1 | 33.71914102 | 109.6798945 | 1.697858408 | $2.84 \mathrm{E}-06$ |
| EGR3 | 75.18603078 | 244.1818075 | 1.696346302 | 0.000134011 |
| SRL | 9.032729501 | 29.15758058 | 1.69015671 | 0.012325865 |
| C2orf50 | 25.07830655 | 80.64755256 | 1.689268718 | 0.000571992 |
| CFAP73 | 12.26934179 | 39.35064209 | 1.680621771 | 0.022494222 |
| INHBB | 208.6110164 | 668.6698564 | 1.678235277 | $1.69 \mathrm{E}-14$ |
| APOC1 | 143.2478445 | 458.5719907 | 1.677861905 | $2.44 \mathrm{E}-10$ |
| ECHDC2 | 207.3081668 | 661.595352 | 1.674628574 | $2.00 \mathrm{E}-05$ |
| TMEM229B | 56.30145944 | 178.6751352 | 1.664282772 | 4.25E-07 |
| EXTL1 | 15.57989799 | 48.97223699 | 1.662995809 | 0.006116719 |
| UPK3B | 146.9874484 | 464.7339425 | 1.662526423 | 8.45E-09 |
| CAMK2B | 27.03467171 | 85.11624772 | 1.654515858 | 0.001354226 |
| CCRL2 | 8.135093719 | 25.40507233 | 1.651118406 | 0.026573927 |
| TMEM130 | 13.82648322 | 43.55306419 | 1.650636862 | 0.005457847 |
| RDH5 | 64.14484158 | 200.0555135 | 1.646958632 | $5.76 \mathrm{E}-07$ |
| PLPPR3 | 31.31844282 | 97.84388861 | 1.646405072 | 0.004919505 |
| INKA1 | 15.1221993 | 47.56626692 | 1.643487124 | 0.001090007 |
| BRSK1 | 244.7571067 | 764.2132448 | 1.643096956 | 3.97E-09 |
| CYR61 | 1434.756686 | 4478.695597 | 1.642168863 | 2.37E-05 |
| SYT13 | 6.975380924 | 21.79235443 | 1.641583778 | 0.04866098 |
| ACHE | 58.55378384 | 181.2251103 | 1.63495329 | 3.22E-05 |
| PRAME | 24.2415867 | 75.19314515 | 1.633056721 | 0.001982472 |
| FAM122C | 228.5409925 | 706.5920718 | 1.629135036 | 4.43E-20 |
| PRRT4 | 72.75374881 | 224.6170098 | 1.626713298 | $1.21 \mathrm{E}-08$ |
| VGLL3 | 136.9003797 | 422.0485445 | 1.626303259 | $1.71 \mathrm{E}-05$ |


| FOS | 253.2775257 | 781.1933093 | 1.623210585 | $3.36 \mathrm{E}-08$ |
| :---: | :---: | :---: | :---: | :---: |
| LYL1 | 57.59522633 | 177.0146215 | 1.620673826 | $4.79 \mathrm{E}-08$ |
| RGCC | 18.88117051 | 57.7668193 | 1.620606187 | 0.001090007 |
| GJB4 | 10.30743724 | 31.95266945 | 1.617783942 | 0.016041767 |
| BLOC1S1-RDH5 | 47.78310851 | 146.4744569 | 1.617461911 | $1.80 \mathrm{E}-06$ |
| PLK2 | 323.1649093 | 991.0090712 | 1.616619988 | 0.035515998 |
| LZTS1 | 19.56592056 | 60.31162627 | 1.615095633 | 0.001209261 |
| ADAMTSL4 | 169.897304 | 519.9063871 | 1.613044869 | $1.46 \mathrm{E}-06$ |
| ZMYND15 | 177.843927 | 543.9698736 | 1.611772899 | $6.82 \mathrm{E}-12$ |
| KLHL30 | 24.72078552 | 75.04665126 | 1.609495047 | 0.000189568 |
| S1PR5 | 81.09488555 | 247.8723768 | 1.609253755 | $6.25 \mathrm{E}-06$ |
| SCIN | 71.80692175 | 219.036626 | 1.608895264 | 0.000371248 |
| C7orf61 | 13.13310114 | 39.73949341 | 1.605553241 | 0.013013735 |
| P2RY2 | 54.88341393 | 167.0483598 | 1.603260136 | $6.21 \mathrm{E}-08$ |
| ZNF878 | 39.75437771 | 120.2590278 | 1.602043022 | 0.000672444 |
| CDKN2A | 25.85834653 | 78.05444153 | 1.601649273 | 0.000344875 |
| DAND5 | 15.82600849 | 48.36833838 | 1.601277238 | 0.002582088 |
| LRRN4 | 84.66132771 | 257.0389325 | 1.600143163 | $5.34 \mathrm{E}-08$ |
| TNFAIP8L3 | 49.54205688 | 150.0899508 | 1.597167593 | $3.35 \mathrm{E}-08$ |
| PDE4A | 43.0416387 | 130.0987872 | 1.595876689 | $6.04 \mathrm{E}-05$ |
| RTBDN | 23.48484194 | 70.95338073 | 1.594727163 | 0.000904446 |
| CATSPER1 | 76.95395465 | 232.9233532 | 1.5937864 | $9.51 \mathrm{E}-10$ |
| TPH1 | 20.92320424 | 63.03559729 | 1.588091178 | 0.002687049 |
| KCND1 | 67.96488283 | 204.2467357 | 1.587635087 | $2.44 \mathrm{E}-06$ |
| CCM2L | 12.73697004 | 38.49813571 | 1.586942536 | 0.0043254 |
| FOXJ1 | 11.72059502 | 35.03571667 | 1.586935486 | 0.037649489 |
| OASL | 34.5915324 | 104.219098 | 1.584767905 | 0.0001499 |
| ESCO2 | 872.3207325 | 2616.14803 | 1.584202667 | 2.67E-09 |
| CLSPN | 1321.136883 | 3958.068331 | 1.582741468 | 8.26E-08 |
| CCDC173 | 11.24937657 | 33.91191133 | 1.58251414 | 0.022609541 |
| CSPG4 | 31.55527543 | 94.32874195 | 1.582163644 | 0.010077388 |
| KIF1A | 67.70051315 | 202.6496963 | 1.579111605 | 0.000154823 |
| SEMA7A | 93.53540458 | 279.2102714 | 1.575569968 | $3.24 \mathrm{E}-05$ |
| ATP12A | 7.320525646 | 21.86986132 | 1.574642079 | 0.040908663 |
| OAS3 | 2835.342574 | 8445.928214 | 1.574515458 | $2.94 \mathrm{E}-11$ |
| ARC | 23.36121497 | 68.97146728 | 1.5724755 | 0.004003844 |
| AMIGO2 | 12.01100907 | 35.85324976 | 1.568473457 | 0.010279557 |
| WNT9A | 44.60840149 | 131.9732232 | 1.568171905 | 0.002353645 |
| TCEA2 | 28.78644548 | 85.46507671 | 1.561321734 | 0.005551179 |
| RRAD | 16.16626548 | 47.94202565 | 1.558238196 | 0.003961994 |
| ACTA2 | 99.9608953 | 294.6286974 | 1.556087145 | $8.44 \mathrm{E}-06$ |
| TMEM191C | 62.64013816 | 183.3031023 | 1.552686759 | $5.08 \mathrm{E}-08$ |
| APOBEC3B | 1458.827921 | 4278.456853 | 1.551939445 | $2.96 \mathrm{E}-05$ |
| SYT11 | 14.01721717 | 40.84958068 | 1.55124628 | 0.005375882 |
| COPZ2 | 137.8142902 | 399.3642245 | 1.533654064 | 8.60E-14 |
| STMND1 | 23.73649183 | 68.69375615 | 1.531325 | 0.000997242 |
| CPA5 | 19.73629784 | 56.96889046 | 1.529951442 | 0.003020994 |
| LYNX1 | 41.10108017 | 118.5525132 | 1.529905004 | 0.000145986 |
| E2F2 | 970.0495528 | 2790.433629 | 1.52405994 | $6.40 \mathrm{E}-12$ |
| STYK1 | 246.5487765 | 709.4319939 | 1.523149139 | 3.54E-15 |
| LPAR6 | 13.90336567 | 39.53394877 | 1.517552671 | 0.012304068 |
| KIF17 | 45.30747705 | 129.2353618 | 1.515795135 | 0.000396325 |
| FOXL1 | 39.89656625 | 114.0942307 | 1.507796674 | 0.001336468 |
| CXCR6 | 35.93758319 | 102.1774621 | 1.50769923 | 0.000245151 |
| CYP26A1 | 19.45760845 | 54.87981409 | 1.506940479 | 0.001586423 |
| AQP2 | 14.95720731 | 42.30565156 | 1.506311716 | 0.042996152 |
| KCP | 126.2865677 | 358.2347822 | 1.504868092 | 8.42E-05 |
| RGS14 | 21.91727339 | 62.42418468 | 1.50465324 | 0.013733836 |
| PLEKHD1 | 59.41135214 | 167.9231273 | 1.503691006 | 3.49E-07 |
| PDCD1 | 58.78213272 | 167.0925248 | 1.502960938 | $1.28 \mathrm{E}-06$ |
| MAFA | 16.91747086 | 48.37908508 | 1.502472726 | 0.010642271 |


| FFAR4 | 15.06617109 | 42.63456532 | 1.501207552 | 0.007279345 |
| :---: | :---: | :---: | :---: | :---: |
| DHRS3 | 68.80064282 | 193.7202605 | 1.49857556 | 0.000418239 |
| FAM57B | 141.4597534 | 399.3322757 | 1.498185003 | 3.24E-05 |
| E2F8 | 1035.176739 | 2923.53296 | 1.497730568 | 1.23E-12 |
| TP53INP2 | 702.5896044 | 1982.647062 | 1.496141559 | $6.49 \mathrm{E}-18$ |
| HIVEP3 | 51.47821946 | 145.4288267 | 1.495486271 | 0.000219811 |
| HPDL | 12.68468613 | 35.56313741 | 1.493247958 | 0.026503118 |
| KIAA1324 | 24.46799219 | 68.72058995 | 1.492114222 | 0.020033811 |
| STRIP2 | 373.8670225 | 1049.802689 | 1.488595243 | $3.12 \mathrm{E}-12$ |
| PTX4 | 10.91286387 | 30.82302422 | 1.488213113 | 0.025312357 |
| TM4SF5 | 20.22607787 | 56.84317545 | 1.486708958 | 0.015265672 |
| GAB3 | 12.66253436 | 35.18637279 | 1.486531078 | 0.039069411 |
| ADAMTSL2 | 56.56109549 | 157.4999142 | 1.483675499 | $6.94 \mathrm{E}-05$ |
| ZNF648 | 10.34001614 | 28.6582377 | 1.475795894 | 0.049731706 |
| EFCAB5 | 14.35747417 | 39.91564334 | 1.473955508 | 0.011751978 |
| COL6A1 | 301.6903807 | 837.1088577 | 1.472138896 | $8.76 \mathrm{E}-05$ |
| AC007906.2 | 11.14415709 | 30.83934949 | 1.46561152 | 0.020425553 |
| NOTCH4 | 28.04127127 | 77.37707919 | 1.464698453 | 0.000450217 |
| NKX3-1 | 243.3632989 | 671.4913777 | 1.463744926 | $2.10 \mathrm{E}-05$ |
| CYP46A1 | 25.75816887 | 71.01590235 | 1.463111968 | 0.000269051 |
| TRIM46 | 23.63990436 | 65.10911611 | 1.462357734 | 0.007906549 |
| KLK14 | 26.75907495 | 73.8952976 | 1.461395488 | 0.015253168 |
| PRADC1 | 188.6900158 | 518.3182711 | 1.456216827 | $3.44 \mathrm{E}-08$ |
| CCND3 | 1026.941841 | 2815.070372 | 1.454466177 | 3.35E-08 |
| SLC35G6 | 36.52998764 | 99.53087884 | 1.453195672 | 0.00022787 |
| ETNK2 | 77.45595689 | 212.2043229 | 1.45318824 | $2.70 \mathrm{E}-06$ |
| LMCD1 | 197.8099007 | 541.9321652 | 1.452724923 | $1.70 \mathrm{E}-10$ |
| SHBG | 31.39418183 | 85.24734588 | 1.450161536 | 0.001367386 |
| PDIA2 | 19.96270333 | 54.21482981 | 1.447759001 | 0.026580564 |
| ALOX15 | 73.51717641 | 200.3178162 | 1.446551647 | 0.005974837 |
| SCUBE3 | 81.43254748 | 220.962496 | 1.445074101 | $1.60 \mathrm{E}-07$ |
| PEA15 | 1041.262032 | 2834.902454 | 1.444858844 | 3.65E-06 |
| SIX1 | 28.21099689 | 76.58896396 | 1.444684686 | 0.000393199 |
| RAET1G | 15.40952071 | 42.32568587 | 1.443989207 | 0.009026068 |
| SLC2A14 | 40.32707135 | 109.411686 | 1.441540777 | 0.00276388 |
| SERTAD4 | 286.8962045 | 775.4951636 | 1.434937012 | $6.90 \mathrm{E}-07$ |
| CD37 | 154.9340656 | 419.3557789 | 1.43461958 | $1.48 \mathrm{E}-06$ |
| PADI1 | 25.40993152 | 68.36977233 | 1.434067294 | 0.002693699 |
| SAMD9L | 55.68072375 | 150.1083374 | 1.433120358 | 0.020972626 |
| DUSP5 | 274.353506 | 740.4653863 | 1.431067401 | 0.000774851 |
| VILL | 240.530158 | 648.3451208 | 1.429431616 | 0.000317521 |
| C1R | 221.0048262 | 593.6944258 | 1.425490028 | 0.000212796 |
| CKLF-CMTM1 | 11.72059502 | 31.26913309 | 1.420523368 | 0.04346043 |
| EFNA2 | 30.76610586 | 82.67154286 | 1.419893773 | 0.001147057 |
| LETM2 | 66.84897602 | 179.4188704 | 1.419391137 | $5.00 \mathrm{E}-07$ |
| SBK3 | 40.00847436 | 106.4626124 | 1.41753533 | 0.000564009 |
| UCP2 | 249.0957452 | 665.9006682 | 1.41685242 | 3.22E-08 |
| EGR4 | 37.55629222 | 100.4367615 | 1.41669264 | 0.000435631 |
| PTGER2 | 21.24554552 | 57.11595664 | 1.412587878 | 0.013130859 |
| PPP1R18 | 775.0373103 | 2063.42477 | 1.412404356 | 1.17E-19 |
| LOXL4 | 17.01944362 | 45.0258176 | 1.411040628 | 0.015183982 |
| HPCAL4 | 45.6034247 | 121.849314 | 1.409234725 | 0.006385577 |
| MSLN | 175.6726081 | 465.412387 | 1.406603516 | 0.004248524 |
| MMEL1 | 53.62891457 | 141.7196498 | 1.403729399 | 0.044382587 |
| HLA-DQB1 | 14.67003999 | 39.09600253 | 1.403582298 | 0.017026874 |
| SLC22A4 | 68.79720672 | 181.6174556 | 1.401166356 | 1.63E-06 |
| GBP3 | 543.3193592 | 1432.806668 | 1.399786868 | $4.76 \mathrm{E}-11$ |
| ZNF491 | 39.98941522 | 104.9795886 | 1.39874613 | $4.86 \mathrm{E}-05$ |
| CHST6 | 26.4108376 | 69.47244153 | 1.397583493 | 0.025562031 |
| RAET1L | 79.2795655 | 209.1536812 | 1.39729655 | 0.000343972 |
| TNFRSF10C | 49.90431155 | 131.0115884 | 1.396249821 | $3.48 \mathrm{E}-05$ |


| NID2 | 9.404913728 | 24.64996492 | 1.394136267 | 0.04722232 |
| :---: | :---: | :---: | :---: | :---: |
| MYBL2 | 4042.672068 | 10608.30146 | 1.391675032 | 8.30E-06 |
| CDKN2C | 909.6440301 | 2386.792005 | 1.391592045 | $1.61 \mathrm{E}-10$ |
| DLK2 | 133.9978391 | 350.468174 | 1.390155499 | 5.15E-07 |
| TUBB6 | 4170.57777 | 10911.33542 | 1.387362784 | 8.33E-07 |
| FAM19A3 | 13.36080416 | 35.1227262 | 1.387029331 | 0.037133137 |
| PTN | 17.43788059 | 45.59773742 | 1.384119563 | 0.01723941 |
| MOGAT3 | 42.9548267 | 111.9742542 | 1.383779092 | 0.009738525 |
| ARHGEF19 | 435.825509 | 1135.962116 | 1.38160171 | $6.95 \mathrm{E}-06$ |
| TNNI2 | 38.8246606 | 100.8462263 | 1.381279871 | 0.041250849 |
| ADGRF4 | 138.3594526 | 360.6628935 | 1.38063551 | $1.56 \mathrm{E}-06$ |
| PRSS35 | 68.83810945 | 178.403694 | 1.378282192 | 0.006837455 |
| KREMEN2 | 451.5981974 | 1174.421466 | 1.377222946 | $1.88 \mathrm{E}-06$ |
| ISG15 | 1705.298046 | 4428.612548 | 1.376511529 | $1.77 \mathrm{E}-13$ |
| KISS1R | 383.6311156 | 994.7564159 | 1.376186486 | $2.50 \mathrm{E}-11$ |
| NR113 | 14.17716733 | 36.47459861 | 1.376070518 | 0.021616938 |
| PALM3 | 133.55007 | 347.0070094 | 1.375950644 | $6.89 \mathrm{E}-05$ |
| C5AR1 | 91.76245047 | 237.4936095 | 1.374358724 | 0.000376594 |
| TNFRSF1B | 104.0754442 | 269.4766102 | 1.374288574 | $2.37 \mathrm{E}-05$ |
| AKAP5 | 372.3444034 | 965.2110062 | 1.373768648 | 8.89E-07 |
| RGS9 | 301.1854578 | 780.4372455 | 1.373580261 | 8.17E-09 |
| REEP1 | 293.2329283 | 760.427768 | 1.373506656 | $6.84 \mathrm{E}-10$ |
| FAM83A | 38.99274521 | 101.0505963 | 1.371981016 | 0.000317521 |
| C17orf107 | 15.42857986 | 39.71019464 | 1.366841576 | 0.02574311 |
| TENT5B | 321.6453828 | 830.2913039 | 1.366759564 | $1.14 \mathrm{E}-05$ |
| ESAM | 483.0051343 | 1244.588726 | 1.365021672 | $1.18 \mathrm{E}-13$ |
| DNAJC5G | 32.38890264 | 83.0046952 | 1.364497316 | 0.031059186 |
| FNDC5 | 92.30534387 | 237.2164048 | 1.361296674 | 0.000503695 |
| CCDC88B | 224.5888464 | 576.9523347 | 1.360591071 | 0.001713027 |
| SYNC | 32.96907908 | 84.63961915 | 1.357062879 | 0.004012098 |
| GJB3 | 541.8863969 | 1388.501477 | 1.35698503 | 0.000419634 |
| OTULINL | 67.28680981 | 172.1381657 | 1.353661362 | 0.000110438 |
| TP53INP1 | 113.5393246 | 289.7809913 | 1.3516229 | 0.000858304 |
| SUSD2 | 129.3060582 | 329.7302679 | 1.351010224 | 0.006921175 |
| GALNT5 | 297.9624956 | 759.9884484 | 1.350515531 | $3.42 \mathrm{E}-07$ |
| MICB | 546.3951571 | 1389.258994 | 1.345741367 | 2.58E-06 |
| C16orf89 | 15.02561183 | 38.31942487 | 1.344756976 | 0.039921116 |
| COL16A1 | 296.4445087 | 751.177336 | 1.343072052 | $6.80 \mathrm{E}-05$ |
| GPR153 | 219.488558 | 554.2494879 | 1.337720051 | 7.83E-10 |
| AC106886.5 | 19.5579402 | 49.28573542 | 1.334527878 | 0.010052803 |
| PADI2 | 76.46287709 | 192.4764378 | 1.331971442 | 7.87E-05 |
| HAP1 | 69.03583442 | 173.3405069 | 1.331156945 | 0.00059248 |
| DLX2 | 65.08074396 | 163.2210478 | 1.327437315 | $2.30 \mathrm{E}-05$ |
| CPNE9 | 16.59252872 | 41.81482858 | 1.327386899 | 0.021715519 |
| RUFY4 | 15.5761537 | 38.85163333 | 1.32588129 | 0.046025887 |
| LCAT | 310.5574723 | 777.1917201 | 1.324476563 | $1.27 \mathrm{E}-06$ |
| WDR62 | 1063.910629 | 2663.051325 | 1.323268883 | 1.53E-06 |
| DRAXIN | 21.73207882 | 54.38269801 | 1.321696167 | 0.027907797 |
| SSTR2 | 26.98368533 | 67.29314608 | 1.321590914 | 0.005303698 |
| TMEM121 | 97.85974074 | 244.9878366 | 1.320963276 | 4.82E-05 |
| GPRIN1 | 393.7117865 | 982.4202801 | 1.318066293 | $3.28 \mathrm{E}-08$ |
| MUC1 | 124.1796844 | 309.8114789 | 1.318006825 | 2.52E-09 |
| AP3B2 | 61.22518528 | 152.8429096 | 1.317237179 | $4.26 \mathrm{E}-05$ |
| CALML6 | 86.40432115 | 214.7969079 | 1.313977744 | 0.000153575 |
| 03-Mar | 39.36133924 | 98.07837477 | 1.312374667 | 0.001956453 |
| AC093512.2 | 107.0887436 | 266.0290077 | 1.311930643 | $3.66 \mathrm{E}-07$ |
| LYPD5 | 295.532003 | 733.7500806 | 1.31149314 | $4.96 \mathrm{E}-10$ |
| CD274 | 66.56833743 | 164.9355864 | 1.309450786 | 4.83E-06 |
| HMSD | 92.73256696 | 230.2813427 | 1.308067568 | 5.17E-06 |
| RELT | 299.0461554 | 740.4231743 | 1.30642826 | 1.16E-09 |
| DENND2C | 228.2572202 | 565.0821093 | 1.305470351 | 1.93E-07 |


| PLXNB3 | 165.7140304 | 408.6565056 | 1.302719841 | 0.001900898 |
| :---: | :---: | :---: | :---: | :---: |
| BEST4 | 54.76207963 | 134.7988549 | 1.302374989 | 0.013752181 |
| MYBPC2 | 59.01995467 | 144.749959 | 1.302129172 | 0.000366092 |
| IFIT3 | 161.8260648 | 398.9251069 | 1.301912899 | 9.95E-07 |
| CLCF1 | 266.7842864 | 657.4461662 | 1.300121833 | $1.33 \mathrm{E}-05$ |
| NFKB2 | 1264.186249 | 3110.265328 | 1.298854819 | 0.000935267 |
| ASGR1 | 100.7179835 | 247.8654582 | 1.298583058 | 2.02E-05 |
| MGLL | 30.4178685 | 74.60693143 | 1.298505799 | 0.028625497 |
| TMSB15B | 20.58474234 | 50.51545963 | 1.298183757 | 0.005733091 |
| CCDC153 | 62.53296948 | 153.3388579 | 1.294720187 | 0.003124132 |
| SOCS1 | 52.5682302 | 128.4821008 | 1.294445189 | 0.00024266 |
| SERTAD1 | 584.4159729 | 1433.401392 | 1.294223944 | 6.95E-06 |
| SLC6A16 | 70.1199623 | 171.9722133 | 1.292679781 | 0.000108833 |
| HYAL1 | 122.5147226 | 300.3977318 | 1.292492365 | 0.000928913 |
| KIF24 | 807.0338088 | 1976.598579 | 1.291916151 | $2.62 \mathrm{E}-12$ |
| DIAPH3 | 1784.226018 | 4369.007105 | 1.291858504 | 0.000263866 |
| CTSV | 691.9487534 | 1693.577203 | 1.290732299 | 2.57E-05 |
| FAM167B | 37.28982504 | 91.00524959 | 1.289029678 | 0.002563907 |
| USP11 | 2494.260264 | 6088.621179 | 1.287407147 | 2.23E-13 |
| IRAK2 | 104.0299914 | 254.0269499 | 1.287274436 | $2.68 \mathrm{E}-05$ |
| HIST1H2AG | 72.12192854 | 176.3500176 | 1.28650993 | $1.62 \mathrm{E}-05$ |
| LPAR5 | 100.1381095 | 244.6644979 | 1.285543018 | 3.53E-05 |
| WNT4 | 40.52464223 | 98.50332436 | 1.283226241 | 0.000961824 |
| LOXL3 | 437.7805414 | 1065.606263 | 1.283022825 | 2.89E-08 |
| KRT71 | 49.25164283 | 119.866686 | 1.281662248 | 0.001111677 |
| NACAD | 26.98353124 | 65.18336716 | 1.279458138 | 0.020180508 |
| KLHDC7A | 276.2444636 | 665.2023812 | 1.269539953 | $1.56 \mathrm{E}-08$ |
| TUBA1A | 1738.470865 | 4190.775665 | 1.268971432 | $1.00 \mathrm{E}-07$ |
| ZNF540 | 32.56855782 | 77.97865505 | 1.268404303 | 0.030494913 |
| TRPV3 | 344.4246731 | 829.1874507 | 1.267629058 | $4.05 \mathrm{E}-08$ |
| COCH | 327.9700969 | 789.503898 | 1.26710832 | $1.53 \mathrm{E}-08$ |
| RNF227 | 569.3334198 | 1368.44747 | 1.265900064 | 0.000282294 |
| ERFE | 351.9267974 | 846.3626773 | 1.265016204 | $1.29 \mathrm{E}-08$ |
| MMRN2 | 74.2936262 | 178.7509679 | 1.26441045 | 0.001131855 |
| GPR37L1 | 38.86911824 | 92.91898651 | 1.263967211 | 0.000838594 |
| ZNF718 | 373.6857379 | 897.3863766 | 1.263858049 | $3.36 \mathrm{E}-13$ |
| ADSSL1 | 257.9967191 | 619.9098711 | 1.263524196 | $2.74 \mathrm{E}-06$ |
| C1QL4 | 58.38699096 | 140.2409837 | 1.260729738 | 0.012013483 |
| OAS1 | 370.5247163 | 887.7495061 | 1.260469069 | 0.000984338 |
| COL17A1 | 60.50167107 | 144.9955526 | 1.258709586 | 0.000828577 |
| FANCI | 4212.554557 | 10074.33158 | 1.257778609 | $1.26 \mathrm{E}-08$ |
| SYNE3 | 328.7986707 | 785.5865519 | 1.256307008 | $6.11 \mathrm{E}-09$ |
| CD24 | 432.9903001 | 1032.97787 | 1.256111537 | 7.50E-08 |
| NECTIN1 | 364.7645909 | 870.8970414 | 1.25546916 | $1.21 \mathrm{E}-07$ |
| ROPN1B | 27.25244517 | 64.83678812 | 1.254327575 | 0.026313625 |
| ILDR2 | 367.407821 | 876.0181578 | 1.253735096 | 8.80E-13 |
| SLPI | 217.0714015 | 517.3166545 | 1.252438088 | 0.001936059 |
| ZNF799 | 212.4351396 | 504.1768744 | 1.246176344 | 4.42E-06 |
| APBB1 | 286.722924 | 677.5897201 | 1.241371874 | $3.71 \mathrm{E}-10$ |
| IGFBP6 | 287.9511717 | 681.2013005 | 1.240971804 | 0.000129092 |
| WNK4 | 78.76389519 | 185.6647217 | 1.239066461 | $1.12 \mathrm{E}-05$ |
| FAM171A2 | 429.8989163 | 1015.39843 | 1.239016937 | $3.36 \mathrm{E}-07$ |
| EMP3 | 102.3153465 | 241.643089 | 1.23755586 | $5.61 \mathrm{E}-05$ |
| MCM8 | 1713.903312 | 4039.813477 | 1.236815889 | $6.98 \mathrm{E}-05$ |
| GVQW2 | 29.52218191 | 69.92472442 | 1.23617882 | 0.0082619 |
| SLC44A4 | 47.20178284 | 111.3738496 | 1.235648997 | 0.006411402 |
| SOX15 | 68.45271366 | 160.9266685 | 1.235286106 | 0.000157155 |
| CCDC15 | 173.2609441 | 408.0157606 | 1.233492338 | 4.42E-07 |
| MPIG6B | 108.775703 | 255.9079277 | 1.2333278 | 0.001338738 |
| AFAP1L2 | 139.5175538 | 327.0013565 | 1.231453518 | $1.21 \mathrm{E}-07$ |
| GOLGA8K | 38.82301959 | 91.05470177 | 1.225419655 | 0.000616994 |


| TMPRSS4 | 564.1595542 | 1318.566135 | 1.224984724 | 0.006041986 |
| :---: | :---: | :---: | :---: | :---: |
| EGR1 | 2244.373775 | 5247.018816 | 1.224955539 | 0.000904446 |
| C21orf58 | 625.0621562 | 1460.542944 | 1.22399679 | 7.35E-07 |
| EFHD1 | 467.7999026 | 1091.489434 | 1.222885258 | $1.10 \mathrm{E}-10$ |
| TMEM38A | 561.8604268 | 1311.221798 | 1.22275884 | 3.64E-14 |
| CD6 | 63.95849779 | 149.5046042 | 1.221965096 | 0.000208088 |
| TUFT1 | 979.3510359 | 2280.670384 | 1.219762799 | $1.43 \mathrm{E}-05$ |
| HUNK | 593.8625 | 1382.58291 | 1.219650304 | $5.88 \mathrm{E}-09$ |
| CDC25A | 1066.13185 | 2481.238946 | 1.218346435 | $6.89 \mathrm{E}-05$ |
| AOC1 | 54.62428125 | 126.8017713 | 1.216687825 | 0.027819891 |
| HIST1H4H | 36.7749547 | 85.08852712 | 1.214106023 | 0.001511717 |
| STXBP5L | 17.91039657 | 41.44510162 | 1.210560968 | 0.038991483 |
| CCDC80 | 77.17336911 | 177.96857 | 1.209349595 | 7.89E-05 |
| TCHH | 180.9528656 | 416.8890476 | 1.206707314 | 0.00014237 |
| CCDC150 | 426.7058134 | 982.651471 | 1.203089142 | $3.32 \mathrm{E}-08$ |
| GSDMA | 113.2257695 | 260.185964 | 1.200047671 | 0.000313719 |
| RIMBP3 | 53.48297593 | 122.4435909 | 1.199025097 | 0.002605121 |
| RASGRP4 | 43.2007831 | 98.73469692 | 1.198207806 | 0.013147395 |
| SHOX2 | 345.5467299 | 793.5203265 | 1.198015371 | $1.11 \mathrm{E}-10$ |
| GPR162 | 82.91540152 | 190.6827183 | 1.197737565 | 0.004485035 |
| BRIP1 | 1127.431364 | 2586.090841 | 1.197557708 | $1.19 \mathrm{E}-06$ |
| SAMD9 | 313.6978232 | 718.7954853 | 1.196541762 | 4.95E-06 |
| MPP2 | 546.9753452 | 1253.669199 | 1.195934494 | 3.03E-05 |
| FAM111B | 1914.868254 | 4384.142848 | 1.195082495 | $3.20 \mathrm{E}-07$ |
| VDR | 679.7947379 | 1555.765543 | 1.194594568 | 7.02E-09 |
| CEP295NL | 36.78358673 | 84.31530122 | 1.194551822 | 0.01065666 |
| CBLN3 | 55.25120799 | 126.0424253 | 1.194014872 | 0.00092986 |
| RAD51AP1 | 1370.147568 | 3132.951657 | 1.192935653 | 3.52E-08 |
| IFI6 | 1253.652926 | 2862.709139 | 1.191292678 | 0.004216422 |
| GINS4 | 763.0825618 | 1741.82767 | 1.189971547 | 0.000160775 |
| SCARF1 | 28.64849301 | 65.17879448 | 1.188814876 | 0.006168795 |
| SEMA3G | 116.4056961 | 265.329242 | 1.185758588 | $2.10 \mathrm{E}-05$ |
| ZNF443 | 350.0295588 | 795.1227547 | 1.184616861 | $1.97 \mathrm{E}-05$ |
| ATAD5 | 1180.463306 | 2682.293165 | 1.183829112 | $1.20 \mathrm{E}-05$ |
| PLEKHO2 | 247.1900698 | 560.7409028 | 1.183566887 | 3.62E-08 |
| CYP26B1 | 78.47397292 | 177.2053462 | 1.178761968 | 0.000230775 |
| ITGA7 | 473.1297007 | 1069.793609 | 1.176944019 | 7.95E-05 |
| PIDD1 | 1401.963207 | 3169.499898 | 1.176716358 | 0.000261727 |
| RBPMS2 | 104.5388248 | 236.9868717 | 1.175546843 | 0.000353895 |
| NAT1 | 84.96037957 | 191.5594443 | 1.174456762 | 7.87E-06 |
| CLU | 3970.47347 | 8956.803715 | 1.173544604 | 0.00017054 |
| ZCCHC12 | 29.26124834 | 66.47764791 | 1.173330789 | 0.021715519 |
| CDC6 | 3661.180441 | 8240.42873 | 1.170300976 | $2.15 \mathrm{E}-06$ |
| PLAT | 589.41904 | 1326.009883 | 1.168803594 | $6.68 \mathrm{E}-05$ |
| CCDC9B | 280.9282758 | 629.0463371 | 1.164111335 | $1.90 \mathrm{E}-05$ |
| CENPU | 1914.112523 | 4285.957479 | 1.162816032 | 2.95E-07 |
| MSX1 | 882.0024859 | 1973.718824 | 1.162531635 | 0.003482174 |
| COX6B2 | 30.06963115 | 67.28330933 | 1.161570328 | 0.005508276 |
| PRRT2 | 175.7841727 | 392.5600824 | 1.159978133 | 0.017026874 |
| TCF19 | 2181.226555 | 4871.789156 | 1.15921766 | 3.91E-12 |
| PALM | 248.5631601 | 554.7187019 | 1.158294574 | 0.000447865 |
| AK1 | 138.3058653 | 308.7464862 | 1.158033721 | 5.67E-07 |
| C2CD3 | 1185.404953 | 2645.077345 | 1.157935838 | $4.70 \mathrm{E}-07$ |
| CELF5 | 33.25395953 | 73.59996394 | 1.156717481 | 0.010928101 |
| MAP7D1 | 1906.676719 | 4251.238036 | 1.156631776 | 0.000175989 |
| RRM2 | 7313.34302 | 16286.70784 | 1.155050295 | $3.75 \mathrm{E}-08$ |
| FOXF1 | 30.01360295 | 66.40617279 | 1.154345792 | 0.014753513 |
| CSRP2 | 375.6057683 | 835.5840703 | 1.152463484 | 1.35E-06 |
| IQGAP3 | 3177.387857 | 7060.364706 | 1.1517951 | 4.07E-08 |
| MELTF | 1232.596568 | 2737.984338 | 1.151320207 | $3.58 \mathrm{E}-05$ |
| CDK2 | 1746.100573 | 3878.247975 | 1.151043941 | $1.38 \mathrm{E}-06$ |


| C17orf53 | 371.0809227 | 824.745172 | 1.151042255 | $2.66 \mathrm{E}-05$ |
| :---: | :---: | :---: | :---: | :---: |
| SDCBP2 | 63.68893798 | 140.9921867 | 1.151012121 | 0.001092137 |
| NTN1 | 561.6339803 | 1247.834934 | 1.150799265 | 6.63E-09 |
| LY6G5C | 82.88527518 | 183.6049904 | 1.150472671 | 0.001144708 |
| KIAA0513 | 416.6860174 | 924.284743 | 1.149901554 | $1.67 \mathrm{E}-10$ |
| EVL | 81.82394494 | 181.7021956 | 1.14958219 | 0.005437043 |
| NOTCH2NLA | 39.03216103 | 86.63866834 | 1.149022444 | 0.001791044 |
| CD74 | 160.8904706 | 356.4735373 | 1.147774586 | $6.19 \mathrm{E}-08$ |
| MYEOV | 199.8011022 | 442.243248 | 1.145585051 | 0.000451296 |
| RCBTB2 | 141.1271391 | 311.7718458 | 1.145530885 | 1.85E-05 |
| POLA2 | 387.8962725 | 858.9729577 | 1.145406977 | $1.06 \mathrm{E}-06$ |
| SH3TC2 | 112.6581471 | 248.2334612 | 1.141454789 | 0.001966944 |
| CLGN | 55.85777807 | 122.986116 | 1.139015365 | 0.00162418 |
| CDCA5 | 2607.773788 | 5741.407144 | 1.138419947 | 1.05E-09 |
| CLDN5 | 234.3724378 | 514.4417324 | 1.132696857 | 0.000159957 |
| RASGRP2 | 136.8200669 | 299.7966092 | 1.13000511 | 0.003642374 |
| CAVIN1 | 5100.640559 | 11148.34567 | 1.128071388 | $2.08 \mathrm{E}-05$ |
| BICDL1 | 523.804212 | 1144.452662 | 1.127071253 | $1.60 \mathrm{E}-09$ |
| VTN | 33.96949338 | 74.19031675 | 1.127066997 | 0.025383708 |
| DDB2 | 822.4938183 | 1795.460754 | 1.125559154 | $1.54 \mathrm{E}-08$ |
| TUBB3 | 56.15438317 | 122.2557347 | 1.125470138 | 0.002958624 |
| ATL1 | 100.2387847 | 217.9548248 | 1.122460863 | $1.65 \mathrm{E}-05$ |
| TAGLN | 300.3037648 | 652.356995 | 1.120076374 | 0.014753513 |
| CFAP44 | 361.186299 | 784.460699 | 1.119884868 | 0.001178784 |
| CORO2B | 34.97609294 | 76.00756464 | 1.118998974 | 0.028019696 |
| GRK4 | 214.4284854 | 465.0913341 | 1.118434764 | $2.10 \mathrm{E}-07$ |
| HRH1 | 198.6801593 | 430.9619995 | 1.117734285 | 0.00065964 |
| PBX3 | 290.3106885 | 629.6422581 | 1.117713622 | $1.74 \mathrm{E}-08$ |
| RAB15 | 1026.884017 | 2226.534823 | 1.116852405 | $1.80 \mathrm{E}-12$ |
| DIO3 | 26.15055568 | 56.23982599 | 1.112427263 | 0.03700619 |
| GDPD5 | 427.0014998 | 922.8714613 | 1.112350023 | 0.000645922 |
| KATNAL1 | 781.7329836 | 1689.598475 | 1.111690259 | $3.58 \mathrm{E}-05$ |
| DTL | 1474.556321 | 3185.658496 | 1.110920024 | $6.24 \mathrm{E}-06$ |
| OVOL2 | 425.5917075 | 918.1941402 | 1.110137273 | $3.34 \mathrm{E}-09$ |
| UHRF1 | 4537.273545 | 9783.245042 | 1.108393952 | $6.84 \mathrm{E}-07$ |
| CBR3 | 67.04753624 | 144.5534638 | 1.108044376 | 0.000153575 |
| ZNF45 | 245.1910421 | 527.5482156 | 1.107920954 | $1.42 \mathrm{E}-05$ |
| DGKA | 600.7205638 | 1295.076566 | 1.107608527 | 0.000562163 |
| C2orf92 | 137.6385687 | 295.4869674 | 1.106439579 | 0.001042171 |
| ASF1B | 2483.501924 | 5342.429545 | 1.104902247 | $1.40 \mathrm{E}-07$ |
| DCLK2 | 77.39015323 | 166.0538131 | 1.104708993 | 0.000379051 |
| KALRN | 206.4775911 | 443.9962076 | 1.102965915 | $3.16 \mathrm{E}-05$ |
| NRGN | 721.4357261 | 1549.966828 | 1.102383979 | 5.02E-06 |
| NPTXR | 321.6338297 | 690.3149596 | 1.100549432 | 0.000635594 |
| CDH24 | 2380.837349 | 5104.626996 | 1.1003758 | 3.57E-14 |
| CMTM1 | 99.27958135 | 212.3174448 | 1.09953849 | 3.48E-05 |
| CEP126 | 56.33208915 | 120.5772944 | 1.099367218 | 0.004511003 |
| MFNG | 64.91445444 | 138.9646296 | 1.098514047 | 0.005160046 |
| EXO1 | 1213.540188 | 2598.029255 | 1.097821744 | 2.93E-06 |
| SPATA33 | 334.4784954 | 715.4760327 | 1.097109169 | $3.29 \mathrm{E}-09$ |
| FZD9 | 28.74328537 | 61.77633614 | 1.096280088 | 0.019330139 |
| TFCP2L1 | 528.1780423 | 1129.680714 | 1.096230149 | 0.000234541 |
| NCAPH2 | 1825.610294 | 3899.788777 | 1.094776253 | 4.66E-09 |
| ORC6 | 1236.560092 | 2638.113683 | 1.092873288 | 0.000992745 |
| DLL4 | 154.7434857 | 330.2830033 | 1.092247056 | 0.000112654 |
| MAP3K14 | 725.4889083 | 1545.945017 | 1.091856401 | 0.000364357 |
| PLEKHH2 | 129.522025 | 276.3230118 | 1.091482951 | 0.013864463 |
| PLPPR2 | 749.1749171 | 1595.663244 | 1.090994876 | $1.93 \mathrm{E}-11$ |
| PMEL | 144.6758196 | 308.1463035 | 1.089174208 | 0.001743815 |
| GPR68 | 65.16381167 | 138.88298 | 1.087441828 | 0.000579194 |
| MYO1A | 86.71883617 | 184.5867589 | 1.086508717 | 0.006073258 |


| HLA-B | 2736.387687 | 5803.493874 | 1.084882237 | 5.71E-09 |
| :---: | :---: | :---: | :---: | :---: |
| ZNF385A | 504.8735188 | 1070.604904 | 1.083122949 | 1.33E-06 |
| STIL | 2329.254683 | 4935.027244 | 1.083005681 | $1.04 \mathrm{E}-06$ |
| GSTT2B | 144.5075751 | 305.9021602 | 1.082991234 | $3.38 \mathrm{E}-05$ |
| RBP7 | 37.42712586 | 79.59541423 | 1.082347924 | 0.011539359 |
| AGFG2 | 577.3301649 | 1222.867556 | 1.082158863 | $9.20 \mathrm{E}-06$ |
| TMEM200B | 301.6590935 | 638.1248011 | 1.081285262 | $1.31 \mathrm{E}-07$ |
| TPM1 | 2563.42671 | 5420.126142 | 1.080391419 | 0.000176211 |
| E2F7 | 1395.435182 | 2949.796105 | 1.07968498 | $3.94 \mathrm{E}-08$ |
| AC233723.1 | 24.38801711 | 51.31865607 | 1.077929603 | 0.039534706 |
| TFEB | 123.2292671 | 260.441414 | 1.077797152 | 8.82E-06 |
| SPC25 | 552.9553183 | 1167.92963 | 1.077769004 | 0.000185343 |
| CCNE1 | 550.1777549 | 1160.500079 | 1.076769223 | 5.47E-08 |
| MRC2 | 1091.85726 | 2303.022248 | 1.076582671 | 0.001265348 |
| ARID5A | 148.7807355 | 314.2514476 | 1.07641442 | 4.29E-05 |
| FKBP5 | 1589.286226 | 3351.744958 | 1.07625726 | 0.000967697 |
| TNFAIP3 | 118.0972351 | 248.3671134 | 1.075646155 | 0.02067205 |
| HOXC9 | 22.82533629 | 47.88577398 | 1.074688994 | 0.028753951 |
| TRAIP | 574.3101827 | 1208.639179 | 1.072582757 | 8.50E-07 |
| RBM24 | 133.1400699 | 280.3939415 | 1.071869389 | 0.023490473 |
| ANKRD33B | 175.3021721 | 367.9479026 | 1.068844813 | 0.000206877 |
| MCM10 | 1476.590232 | 3097.761025 | 1.068700539 | 0.000214616 |
| CCDC62 | 55.22172173 | 115.8856043 | 1.068527206 | 0.00106608 |
| PRSS36 | 54.62557878 | 114.57926 | 1.067793185 | 0.002861728 |
| DONSON | 1328.570193 | 2785.020683 | 1.067551728 | $1.29 \mathrm{E}-05$ |
| RHBDL2 | 60.71699777 | 127.4153148 | 1.067082687 | 0.00149835 |
| CMPK2 | 101.9055358 | 214.1194033 | 1.066901305 | 0.002115085 |
| IL27RA | 747.1360774 | 1564.721936 | 1.066183249 | $4.49 \mathrm{E}-05$ |
| SCEL | 225.0213359 | 470.4014813 | 1.066091778 | 0.004524509 |
| HPSE | 935.1888818 | 1958.60883 | 1.066022288 | 2.73E-05 |
| HEG1 | 756.4404102 | 1582.544587 | 1.065118622 | $2.36 \mathrm{E}-05$ |
| HIST1H3H | 62.38604151 | 130.7659982 | 1.064440558 | 0.0020571 |
| TGM1 | 289.6819961 | 604.7097872 | 1.063924957 | 0.000167136 |
| LHFPL6 | 32.11265422 | 66.66586139 | 1.063851428 | 0.031201014 |
| ZMYND10 | 50.04390504 | 104.4058524 | 1.063406019 | 0.038479893 |
| HIST1H2BD | 173.5940676 | 362.0004985 | 1.062732491 | 0.000700375 |
| CARMIL2 | 61.6011138 | 128.9762027 | 1.062443622 | 0.000979114 |
| ZGLP1 | 46.87798414 | 97.30560208 | 1.0609525 | 0.008910647 |
| HIST1H4I | 101.0274567 | 210.7325026 | 1.060793782 | $6.88 \mathrm{E}-05$ |
| C18orf54 | 416.9200366 | 870.2881863 | 1.060766533 | 0.000264509 |
| PRRT1 | 58.27753541 | 121.306908 | 1.060641112 | 0.001167692 |
| RHOD | 1018.283967 | 2122.185095 | 1.059465257 | 0.000307833 |
| TNFRSF11A | 278.1902123 | 579.0720591 | 1.056286642 | $2.32 \mathrm{E}-07$ |
| CENPO | 966.8902911 | 2010.19637 | 1.055468752 | $1.89 \mathrm{E}-07$ |
| APOL2 | 826.6036746 | 1717.458937 | 1.055302914 | $2.10 \mathrm{E}-10$ |
| IER5 | 1035.123797 | 2150.27597 | 1.05463392 | 7.64E-12 |
| CLIC5 | 79.97363451 | 165.3724804 | 1.054248578 | 0.024206083 |
| SYNJ1 | 461.8278392 | 958.5197906 | 1.053923386 | $2.30 \mathrm{E}-06$ |
| AKAP12 | 1238.708134 | 2571.231807 | 1.05334151 | 0.007320222 |
| WDR53 | 294.2955618 | 610.4367608 | 1.053187103 | 0.0002447 |
| LMF2 | 2768.92493 | 5738.040364 | 1.05112144 | 8.90E-13 |
| TMEM270 | 65.46774547 | 136.1062282 | 1.049361943 | 0.007932635 |
| COL11A2 | 297.6376004 | 614.9456912 | 1.047116854 | 0.016137556 |
| GLIPR2 | 248.1845955 | 513.3794891 | 1.04680717 | $6.18 \mathrm{E}-07$ |
| SOCS3 | 71.44306136 | 146.4846046 | 1.043520831 | 0.020176598 |
| RUSC1 | 1567.816234 | 3226.677791 | 1.041003804 | $5.00 \mathrm{E}-10$ |
| RAD51C | 1150.586352 | 2367.235279 | 1.040565181 | 8.04E-06 |
| MALL | 77.94019753 | 160.9264304 | 1.040000066 | 0.000874987 |
| IL22RA1 | 252.6718203 | 519.5957075 | 1.039660381 | 2.47E-06 |
| TMEM79 | 308.2241777 | 633.1346708 | 1.038428972 | 8.37E-07 |
| SGK1 | 62.80382682 | 128.7422657 | 1.036332229 | 0.03288868 |


| TMCC2 | 153.4468098 | 314.0086566 | 1.03422633 | 0.000133931 |
| :---: | :---: | :---: | :---: | :---: |
| BIRC3 | 209.5351999 | 428.9843478 | 1.034199335 | 0.007001157 |
| FGD2 | 72.09863333 | 148.2546307 | 1.033888283 | 0.009411109 |
| SRRM3 | 207.1039073 | 422.5583867 | 1.029411599 | 7.97E-05 |
| TAP2 | 636.604181 | 1299.29587 | 1.029018276 | 0.000429742 |
| CCDC69 | 690.7582626 | 1409.275314 | 1.028637184 | $3.97 \mathrm{E}-05$ |
| B2M | 3118.917372 | 6358.647512 | 1.027659466 | $1.38 \mathrm{E}-12$ |
| HERC5 | 548.2220356 | 1117.972445 | 1.027641004 | 2.07E-07 |
| VWA5B2 | 365.1144514 | 743.7355627 | 1.02539601 | $1.44 \mathrm{E}-06$ |
| C16orf86 | 110.1222514 | 224.084325 | 1.025117013 | 0.021807283 |
| RFWD3 | 3711.523131 | 7551.465422 | 1.02465488 | 4.63E-05 |
| MAP3K6 | 930.4583778 | 1891.138903 | 1.0227826 | $6.38 \mathrm{E}-06$ |
| GAL3ST4 | 204.6815196 | 416.2530083 | 1.022609716 | 0.001331487 |
| DSCC1 | 780.4122902 | 1582.816448 | 1.019797407 | 0.002604334 |
| WDR76 | 1522.651871 | 3087.748551 | 1.019718393 | $3.58 \mathrm{E}-05$ |
| BRICD5 | 289.1007893 | 586.8229802 | 1.019456841 | $2.78 \mathrm{E}-06$ |
| SMTNL1 | 44.14467163 | 89.49838654 | 1.01921236 | 0.020095199 |
| TK1 | 4233.282715 | 8573.847279 | 1.018008559 | $1.66 \mathrm{E}-05$ |
| ULBP2 | 396.8356729 | 803.0049429 | 1.016908021 | 0.00063137 |
| LIMK2 | 1651.52084 | 3341.858488 | 1.016802348 | $1.27 \mathrm{E}-11$ |
| TMPRSS3 | 640.26125 | 1295.533034 | 1.016479755 | 0.001187704 |
| BTG2 | 397.4202747 | 804.2283646 | 1.016411877 | 8.34E-06 |
| CSRNP1 | 809.7348506 | 1637.73417 | 1.01622942 | 0.001068441 |
| ICA1L | 310.0753234 | 626.7384709 | 1.016177216 | $4.00 \mathrm{E}-06$ |
| FHDC1 | 425.6210044 | 860.9100344 | 1.01575675 | $7.70 \mathrm{E}-09$ |
| CIP2A | 1320.367506 | 2668.053121 | 1.014721098 | 0.0025651 |
| ADM | 123.7931746 | 249.6505816 | 1.014077367 | $2.61 \mathrm{E}-05$ |
| KIF3C | 541.3889916 | 1094.130756 | 1.01377057 | $2.40 \mathrm{E}-05$ |
| KLK7 | 1057.783473 | 2136.72831 | 1.013663008 | 0.002232396 |
| UBXN11 | 897.9390402 | 1812.038686 | 1.012626277 | $1.66 \mathrm{E}-10$ |
| C12orf75 | 1674.451511 | 3375.742277 | 1.011306176 | 0.002787929 |
| TNS1 | 246.0375259 | 495.6237269 | 1.010407552 | 0.001064814 |
| CHAD | 47.75721244 | 96.04976549 | 1.010362906 | 0.035788879 |
| ITPRIP | 295.7104736 | 595.8824088 | 1.010159289 | 0.00723688 |
| PTGES3L | 28.99119097 | 58.59005005 | 1.00857182 | 0.048610825 |
| DDIAS | 463.4748268 | 931.968764 | 1.007309396 | 0.020457846 |
| TCAP | 31.6064159 | 63.14350479 | 1.005900931 | 0.028911984 |
| CTXN1 | 514.0500599 | 1031.978486 | 1.004595482 | $2.15 \mathrm{E}-05$ |
| IL17RB | 650.2906553 | 1304.876312 | 1.004409923 | $2.01 \mathrm{E}-05$ |
| RND1 | 72.4032188 | 145.5259875 | 1.004101432 | 0.001374907 |
| SIPA1 | 594.7149617 | 1193.471698 | 1.004012119 | 9.67E-07 |
| TICRR | 1450.415113 | 2907.770332 | 1.003019704 | 0.000286638 |
| C19orf57 | 411.731857 | 823.5246001 | 1.001040389 | 0.000188726 |
| SMPD1 | 803.6542138 | 1607.117234 | 0.999975424 | $6.25 \mathrm{E}-07$ |
| FSTL3 | 504.4846618 | 1006.702146 | 0.998128943 | 0.000178517 |
| IRF1 | 447.9401377 | 892.4742559 | 0.995776336 | $1.02 \mathrm{E}-06$ |
| XRCC2 | 1292.799711 | 2578.223952 | 0.995625892 | $3.16 \mathrm{E}-05$ |
| IQCC | 302.2423741 | 601.9398616 | 0.994777594 | 8.33E-07 |
| TUBG1 | 1102.171353 | 2196.072681 | 0.994165124 | 0.004769398 |
| IFI27L2 | 299.1841137 | 596.5257714 | 0.993962332 | $2.00 \mathrm{E}-05$ |
| SERPINB5 | 142.0928654 | 282.749632 | 0.992200079 | 0.00298979 |
| INTS7 | 1165.926022 | 2317.724519 | 0.991307052 | 0.000409491 |
| FAM69B | 93.22788638 | 185.2114064 | 0.988795278 | 0.009602194 |
| CHST13 | 35.8649426 | 70.94186631 | 0.988333233 | 0.018110803 |
| STAT1 | 4670.750949 | 9266.358554 | 0.988256371 | 7.89E-09 |
| GRHL3 | 820.6087667 | 1628.646128 | 0.988087811 | $1.10 \mathrm{E}-06$ |
| KLF10 | 1432.169394 | 2840.442326 | 0.98797531 | 0.000361261 |
| AUNIP | 536.4427705 | 1063.287919 | 0.986521062 | 0.002072214 |
| RAET1E | 55.94149744 | 110.4970703 | 0.986335698 | 0.003756375 |
| SLC25A42 | 580.1382445 | 1149.734056 | 0.986025318 | $3.94 \mathrm{E}-08$ |
| SLC35E4 | 234.7886232 | 464.5594864 | 0.985772601 | $2.24 \mathrm{E}-05$ |


| PIGZ | 278.1167833 | 550.1556255 | 0.984376573 | 0.01065666 |
| :---: | :---: | :---: | :---: | :---: |
| TBX6 | 77.01471648 | 152.6226479 | 0.984077485 | 0.029953981 |
| ENKD1 | 247.1812895 | 487.3989602 | 0.980205425 | 0.013935977 |
| FOXM1 | 3327.951812 | 6565.597001 | 0.980167283 | 0.000334278 |
| FEN1 | 2749.238976 | 5423.517511 | 0.979995955 | $1.52 \mathrm{E}-05$ |
| NEURL1 | 41.30842651 | 81.33242892 | 0.979145358 | 0.025593791 |
| RFC2 | 1216.47398 | 2396.352529 | 0.977790544 | 8.26E-05 |
| LAMB2 | 10920.9474 | 21505.24289 | 0.977614612 | $4.69 \mathrm{E}-05$ |
| NFKBIE | 359.5070779 | 707.5224978 | 0.976864396 | 0.012565035 |
| SKA3 | 1374.43653 | 2704.756764 | 0.97648363 | 0.000129905 |
| CENPL | 650.478244 | 1279.392672 | 0.97583295 | 0.001059884 |
| CRY1 | 929.5118179 | 1827.166315 | 0.975113006 | 0.022725462 |
| C2orf72 | 363.6891067 | 714.7895851 | 0.974863356 | 0.000265308 |
| DUSP1 | 236.7952878 | 465.1689069 | 0.97468755 | 0.003675068 |
| PRR29 | 39.18901856 | 76.77650921 | 0.972791818 | 0.036978834 |
| MYORG | 1528.329829 | 2997.916596 | 0.971790252 | 0.00011702 |
| CAPG | 678.15271 | 1330.413876 | 0.971432586 | $9.28 \mathrm{E}-05$ |
| HIST1H2BK | 295.3771241 | 578.5319989 | 0.970343531 | 3.17E-05 |
| IL32 | 1151.896506 | 2253.673506 | 0.968249022 | 0.016223488 |
| SCML1 | 786.5901 | 1539.184217 | 0.96805392 | 8.32E-05 |
| ACOT4 | 138.4721901 | 269.9350671 | 0.967450523 | 0.000565114 |
| HAS3 | 177.0979412 | 346.2957721 | 0.966415805 | 0.000127531 |
| CENPI | 779.8197727 | 1522.566915 | 0.964454477 | 0.0001654 |
| SCHIP1 | 31.53327775 | 61.59192763 | 0.963771561 | 0.032690227 |
| HCN2 | 66.47728936 | 129.4367673 | 0.963214033 | 0.005943576 |
| AC011043.1 | 314.2327126 | 612.105517 | 0.962438184 | $3.44 \mathrm{E}-07$ |
| FSD1 | 92.81059284 | 181.1119155 | 0.961720504 | 0.005596292 |
| MFGE8 | 2765.202962 | 5384.012652 | 0.961270507 | 5.35E-06 |
| LIG1 | 2816.305126 | 5470.693435 | 0.957705057 | 3.29E-06 |
| RNASEH2A | 64.06746157 | 124.2938962 | 0.95648413 | 0.004012098 |
| EN1 | 38.27232363 | 73.92282278 | 0.956196937 | 0.018821119 |
| RBMS1 | 130.0758193 | 252.0930596 | 0.953114351 | 0.000216526 |
| MESP1 | 108.6558088 | 210.9536048 | 0.953047109 | 0.0077764 |
| SSC5D | 43.51400059 | 84.06054258 | 0.95229136 | 0.03488204 |
| SPOCD1 | 334.6453352 | 646.9665764 | 0.951850121 | 0.020227233 |
| SDC4 | 2530.87682 | 4889.228449 | 0.950156826 | $3.21 \mathrm{E}-05$ |
| FBXO5 | 1372.036981 | 2651.115915 | 0.950141044 | 0.000108007 |
| BTNL9 | 387.9153785 | 748.5943994 | 0.948990144 | $2.95 \mathrm{E}-06$ |
| SFXN5 | 604.0399061 | 1166.296143 | 0.948521058 | 6.83E-08 |
| TP73 | 1170.635303 | 2259.435446 | 0.94851697 | 1.03E-07 |
| GAREM2 | 198.5145157 | 383.3486599 | 0.947535229 | $9.80 \mathrm{E}-05$ |
| ZWILCH | 1206.910545 | 2327.143325 | 0.947046534 | 0.007560744 |
| TMOD1 | 51.45477015 | 99.1364258 | 0.946390934 | 0.008130848 |
| USP49 | 605.2395323 | 1165.77609 | 0.945777001 | $4.66 \mathrm{E}-08$ |
| ZNF433 | 49.01286103 | 94.29410277 | 0.944684297 | 0.013593566 |
| MELK | 3478.715626 | 6696.031323 | 0.944615575 | 0.000642736 |
| FUZ | 103.9462778 | 200.0422059 | 0.94388387 | 0.00621851 |
| FAM111A | 6606.143211 | 12705.04723 | 0.943567825 | $1.89 \mathrm{E}-05$ |
| ZNF850 | 231.7996025 | 445.2792421 | 0.943261244 | 8.93E-06 |
| SLC2A6 | 348.4604976 | 670.1137341 | 0.942516552 | 0.000129996 |
| EVA1A | 56.66516574 | 108.9894395 | 0.942261458 | 0.025394295 |
| BLM | 1466.622162 | 2814.641952 | 0.940335488 | 7.72E-06 |
| HELLS | 3293.885629 | 6316.875541 | 0.939244137 | 1.25E-05 |
| ELL2 | 404.0839014 | 774.3887357 | 0.939241937 | 0.003312365 |
| IFRD1 | 2078.193623 | 3982.728201 | 0.93861641 | 0.004959691 |
| TLE2 | 1323.73474 | 2533.407093 | 0.936518672 | $3.04 \mathrm{E}-05$ |
| KCNAB3 | 119.2764693 | 228.3865578 | 0.935592569 | 0.000758852 |
| UACA | 1282.029106 | 2451.605925 | 0.935086626 | $2.91 \mathrm{E}-05$ |
| ITGA10 | 53.59014461 | 102.1935723 | 0.933731935 | 0.010801744 |
| ZWINT | 4052.947205 | 7736.556742 | 0.932597621 | $3.96 \mathrm{E}-08$ |
| FAM126A | 439.5774539 | 838.8030197 | 0.932278372 | 0.000748001 |


| ZNF280A | 56.26269528 | 107.3470247 | 0.931763972 | 0.005300486 |
| :---: | :---: | :---: | :---: | :---: |
| PHLDA3 | 514.3409953 | 981.4329894 | 0.931584895 | $1.39 \mathrm{E}-06$ |
| CENPN | 857.2793256 | 1634.66327 | 0.931026523 | 0.000511678 |
| ZSCAN12 | 136.3130229 | 259.2997248 | 0.930524912 | 0.004790564 |
| EEPD1 | 169.386978 | 323.3198933 | 0.928820492 | 0.000604291 |
| GIPR | 664.991354 | 1265.321211 | 0.928140701 | 0.006920916 |
| NPL | 108.0964866 | 205.8257652 | 0.927891793 | 0.000204105 |
| PSMC3IP | 408.545349 | 777.3494106 | 0.92703621 | $4.78 \mathrm{E}-06$ |
| HOXA4 | 32.58402676 | 61.88189775 | 0.926292799 | 0.048553992 |
| PLAU | 488.6975793 | 928.7626566 | 0.924975008 | 0.01933562 |
| HES4 | 1436.200151 | 2726.017563 | 0.924564779 | 3.49E-07 |
| CDR2L | 1471.425159 | 2793.033466 | 0.924426677 | 0.000110735 |
| ITGA1 | 102.2516757 | 193.7166209 | 0.922944048 | 0.001724157 |
| SLC29A4 | 237.3163671 | 450.4186724 | 0.922851235 | 0.008910647 |
| EME1 | 637.490424 | 1209.109267 | 0.922475013 | 0.004639464 |
| RASD2 | 135.9387354 | 257.3800324 | 0.921482174 | 0.002516359 |
| SPTB | 1580.16961 | 2992.574582 | 0.921154546 | $4.26 \mathrm{E}-05$ |
| CIT | 4044.365369 | 7657.101565 | 0.920751108 | 0.000281281 |
| MASTL | 1771.257481 | 3353.587946 | 0.92062326 | 0.0004953 |
| NCAPH | 1759.018219 | 3328.473733 | 0.919821556 | 0.003886243 |
| POLD3 | 1407.84615 | 2663.062582 | 0.919316661 | $6.38 \mathrm{E}-05$ |
| TGFB1I1 | 507.4371526 | 958.9411006 | 0.919078288 | $3.50 \mathrm{E}-05$ |
| SERINC2 | 2173.358207 | 4108.159533 | 0.918533168 | 0.000116759 |
| GPRASP2 | 115.6968451 | 218.6475297 | 0.91714139 | 0.000678371 |
| ACBD7 | 241.6538737 | 456.3058707 | 0.915823273 | 0.010896555 |
| DUSP14 | 1038.049248 | 1957.882683 | 0.915479174 | 0.003312365 |
| RNFT1 | 350.2790759 | 659.56471 | 0.913135932 | $5.56 \mathrm{E}-05$ |
| SLFNL1 | 108.7590907 | 204.2900566 | 0.913012321 | 0.004988845 |
| NMI | 556.9371691 | 1047.234724 | 0.911753592 | 0.000213386 |
| SKOR1 | 36.46792248 | 68.71982224 | 0.909746414 | 0.049292642 |
| NEIL3 | 575.4324583 | 1079.568307 | 0.907322198 | 6.89E-05 |
| FAM13B | 966.8373241 | 1811.831409 | 0.906825925 | 0.004868129 |
| NTF4 | 162.4578909 | 304.4840375 | 0.90659326 | 0.045952785 |
| IL23A | 65.83993549 | 123.0981626 | 0.906103703 | 0.009355363 |
| PPFIA3 | 396.8124071 | 743.6397152 | 0.90571862 | $4.18 \mathrm{E}-07$ |
| MORN3 | 101.3063002 | 190.0991881 | 0.90503805 | 0.003116227 |
| ZNF132 | 61.604704 | 114.9779713 | 0.904399965 | 0.014114741 |
| PRKACA | 2760.132887 | 5162.651438 | 0.903208465 | 0.000151886 |
| DBNDD2 | 63.78128358 | 119.0699977 | 0.902607002 | 0.02215841 |
| PLXNC1 | 136.4931756 | 254.8085339 | 0.902205578 | 0.000200662 |
| CD83 | 245.4397477 | 458.0285256 | 0.901986482 | $1.79 \mathrm{E}-05$ |
| MATN2 | 1633.424875 | 3050.939281 | 0.901319392 | 0.001571788 |
| SH3D21 | 486.52226 | 908.6708982 | 0.901186171 | 0.019496649 |
| UFD1 | 1771.178323 | 3308.674894 | 0.901175936 | $1.34 \mathrm{E}-05$ |
| GPR161 | 608.2800311 | 1136.252644 | 0.901004633 | $2.48 \mathrm{E}-07$ |
| SAMHD1 | 1460.539038 | 2727.433488 | 0.900907243 | $1.20 \mathrm{E}-05$ |
| COTL1 | 2817.115856 | 5259.749171 | 0.900784076 | 0.021941862 |
| ATAD2 | 6938.122152 | 12953.73112 | 0.900710756 | 0.000969849 |
| SLC4A11 | 271.1348563 | 506.5679452 | 0.899667338 | 0.000979959 |
| HRCT1 | 211.5687852 | 394.8122357 | 0.898847294 | 0.009113473 |
| TINAGL1 | 1723.042929 | 3211.390513 | 0.898429318 | 0.020485998 |
| TAP1 | 1220.774576 | 2270.101138 | 0.894740561 | $1.40 \mathrm{E}-05$ |
| INPP1 | 566.3469295 | 1052.909112 | 0.89454062 | 0.000281281 |
| RASSF1 | 647.9492262 | 1204.116833 | 0.894329055 | 0.000266859 |
| NGEF | 400.904609 | 745.9680922 | 0.894200529 | 0.000212066 |
| DLC1 | 1048.484988 | 1946.610501 | 0.892300367 | 0.003806029 |
| FOXO6 | 177.6934441 | 329.4431165 | 0.892076937 | 0.001327305 |
| MITF | 244.4155348 | 453.3276138 | 0.891964233 | 0.008910647 |
| C19orf47 | 639.5121126 | 1186.529081 | 0.891416011 | 0.000461992 |
| IQCD | 119.3551411 | 222.0461599 | 0.891169209 | 0.004080291 |
| HAT1 | 2110.500345 | 3909.748145 | 0.889322247 | 0.00367597 |


| COL9A3 | 462.3397826 | 855.4092793 | 0.887228584 | 0.033474018 |
| :---: | :---: | :---: | :---: | :---: |
| HOXD11 | 70.55665266 | 130.2411616 | 0.887117409 | 0.010036374 |
| CENPM | 1289.84507 | 2385.173028 | 0.886455948 | 5.37E-05 |
| TEDC2 | 745.6432586 | 1378.989208 | 0.886026336 | $5.10 \mathrm{E}-05$ |
| SLF2 | 1247.797919 | 2302.406018 | 0.884073539 | 3.01E-08 |
| SHCBP1 | 1324.584431 | 2440.653339 | 0.881262523 | 0.001546888 |
| ZNF431 | 846.590319 | 1558.262178 | 0.880698596 | 0.001646198 |
| HAUS5 | 1397.45616 | 2571.489894 | 0.879285526 | $1.30 \mathrm{E}-05$ |
| SLC10A3 | 594.9746093 | 1093.190151 | 0.877906573 | $4.55 \mathrm{E}-05$ |
| HSD17B6 | 267.5801388 | 492.2383546 | 0.877810951 | $4.30 \mathrm{E}-05$ |
| STEAP4 | 269.1079891 | 494.0421792 | 0.877091951 | 0.000372322 |
| RASSF5 | 222.339117 | 408.3386426 | 0.875347009 | 0.000184504 |
| EED | 876.1635593 | 1606.599462 | 0.874296292 | 0.000327748 |
| RIBC1 | 47.83539242 | 87.74851743 | 0.874151843 | 0.020258786 |
| CCNI2 | 145.3081316 | 266.1152495 | 0.87412251 | 0.0001499 |
| RAD18 | 1044.140976 | 1913.994296 | 0.874102105 | 0.012528075 |
| PRICKLE2 | 47.59531309 | 86.90182779 | 0.872899863 | 0.037556258 |
| IL4R | 1329.236144 | 2434.995316 | 0.872894327 | 0.000774851 |
| STON2 | 140.6735165 | 257.6484328 | 0.87273241 | 0.004041471 |
| C1orf112 | 571.8972565 | 1047.265604 | 0.87236357 | 0.003357441 |
| RGS19 | 302.9205839 | 554.8098136 | 0.872286674 | 0.004664491 |
| DZIP1L | 255.1290385 | 466.6537574 | 0.871145491 | 3.92E-05 |
| AURKB | 2299.831535 | 4207.406152 | 0.87113136 | 0.000996498 |
| ARHGEF37 | 422.9256503 | 773.6675866 | 0.870648537 | $1.55 \mathrm{E}-06$ |
| UBE2T | 1123.220826 | 2053.801616 | 0.870204582 | 0.00546914 |
| IGFL2 | 614.4510759 | 1123.398672 | 0.870067674 | 0.000385427 |
| PLEK2 | 607.8819392 | 1111.470975 | 0.869981476 | $1.30 \mathrm{E}-05$ |
| ACYP1 | 407.3646221 | 745.2834273 | 0.869914616 | 0.000127418 |
| NEURL1B | 1314.674876 | 2401.808394 | 0.869511672 | 0.003473372 |
| BATF | 95.23263706 | 173.8929879 | 0.868312761 | 0.005265431 |
| HIST1H2BN | 45.18499352 | 82.33312646 | 0.868176137 | 0.041514379 |
| TMEM198 | 83.03968594 | 150.9863307 | 0.866456366 | 0.0120037 |
| C4BPB | 1678.879196 | 3059.683447 | 0.866303839 | 0.008806666 |
| POLA1 | 1285.155185 | 2342.259437 | 0.865663981 | 0.003178606 |
| MTMR11 | 405.8718385 | 740.0357266 | 0.865635123 | 0.037731965 |
| PCLAF | 1185.954215 | 2159.2483 | 0.864483771 | 0.000263866 |
| CLIC3 | 1135.448487 | 2065.437495 | 0.863115533 | 0.003415022 |
| WDHD1 | 1982.868384 | 3605.891699 | 0.862465109 | 0.003237671 |
| TMEM107 | 546.106058 | 993.3065331 | 0.862247743 | 0.000250279 |
| RUSC2 | 487.1946106 | 885.3523203 | 0.862201556 | 1.59E-05 |
| TEX14 | 143.74205 | 260.7592469 | 0.861491983 | 0.005902654 |
| ARL4D | 116.9102934 | 213.0344954 | 0.861450246 | 0.013147395 |
| DNAJA1 | 2759.457704 | 5012.987624 | 0.86121513 | 3.95E-05 |
| HAUS8 | 543.9832024 | 988.244242 | 0.860827811 | 0.002381711 |
| RTKN2 | 944.1826211 | 1714.226044 | 0.860689422 | 0.000102979 |
| ARHGAP29 | 1642.884794 | 2983.561667 | 0.860648956 | 0.000589406 |
| OIP5 | 456.5659423 | 829.2370578 | 0.860369056 | 0.006206849 |
| LRRC8C | 534.9553722 | 971.1535566 | 0.860188537 | 0.000518914 |
| PHKG2 | 1014.107121 | 1839.741565 | 0.859338973 | $3.51 \mathrm{E}-06$ |
| NUSAP1 | 647.1810534 | 1174.830613 | 0.859277957 | 0.001123392 |
| FAM189A2 | 134.9472671 | 244.2084031 | 0.858638051 | 0.010801744 |
| DSN1 | 1088.827391 | 1974.470834 | 0.85804793 | 0.000260575 |
| CRISPLD2 | 191.1620628 | 346.8426317 | 0.857787649 | 0.000511678 |
| CMC2 | 649.8724797 | 1177.983947 | 0.85752858 | 0.000579194 |
| E2F1 | 1969.625429 | 3568.9891 | 0.857342664 | 0.000219811 |
| EEF1A2 | 3041.774523 | 5510.399195 | 0.857269002 | 0.000383955 |
| CCP110 | 1632.80321 | 2957.044353 | 0.856976953 | $2.66 \mathrm{E}-05$ |
| GINS3 | 433.1692273 | 784.5617433 | 0.856953597 | 0.001079196 |
| CLTB | 2109.769352 | 3819.19497 | 0.856309077 | 0.000915023 |
| SDR42E1 | 229.3705672 | 414.0193203 | 0.854858958 | 0.00313915 |
| PXDN | 235.6703219 | 426.221424 | 0.854582925 | 0.02558872 |


| ZNF519 | 349.574461 | 631.5504233 | 0.853312791 | $6.75 \mathrm{E}-06$ |
| :---: | :---: | :---: | :---: | :---: |
| TBX1 | 143.4226473 | 258.7575905 | 0.85304783 | 0.041477085 |
| RRM1 | 6370.092653 | 11504.8383 | 0.852805023 | 0.000856484 |
| PLEKHA4 | 1360.634953 | 2457.634496 | 0.852489925 | $6.29 \mathrm{E}-06$ |
| BARD1 | 1432.064678 | 2585.24657 | 0.852110919 | 0.000639545 |
| ERCC6L | 615.1141544 | 1110.960767 | 0.851943368 | 0.001285418 |
| LRR1 | 553.8971094 | 999.1920699 | 0.85074646 | 0.006042486 |
| SAC3D1 | 801.0738135 | 1444.297815 | 0.850375218 | 0.000563262 |
| RFC3 | 1387.681303 | 2501.682065 | 0.850001713 | 0.004678441 |
| FN3KRP | 1009.882395 | 1820.502604 | 0.84963047 | 5.62E-05 |
| CYB5R2 | 226.5727428 | 408.1318539 | 0.849586753 | 7.77E-05 |
| GPS2 | 142.3866802 | 257.0213135 | 0.849412387 | 0.002340581 |
| CDK1 | 4147.393951 | 7469.598123 | 0.848725827 | 0.0012061 |
| CAMK2N2 | 159.6043406 | 287.7213524 | 0.848641675 | 0.010659122 |
| CKAP2L | 1288.486352 | 2319.244757 | 0.847852484 | 0.001799013 |
| DUSP4 | 205.4936409 | 369.5121353 | 0.847412438 | 0.038918944 |
| GFPT2 | 126.9794522 | 228.635887 | 0.847284195 | 0.01436992 |
| IQCJ-SCHIP1 | 162.7370367 | 292.4834816 | 0.846554371 | 0.013905421 |
| KIF23 | 3377.604503 | 6071.289459 | 0.845915983 | 0.002791857 |
| MAST2 | 4147.004956 | 7451.977822 | 0.845408974 | 7.46E-08 |
| PRR19 | 49.30701937 | 88.57811408 | 0.845334177 | 0.045232142 |
| TLR3 | 331.9323678 | 594.882635 | 0.842993441 | 0.002014686 |
| PDXP | 199.5753426 | 358.109629 | 0.842540449 | 0.025991179 |
| ZDHHC14 | 285.9616055 | 512.1147418 | 0.842039516 | 3.95E-05 |
| MAPK8IP2 | 268.7537206 | 481.6340883 | 0.841211276 | 0.000442606 |
| PSORS1C1 | 83.15029072 | 148.4738171 | 0.841162455 | 0.026159964 |
| PDLIM7 | 1350.626183 | 2417.536525 | 0.839645467 | 0.001663378 |
| C12orf4 | 779.5110096 | 1394.059541 | 0.83905997 | 0.0004953 |
| CDKN2D | 341.2031805 | 610.1063487 | 0.837064033 | $9.73 \mathrm{E}-05$ |
| ZNF107 | 799.6980036 | 1428.417145 | 0.836873471 | $1.34 \mathrm{E}-05$ |
| CHST3 | 1103.297496 | 1970.377337 | 0.836844781 | 0.001615086 |
| ASB16 | 173.8574421 | 310.1258179 | 0.836244163 | 0.008572565 |
| SYT17 | 355.7587758 | 634.4095959 | 0.835270195 | 0.01472204 |
| GPR137 | 1018.926238 | 1817.527136 | 0.835182405 | 0.000185736 |
| SPDYE2 | 111.571229 | 199.3585736 | 0.83397016 | 0.005343869 |
| FANCA | 2118.6815 | 3775.99999 | 0.833393717 | 0.000501764 |
| WAS | 71.02493258 | 126.2478741 | 0.832326771 | 0.021289125 |
| RAB27A | 406.7603331 | 724.5804009 | 0.832165952 | 0.001663378 |
| POLE | 5062.83585 | 9005.898872 | 0.83080836 | 1.42E-05 |
| FGFR3 | 994.1031528 | 1768.025561 | 0.830777931 | 0.019003787 |
| EMP1 | 633.9168193 | 1127.467925 | 0.829853018 | 0.017413898 |
| SLC25A35 | 334.5484999 | 595.3937571 | 0.829684051 | 0.003743498 |
| THAP10 | 201.967758 | 358.6554827 | 0.829272423 | 0.002024064 |
| BAIAP3 | 272.5026197 | 483.0774203 | 0.827625107 | 0.040683628 |
| NCMAP | 80.99211282 | 143.6358517 | 0.82690364 | 0.010868153 |
| CEP19 | 163.1072718 | 289.1204964 | 0.826340197 | 0.006147982 |
| ZNF789 | 1013.580864 | 1796.114458 | 0.825854505 | 1.95E-06 |
| CCL26 | 118.277696 | 209.8514883 | 0.824672998 | 0.003675068 |
| PCDH1 | 2153.797719 | 3813.898884 | 0.824223092 | 1.22E-07 |
| CILP2 | 339.6945787 | 601.7413119 | 0.823369474 | 0.000458863 |
| TRPV1 | 641.4480313 | 1134.329431 | 0.822575537 | 0.000719274 |
| PIK3IP1 | 165.8651828 | 293.214922 | 0.82182076 | 0.001090007 |
| GAL3ST1 | 64.97178018 | 115.1511799 | 0.821557279 | 0.034568454 |
| S100A13 | 544.457412 | 961.7484357 | 0.820760759 | 0.000130864 |
| CENPK | 1129.506942 | 1995.449205 | 0.820758225 | 0.000352412 |
| PTPRS | 137.8418215 | 243.6696171 | 0.820423239 | 0.009604952 |
| RAD54L | 961.843389 | 1698.889732 | 0.820080386 | 0.007235464 |
| OSR2 | 132.7260641 | 233.9539714 | 0.819942624 | 0.014839319 |
| PRSS51 | 124.324509 | 219.0616366 | 0.819155157 | 0.022098963 |
| PKMYT1 | 3006.562474 | 5298.804809 | 0.817368129 | 0.000507151 |
| RAD9A | 1157.059161 | 2038.080484 | 0.816432816 | 0.007128176 |


| WNT7B | 394.21758 | 693.7433383 | 0.815660194 | 0.007868595 |
| :---: | :---: | :---: | :---: | :---: |
| AGBL3 | 59.44702366 | 104.3521848 | 0.815478954 | 0.025747358 |
| SBDS | 1559.748733 | 2740.794423 | 0.813406441 | 0.031908096 |
| ARHGAP23 | 1926.642074 | 3384.190942 | 0.812886782 | 4.03E-05 |
| PRIMPOL | 535.1298372 | 939.3610991 | 0.812058873 | 0.000120409 |
| LTB4R | 479.6468558 | 841.7260539 | 0.811692572 | 0.001061443 |
| C4orf46 | 1116.001011 | 1958.832794 | 0.811611345 | 0.001445721 |
| TGFA | 1252.409187 | 2197.76182 | 0.811553805 | 0.007905553 |
| PDZD7 | 186.0586876 | 326.4659685 | 0.810951316 | 0.020161666 |
| TMSB4Y | 304.9052919 | 535.0316624 | 0.810733293 | 0.002732512 |
| RAB36 | 381.6354593 | 668.8809195 | 0.809991234 | 0.005443601 |
| CKB | 415.7528937 | 728.9304327 | 0.809768667 | 0.010784462 |
| YPEL3 | 1710.056451 | 2996.964665 | 0.809536912 | 0.030132885 |
| DNA2 | 1600.973548 | 2804.560679 | 0.808547215 | 0.003312365 |
| ACSF2 | 855.9377471 | 1498.766863 | 0.807890525 | 0.005049599 |
| DMRT2 | 117.0042858 | 204.4885404 | 0.805955284 | 0.004917308 |
| PCNA | 6991.571376 | 12211.66462 | 0.804490044 | 0.000656158 |
| A4GALT | 152.8219863 | 267.1253306 | 0.804363748 | 0.00069219 |
| MAD2L2 | 1443.190861 | 2519.422975 | 0.80353991 | 0.000904473 |
| DNAH12 | 173.0312977 | 302.0079493 | 0.802848557 | 0.001315539 |
| CDA | 142.7859098 | 249.3403194 | 0.80234873 | 0.04206216 |
| PREX1 | 85.16234061 | 148.8975689 | 0.800982871 | 0.014103777 |
| BTBD19 | 361.1295838 | 628.9130816 | 0.800454312 | 0.006070156 |
| TRIM29 | 201.4548721 | 350.1819661 | 0.799846097 | 0.002029683 |
| LRRC8E | 67.53242853 | 117.7436423 | 0.799736234 | 0.015183982 |
| SCARA3 | 3203.788203 | 5577.050293 | 0.799701129 | 0.000106873 |
| RELL2 | 390.9941087 | 681.0567616 | 0.798882624 | 0.000273416 |
| PARP2 | 1112.491894 | 1935.942076 | 0.798642993 | 0.000261727 |
| ALPK3 | 356.3529227 | 619.4989506 | 0.796767815 | 0.008881072 |
| CCDC102A | 539.279761 | 935.8447974 | 0.796643961 | 0.000600631 |
| COQ10A | 318.6220171 | 553.5914685 | 0.796637729 | 0.000139499 |
| PARD6A | 344.6152177 | 598.581426 | 0.795951327 | $2.42 \mathrm{E}-05$ |
| PIK3R3 | 605.6278313 | 1052.056193 | 0.795885183 | 0.000141334 |
| WNT5B | 271.846 | 471.5966821 | 0.795143624 | 0.000511678 |
| PAK6 | 300.983959 | 522.0067951 | 0.794960466 | 0.002315099 |
| TIAM1 | 658.2058138 | 1141.754903 | 0.79384483 | 0.005443289 |
| TCTEX1D2 | 73.00849133 | 126.4571277 | 0.792742812 | 0.009430471 |
| POU2F2 | 196.1186699 | 340.4664199 | 0.792546832 | 0.017776665 |
| RAD1 | 948.8606224 | 1641.246766 | 0.79047844 | 0.011349444 |
| SPAG1 | 855.9451593 | 1479.624547 | 0.789631948 | 0.007235464 |
| SH3BP1 | 337.4816702 | 583.726764 | 0.789213243 | 0.002938177 |
| TDRD1 | 83.13856028 | 143.6066489 | 0.789108489 | 0.028416348 |
| POLD1 | 2939.860752 | 5079.404321 | 0.788681176 | 0.0012136 |
| FLVCR2 | 106.5269688 | 183.7270691 | 0.787763254 | 0.004218179 |
| SWI5 | 380.3869795 | 656.5989076 | 0.787727529 | 0.000125292 |
| DCLRE1B | 566.6239547 | 978.3044304 | 0.787187197 | 0.022448807 |
| SP110 | 342.6696174 | 590.9905514 | 0.786246538 | 0.001349083 |
| TOP2A | 22037.95482 | 37997.91459 | 0.78591942 | 0.001020959 |
| MTSS1L | 868.7111355 | 1497.643156 | 0.785481175 | $1.32 \mathrm{E}-05$ |
| BCL2L15 | 569.4330589 | 981.0810954 | 0.785274759 | 0.04975029 |
| UPP1 | 416.8815922 | 718.4664121 | 0.784878113 | 0.015868152 |
| MXD3 | 1250.820662 | 2155.114212 | 0.784699702 | 0.01065666 |
| KIAA1841 | 456.9949779 | 787.8441948 | 0.784607697 | 0.000103481 |
| HOXC6 | 465.6177657 | 801.4151076 | 0.783756565 | 0.000749656 |
| MLLT11 | 238.6332514 | 411.1590599 | 0.783290107 | 0.002240182 |
| SPC24 | 1080.305331 | 1857.644857 | 0.781475603 | 0.000934024 |
| EHD4 | 1962.328489 | 3372.111457 | 0.781035441 | 0.010687781 |
| EIF1AD | 684.2304615 | 1175.900158 | 0.78103131 | 0.003131007 |
| DENND2A | 125.9759453 | 216.4640488 | 0.780737458 | 0.002535341 |
| USP1 | 4380.683451 | 7520.014719 | 0.779557508 | 0.002276175 |
| DDX58 | 711.4172802 | 1220.820259 | 0.779013793 | 4.55E-06 |


| BX255925.3 | 679.0123932 | 1165.236894 | 0.778862024 | 0.000352086 |
| :---: | :---: | :---: | :---: | :---: |
| SEMA4A | 243.0939401 | 416.7470605 | 0.778515606 | 0.034782552 |
| TOP3A | 1839.347073 | 3153.232433 | 0.777667322 | 0.000272091 |
| WNT3 | 334.9615984 | 573.9711956 | 0.777169379 | $6.05 \mathrm{E}-05$ |
| KIAA0319 | 160.7051277 | 275.1050633 | 0.776479483 | 0.03434088 |
| POLR2J2 | 69.11351684 | 118.5515073 | 0.776405333 | 0.035027053 |
| STXBP6 | 801.0179747 | 1371.512145 | 0.776295038 | 0.011743256 |
| IL1RN | 127.4641904 | 218.2255514 | 0.775627484 | 0.005731182 |
| KIF18B | 3061.229643 | 5240.55863 | 0.775405371 | 0.001764143 |
| CLEC2D | 170.5888968 | 292.1537146 | 0.775388714 | 0.017369756 |
| LRP11 | 170.1227202 | 291.0203072 | 0.77468131 | 0.000848889 |
| KRT7 | 231.5370042 | 395.9178393 | 0.774394236 | 0.006203544 |
| VRK1 | 1050.235304 | 1796.177016 | 0.773832663 | 0.013790582 |
| KLHL25 | 426.2249678 | 728.962616 | 0.773542253 | 0.000399491 |
| TEAD3 | 1708.709823 | 2920.589317 | 0.773073075 | $4.69 \mathrm{E}-06$ |
| FRMD8 | 985.9296925 | 1683.738736 | 0.772639555 | $3.21 \mathrm{E}-05$ |
| FAS | 708.4814744 | 1210.283464 | 0.771864645 | 0.003695131 |
| NCAPD3 | 5520.47676 | 9424.005603 | 0.771458279 | 0.009507613 |
| PXMP4 | 513.2365165 | 875.8781061 | 0.771367588 | $1.98 \mathrm{E}-05$ |
| NDC80 | 1386.018343 | 2364.795491 | 0.770484732 | 0.001103888 |
| GINS2 | 1031.204011 | 1759.427135 | 0.770253442 | 0.000934024 |
| KRT10 | 435.5902642 | 742.5850056 | 0.769716761 | 0.014642471 |
| CPNE2 | 1046.073482 | 1783.413056 | 0.769432381 | $1.97 \mathrm{E}-05$ |
| LUZP1 | 2536.529428 | 4322.382774 | 0.769033752 | 0.000798383 |
| ZNF367 | 1620.764772 | 2761.731335 | 0.768770592 | 0.003893305 |
| CRABP2 | 2286.992408 | 3897.477311 | 0.768718534 | 0.002663331 |
| HJURP | 3477.70185 | 5922.078993 | 0.76781578 | 0.00057685 |
| CHST14 | 996.9359927 | 1697.310701 | 0.767641932 | $1.56 \mathrm{E}-05$ |
| GINS1 | 1929.198928 | 3284.593443 | 0.767435817 | 0.007559909 |
| ZNF620 | 525.034835 | 892.9560724 | 0.767395643 | 0.000687561 |
| MYLK | 73.3111276 | 124.5380736 | 0.765785545 | 0.047504815 |
| ISYNA1 | 926.8185477 | 1575.224272 | 0.764956511 | 0.006027639 |
| RTTN | 970.309255 | 1649.322294 | 0.764667426 | 0.014867696 |
| 03-Sep | 862.6981917 | 1463.777531 | 0.763054216 | 0.00694816 |
| RABIF | 416.852947 | 706.9714101 | 0.762469411 | 0.007950174 |
| UBR7 | 1738.652877 | 2948.946202 | 0.762102106 | 1.83E-05 |
| CDC42BPG | 3463.950683 | 5874.852625 | 0.762022986 | 0.003167164 |
| TYMS | 1598.923202 | 2711.814024 | 0.76193672 | 0.00472561 |
| ZGRF1 | 1002.99744 | 1700.99644 | 0.761559147 | 0.002604668 |
| MGME1 | 1393.988633 | 2361.566675 | 0.760302523 | 5.25E-06 |
| SLC25A19 | 352.3968371 | 596.7252471 | 0.759754912 | 0.009938091 |
| DUSP2 | 221.463633 | 375.5737076 | 0.759531926 | 0.001820946 |
| ENO2 | 2513.07034 | 4252.24459 | 0.758630244 | $2.42 \mathrm{E}-05$ |
| SNRNP25 | 984.9343398 | 1665.307409 | 0.757040375 | 0.019263187 |
| ING2 | 421.423382 | 712.2546507 | 0.756772741 | 0.005346731 |
| ZNF584 | 420.0903592 | 709.8165766 | 0.756508227 | 0.005632617 |
| ATRIP | 643.7670376 | 1087.652155 | 0.756152244 | 0.012477706 |
| ROR2 | 64.79326844 | 109.1816534 | 0.755029786 | 0.048442286 |
| ZNF567 | 273.9216077 | 461.1370862 | 0.753672926 | 0.001815046 |
| POLQ | 1926.132284 | 3247.170108 | 0.753208784 | 0.010865872 |
| CLDN9 | 465.3943944 | 785.1486092 | 0.752929215 | 0.006064185 |
| CTHRC1 | 183.6578 | 309.8998817 | 0.752659449 | 0.037408577 |
| JUNB | 2427.080593 | 4087.209103 | 0.751667755 | 9.32E-06 |
| FANCD2 | 2353.530419 | 3961.245375 | 0.750883172 | 0.006295777 |
| CDC45 | 1067.066419 | 1794.770964 | 0.749521589 | 0.023554916 |
| IL6ST | 2983.942396 | 5015.053774 | 0.749161237 | 0.021941862 |
| ATP6V1D | 1432.211493 | 2405.8034 | 0.748559297 | 0.00041977 |
| PLEKHA6 | 1513.922037 | 2540.399408 | 0.74661166 | 7.89E-06 |
| KCTD11 | 824.7473562 | 1382.421573 | 0.746086486 | 0.001737474 |
| NPR1 | 327.1316892 | 549.3649193 | 0.745633943 | 0.033354359 |
| CEP295 | 1168.606275 | 1959.509313 | 0.745539373 | 0.000545634 |


| SPTAN1 | 22683.25578 | 38006.53448 | 0.744620161 | 0.000385427 |
| :---: | :---: | :---: | :---: | :---: |
| NANOS1 | 548.2687975 | 917.8766518 | 0.743327325 | 0.000127433 |
| SLC25A18 | 53.56440264 | 89.79230387 | 0.742799945 | 0.044422134 |
| MOSPD1 | 773.9417718 | 1294.53248 | 0.742641943 | 0.041382458 |
| GPSM1 | 458.2008009 | 766.7732717 | 0.742334291 | 0.001187704 |
| GRHL1 | 478.1042061 | 800.0184911 | 0.742073274 | 0.000909004 |
| CSRNP2 | 1083.919655 | 1810.619476 | 0.740352205 | 0.005153651 |
| PARP9 | 1443.391932 | 2411.700967 | 0.7403177 | 0.001372614 |
| C1orf216 | 1034.707428 | 1728.501983 | 0.740194343 | 0.000612764 |
| PLCL2 | 126.503346 | 211.3130151 | 0.740055397 | 0.00942071 |
| HES6 | 611.7998771 | 1021.693054 | 0.739419737 | 0.000119056 |
| TAF5 | 417.2153326 | 696.7100402 | 0.738899618 | 0.040908663 |
| NCAPG | 4057.073765 | 6768.513366 | 0.738314657 | 0.004301189 |
| MTHFS | 79.01684261 | 131.9360462 | 0.738031709 | 0.025923497 |
| PYGL | 394.7301108 | 659.0939122 | 0.737747374 | 0.02245428 |
| RARRES2 | 313.1396092 | 522.2791567 | 0.736978947 | 0.004823348 |
| DNAJC22 | 1178.542783 | 1964.615018 | 0.736950905 | 0.000344841 |
| PCBP4 | 1477.942585 | 2462.962722 | 0.73677111 | $1.28 \mathrm{E}-05$ |
| PXMP2 | 231.6472892 | 386.0834967 | 0.73640565 | 0.000890964 |
| C9orf40 | 1136.246645 | 1890.061468 | 0.734030491 | 0.000883533 |
| MSH2 | 3825.549504 | 6362.54486 | 0.733901047 | 0.004395746 |
| TRNP1 | 556.0492382 | 924.8788639 | 0.733753327 | 0.019973142 |
| ASIC3 | 183.08449 | 303.881783 | 0.733321611 | 0.00562512 |
| IFI35 | 608.2803978 | 1011.039733 | 0.733163085 | 0.047150767 |
| MLPH | 433.3577154 | 719.869531 | 0.731811694 | 0.034590636 |
| ZNF266 | 950.1201148 | 1577.917137 | 0.73169827 | 5.37E-05 |
| CORO2A | 439.4523696 | 730.4502855 | 0.731513482 | 0.001397856 |
| EFR3B | 393.6805405 | 653.656779 | 0.731504274 | 0.00915154 |
| TICAM1 | 790.1548774 | 1312.146461 | 0.731316347 | 0.011352754 |
| SERPINH1 | 5458.778615 | 9061.749609 | 0.731135553 | $4.40 \mathrm{E}-05$ |
| MAST3 | 1069.113967 | 1773.334017 | 0.729635774 | 0.002715511 |
| NOSTRIN | 232.128443 | 384.7327262 | 0.729446417 | 0.001063596 |
| ZNF180 | 317.6781344 | 525.934067 | 0.729387706 | 0.003094289 |
| PEAR1 | 268.5348095 | 445.0105804 | 0.729101125 | 0.021212033 |
| HECTD2 | 539.7776992 | 893.9351343 | 0.729020212 | 0.000659542 |
| TMEM106C | 3914.827617 | 6487.683897 | 0.728754613 | 5.17E-06 |
| RILP | 133.0593006 | 220.7251644 | 0.728322442 | 0.007032425 |
| SHROOM1 | 1280.847607 | 2121.192111 | 0.728100063 | $3.35 \mathrm{E}-05$ |
| TMEM255B | 106.3233668 | 175.800693 | 0.72789908 | 0.01723941 |
| HAUS2 | 1397.478478 | 2313.62294 | 0.727359287 | 0.021715519 |
| LRRC8A | 2276.53928 | 3768.271666 | 0.726829903 | $1.29 \mathrm{E}-05$ |
| NCAPG2 | 4615.288375 | 7633.448807 | 0.72579087 | 0.01428913 |
| EHBP1L1 | 1450.078985 | 2398.568163 | 0.72550525 | 0.000838799 |
| SPINDOC | 1236.604471 | 2043.950485 | 0.724656414 | 0.001850717 |
| ZNF684 | 124.4839558 | 205.5183217 | 0.723994639 | 0.019551591 |
| CHTF18 | 2486.668272 | 4107.096573 | 0.723590918 | 0.008498748 |
| RFC5 | 1820.647958 | 3006.327026 | 0.723224723 | 0.002469545 |
| CCDC18 | 742.1868048 | 1225.198539 | 0.722919066 | 0.000235344 |
| C5orf34 | 376.6926569 | 621.9003401 | 0.722475751 | 0.003944132 |
| NXF1 | 2920.780412 | 4816.980294 | 0.722005799 | 0.001135524 |
| SPICE1 | 142.0436741 | 234.1246654 | 0.721699131 | 0.005131731 |
| GOLT1A | 123.0012559 | 202.2897865 | 0.721419844 | 0.023128272 |
| CCR10 | 77.6621598 | 128.3313719 | 0.721320671 | 0.034210129 |
| WDR97 | 147.7901083 | 243.4277591 | 0.720913423 | 0.014985088 |
| PLEKHG2 | 1688.122591 | 2781.728794 | 0.720575648 | 8.42E-05 |
| PALLD | 815.7532797 | 1344.48239 | 0.720372194 | 0.004042301 |
| SFXN3 | 1565.650253 | 2579.153237 | 0.719689128 | 0.000973775 |
| HAUS3 | 814.4929386 | 1340.814112 | 0.718789241 | 0.000453939 |
| TEX30 | 533.8474515 | 878.2226024 | 0.718013233 | 0.003788201 |
| FGF2 | 491.1727658 | 807.8077197 | 0.717903198 | 0.046703966 |
| NRP1 | 434.7130557 | 714.3854502 | 0.717901608 | 0.002851174 |


| SPATS2L | 1872.162127 | 3078.514477 | 0.717452546 | 0.004853929 |
| :---: | :---: | :---: | :---: | :---: |
| SKA1 | 1176.46685 | 1932.990725 | 0.7164045 | 0.01764542 |
| SMIM4 | 307.0492984 | 504.4544896 | 0.716240038 | 0.023953907 |
| CCDC142 | 721.4463715 | 1184.760167 | 0.716189301 | $4.72 \mathrm{E}-05$ |
| PLXND1 | 1065.085058 | 1749.306339 | 0.715254797 | 0.001043938 |
| TONSL | 2389.290206 | 3921.337988 | 0.714468178 | 0.000545634 |
| DRP2 | 70.14520671 | 115.2630114 | 0.714426337 | 0.042051168 |
| DHRS7B | 551.2235809 | 904.6478575 | 0.714230685 | 0.004553128 |
| CENPQ | 411.186642 | 673.8347433 | 0.712382273 | 0.002528891 |
| MEA1 | 1334.928558 | 2185.49637 | 0.710900076 | 0.005930116 |
| SDC3 | 1928.712593 | 3157.412918 | 0.710815023 | 0.00313915 |
| SLC27A3 | 1008.988314 | 1651.871949 | 0.710500273 | 0.014070408 |
| ZNF527 | 146.1270899 | 238.961744 | 0.710486599 | 0.005724798 |
| MICALL2 | 2037.834637 | 3333.698622 | 0.709947458 | 0.041514379 |
| CCDC74A | 285.5539391 | 466.9599141 | 0.709688458 | 0.045169883 |
| N4BP3 | 446.4598903 | 729.5031826 | 0.709272222 | 0.012011653 |
| POLE2 | 458.5073066 | 749.3793975 | 0.707993899 | 0.016816221 |
| DNAJC9 | 1456.764728 | 2379.901391 | 0.707862573 | 0.000541907 |
| KANK2 | 3425.570142 | 5593.988564 | 0.707488327 | $7.77 \mathrm{E}-05$ |
| CCDC134 | 320.121827 | 522.6263543 | 0.70615519 | 0.000455135 |
| PEAK1 | 1413.606097 | 2305.556789 | 0.705755545 | 4.83E-05 |
| ZNF250 | 316.1716301 | 515.0636235 | 0.704266572 | 0.000385293 |
| SLC41A2 | 608.059165 | 990.2958801 | 0.704078834 | 0.00088113 |
| PPME1 | 1733.006288 | 2821.750625 | 0.703465754 | 0.003358693 |
| 08-Sep | 4054.672822 | 6602.470525 | 0.70334338 | 0.000124008 |
| PSMB8 | 984.2894544 | 1602.793081 | 0.703328652 | $4.22 \mathrm{E}-05$ |
| CNFN | 131.2275518 | 214.0664075 | 0.703271744 | 0.033495404 |
| SLC51A | 115.0280615 | 187.1408268 | 0.702998953 | 0.021212033 |
| TAOK2 | 3347.350811 | 5449.607689 | 0.702981635 | $7.48 \mathrm{E}-06$ |
| TRIM47 | 530.7261366 | 863.5275005 | 0.701793491 | 0.039433669 |
| FGFR4 | 161.2450473 | 262.8052602 | 0.701411241 | 0.016220356 |
| CKS1B | 2713.70445 | 4411.656234 | 0.700899696 | 0.012304068 |
| MPC2 | 1130.035297 | 1836.099654 | 0.699846355 | 0.005843136 |
| POLH | 687.4148072 | 1117.050149 | 0.699758574 | 0.000481412 |
| AGAP2 | 215.6673675 | 350.5111712 | 0.699613177 | 0.00714626 |
| RMI1 | 1166.398302 | 1894.294076 | 0.699261715 | 0.012505056 |
| MRPL53 | 133.3013586 | 215.9806936 | 0.698695121 | 0.011292585 |
| INO80C | 311.9819997 | 506.2670989 | 0.69840873 | 0.006414203 |
| EID2 | 885.2696221 | 1435.514618 | 0.69760685 | 0.023255346 |
| STOM | 107.3574976 | 174.2746824 | 0.69738442 | 0.028249186 |
| CXCL16 | 2385.153072 | 3865.08627 | 0.696502542 | 0.006844383 |
| SEC14L2 | 213.8281006 | 346.2741295 | 0.696455218 | 0.009938091 |
| EPPK1 | 3002.929194 | 4866.366559 | 0.696372255 | 0.010202823 |
| CEP78 | 3074.330977 | 4981.175903 | 0.69613453 | 0.007859919 |
| TEAD1 | 6920.917369 | 11205.87013 | 0.695237041 | 0.024913127 |
| MMS22L | 1505.928765 | 2434.59645 | 0.692726832 | 0.002276175 |
| PRRG4 | 1039.55705 | 1680.155393 | 0.692313788 | 0.000541907 |
| ZNF821 | 134.0861028 | 216.9245671 | 0.69223102 | 0.011899544 |
| CYLD | 1031.593222 | 1663.042661 | 0.689473366 | 0.016583912 |
| SHH | 151.6922574 | 244.0211492 | 0.68854353 | 0.007501743 |
| DDX11 | 3612.068016 | 5822.007985 | 0.688494234 | 0.000443364 |
| CCNYL1 | 525.4930974 | 846.9751281 | 0.688427754 | 0.034530964 |
| LRP4 | 328.6815372 | 530.1641901 | 0.688306157 | 0.008208966 |
| CAMK1 | 337.1071933 | 543.1666702 | 0.687069601 | 0.039536897 |
| RB1 | 2563.27781 | 4126.477507 | 0.686931659 | 0.004664638 |
| KLHL22 | 1274.103211 | 2050.369635 | 0.686420126 | 0.000507151 |
| NEMP1 | 6651.211416 | 10699.10996 | 0.685733954 | 0.0001709 |
| C1orf210 | 468.4486081 | 753.3853938 | 0.685274726 | 0.001704531 |
| LTB4R2 | 112.1243717 | 180.031193 | 0.684846836 | 0.043564962 |
| CEP85 | 1270.58713 | 2043.060954 | 0.684832073 | 0.007220593 |
| ZNF695 | 124.0578467 | 199.3724535 | 0.684040465 | 0.025302941 |


| ABCA7 | 2925.76724 | 4700.80208 | 0.683984645 | 0.015562238 |
| :---: | :---: | :---: | :---: | :---: |
| SYNJ2 | 1910.840795 | 3069.046982 | 0.683681226 | 0.006005785 |
| DNAH17 | 102.3176334 | 164.1179574 | 0.682731631 | 0.015668715 |
| RECQL4 | 3252.032863 | 5220.55744 | 0.682653928 | 0.011130246 |
| HYAL3 | 239.4346489 | 383.774109 | 0.681984855 | 0.00634989 |
| ZNF100 | 284.6955124 | 456.7666999 | 0.681503693 | 0.037731965 |
| NAV2 | 206.4740362 | 330.7532161 | 0.681384421 | 0.009536785 |
| NFATC2 | 93.24923239 | 149.34784 | 0.680900846 | 0.040840935 |
| PTCH2 | 110.903743 | 178.0818873 | 0.680741606 | 0.02718149 |
| RCAN1 | 350.9721382 | 562.5289674 | 0.680735377 | 0.031635784 |
| CDC7 | 1277.532361 | 2046.538013 | 0.679586083 | 0.029026284 |
| CLDN23 | 388.6877405 | 622.0401536 | 0.679049904 | 0.00121145 |
| BLCAP | 1539.82247 | 2464.178943 | 0.678769067 | 0.000281281 |
| DYRK1B | 190.2970059 | 304.1755117 | 0.676754576 | 0.008483632 |
| RNF168 | 1162.551943 | 1857.887922 | 0.676061238 | 0.003336638 |
| SERPINF1 | 246.3908166 | 393.0762696 | 0.675942521 | 0.010573318 |
| OPTN | 2546.496791 | 4063.435151 | 0.674390886 | 8.59E-05 |
| EPAS1 | 1462.235979 | 2332.452088 | 0.673533651 | $3.70 \mathrm{E}-05$ |
| TBC1D1 | 2228.007669 | 3552.173687 | 0.672719304 | 0.003513883 |
| BRI3BP | 2543.036401 | 4053.199615 | 0.672350511 | 0.025959906 |
| NR4A1 | 762.7876562 | 1216.043207 | 0.672337366 | 0.003711629 |
| PLAUR | 2278.392305 | 3631.266073 | 0.672182877 | 0.003753137 |
| NUP62CL | 368.5170039 | 588.0332459 | 0.672153222 | 0.02215841 |
| FAM53C | 2200.382997 | 3505.708876 | 0.671830273 | $3.10 \mathrm{E}-05$ |
| AHDC1 | 1711.639421 | 2726.736377 | 0.671543914 | 0.00061335 |
| ZNF846 | 316.9635899 | 504.3210524 | 0.671128196 | 0.011704825 |
| ELF4 | 1329.29787 | 2114.303815 | 0.669677958 | 0.00109339 |
| MYL6B | 1387.972017 | 2207.469779 | 0.669242842 | 0.0001302 |
| RHOV | 419.2337803 | 666.997471 | 0.668634303 | 0.003891262 |
| HACD1 | 709.0213992 | 1127.157666 | 0.66851583 | 0.017541526 |
| EZH2 | 3500.666459 | 5562.599494 | 0.668016129 | 0.000346532 |
| SEMA6C | 337.6002727 | 536.2414321 | 0.666936535 | 0.00475018 |
| CCDC84 | 1759.838376 | 2791.32155 | 0.665287633 | 0.000289491 |
| HCFC2 | 416.3985303 | 659.8014426 | 0.664865013 | 0.007806664 |
| PHTF2 | 1992.962388 | 3159.527863 | 0.664793488 | 0.001755316 |
| KLHL23 | 2307.69086 | 3655.4741 | 0.663528878 | 0.006662175 |
| CASP7 | 1110.611623 | 1758.347944 | 0.662664452 | 0.000351287 |
| NDOR1 | 1104.538926 | 1747.193754 | 0.661185022 | 0.000316414 |
| DHRS1 | 1103.219795 | 1744.317318 | 0.660511044 | 0.000487027 |
| SLC16A3 | 1081.243815 | 1709.016709 | 0.660384088 | 0.031440237 |
| RFC4 | 1896.888939 | 2998.59516 | 0.660335875 | 0.010083963 |
| SIVA1 | 2033.20984 | 3211.807919 | 0.659530971 | 0.00048893 |
| HOXD10 | 361.2357869 | 569.8315829 | 0.658964796 | 0.002888234 |
| FOXD2 | 183.0786013 | 289.2303694 | 0.658501559 | 0.02584353 |
| FAM222A | 297.0967929 | 468.2475768 | 0.657770384 | 0.018339206 |
| NTAN1 | 545.0095185 | 858.9655826 | 0.65510588 | 0.011479604 |
| ZC2HC1C | 125.2594221 | 197.1852868 | 0.654807936 | 0.014528242 |
| CAP2 | 797.8217618 | 1255.714712 | 0.654325971 | 0.010869632 |
| AVPI1 | 330.6519197 | 520.3467382 | 0.654070605 | 0.011224595 |
| OPA3 | 863.6456776 | 1357.863825 | 0.652915747 | 0.034570179 |
| ADPRHL2 | 772.1288932 | 1214.004125 | 0.652784489 | 0.035064192 |
| BRCA1 | 2860.873477 | 4497.330768 | 0.652393373 | 0.000909004 |
| PPP1R12B | 598.1527703 | 939.8639695 | 0.651808056 | 0.001633237 |
| MAPK7 | 502.0252466 | 788.6423353 | 0.651104647 | 0.002563504 |
| VAMP1 | 540.4362271 | 848.0973726 | 0.650446473 | 0.027684819 |
| BAZ1A | 2781.943269 | 4366.08208 | 0.650236216 | 0.021850566 |
| PI4K2A | 1002.492025 | 1572.997743 | 0.649913256 | 0.003574319 |
| KNL1 | 2781.977235 | 4362.979902 | 0.649173652 | 0.026898079 |
| ARTN | 243.7485111 | 382.6786694 | 0.64880209 | 0.01993611 |
| CADM4 | 464.2791803 | 727.1585694 | 0.647723985 | 0.025731691 |
| KIF4A | 2096.905397 | 3284.255731 | 0.647148099 | 0.019097022 |


| STMN1 | 10011.6362 | 15678.61217 | 0.647066635 | 0.010692763 |
| :---: | :---: | :---: | :---: | :---: |
| MOK | 245.2465728 | 383.7012211 | 0.646744811 | 0.009765334 |
| C3orf62 | 396.3330716 | 619.8633995 | 0.646601378 | 0.020095199 |
| CDC42EP3 | 743.3739122 | 1162.601599 | 0.645933488 | 0.002556233 |
| NOTCH1 | 1794.039762 | 2805.934697 | 0.645042383 | $7.86 \mathrm{E}-05$ |
| KIFC1 | 3484.790585 | 5449.855792 | 0.644968234 | 0.021061853 |
| DAGLB | 1060.443404 | 1658.0338 | 0.644582034 | 0.009141265 |
| LBX2 | 311.5500545 | 486.9875333 | 0.644359664 | 0.037240542 |
| TCF7 | 898.9695867 | 1404.59718 | 0.644179252 | 0.00041576 |
| GGT7 | 868.2778209 | 1356.833245 | 0.644031753 | 0.049228726 |
| GMNN | 703.6022062 | 1099.775666 | 0.643913934 | 0.027217524 |
| C3orf52 | 417.7826641 | 652.8503465 | 0.643726008 | 0.00885351 |
| BCL2L12 | 1404.491913 | 2194.229774 | 0.643319296 | 0.037650107 |
| CEP192 | 2482.40177 | 3877.394679 | 0.64322233 | 0.00110679 |
| SYTL2 | 534.6519475 | 835.4753559 | 0.643162375 | 0.001724157 |
| TLR2 | 280.5835818 | 437.8311883 | 0.642897249 | 0.032020346 |
| FANCG | 1890.538582 | 2952.10052 | 0.642597687 | 0.005700152 |
| TBC1D2B | 1300.1666 | 2029.807884 | 0.642526608 | $9.20 \mathrm{E}-05$ |
| DNMT1 | 9858.195854 | 15388.19672 | 0.642387695 | 0.039178111 |
| RFX5 | 2031.413201 | 3170.318501 | 0.641822733 | 0.00466515 |
| MAPK11 | 324.3635636 | 506.3871035 | 0.641618375 | 0.031757254 |
| PPM1D | 607.0152824 | 946.1090462 | 0.640719619 | 0.002257295 |
| C1orf35 | 867.8173923 | 1352.989464 | 0.640454843 | 0.003313074 |
| CHAMP1 | 1837.098074 | 2861.479302 | 0.639217716 | 0.030365789 |
| ADAL | 380.3892606 | 592.2767817 | 0.638889443 | 0.008526127 |
| ZNF230 | 185.9679772 | 288.7639384 | 0.637599273 | 0.025472645 |
| NUDT8 | 458.927728 | 714.4604725 | 0.637372971 | 0.016760576 |
| KLK10 | 1332.032551 | 2070.969874 | 0.63698714 | 0.001115133 |
| BORCS8 | 231.1156524 | 359.6114466 | 0.636841154 | 0.009457452 |
| AAMDC | 158.0395623 | 245.3258194 | 0.634346849 | 0.009222017 |
| CSGALNACT2 | 938.6257243 | 1456.186618 | 0.633858198 | 0.022682105 |
| RINT1 | 819.5267716 | 1271.326724 | 0.633620637 | 0.025221904 |
| RNASEH2C | 1647.19209 | 2555.889068 | 0.633431995 | 0.000371424 |
| PHTF1 | 791.4297803 | 1228.05982 | 0.632893497 | 0.003780787 |
| MRPS6 | 668.2666604 | 1036.327759 | 0.632742322 | 0.00584105 |
| CHAF1B | 1584.345621 | 2457.087895 | 0.632691498 | 0.038388794 |
| PLAGL1 | 1808.15135 | 2802.321535 | 0.632264021 | 0.000381938 |
| CENPP | 174.0686753 | 270.1622046 | 0.631428893 | 0.025463081 |
| SMC1A | 7932.710794 | 12288.47394 | 0.63135985 | 0.029905941 |
| LRG1 | 399.3048109 | 618.1824479 | 0.630866532 | 0.002554112 |
| PAX6 | 167.342995 | 259.2941035 | 0.630864065 | 0.024155068 |
| TNK1 | 978.2757115 | 1514.557949 | 0.630862741 | 0.001114636 |
| GTF2A2 | 1040.975404 | 1611.826003 | 0.630822686 | 0.032910612 |
| HLA-F | 545.5317702 | 844.8139293 | 0.630469909 | 0.022325703 |
| GRK5 | 162.3073669 | 251.3579634 | 0.629617781 | 0.024236355 |
| PHLDB1 | 2051.273882 | 3172.978654 | 0.629292128 | 0.006061195 |
| KNTC1 | 3312.231608 | 5121.227018 | 0.628507677 | 0.017383799 |
| INAFM1 | 380.8578839 | 589.0322889 | 0.628277784 | 0.001950054 |
| FAM122B | 2673.738256 | 4131.770473 | 0.627857332 | 0.003756375 |
| TRIM26 | 2403.220367 | 3713.214622 | 0.627738742 | 0.000561536 |
| ZNF69 | 275.6896799 | 425.8185597 | 0.627687119 | 0.007610464 |
| MIB2 | 2065.743885 | 3191.560483 | 0.627626767 | 0.036397142 |
| ZUP1 | 854.8539936 | 1320.542243 | 0.626732705 | 0.022738471 |
| DIABLO | 139.8866454 | 215.5950981 | 0.626573395 | 0.029882094 |
| CHAF1A | 3050.167767 | 4709.110787 | 0.626317312 | 0.037494382 |
| SMAP2 | 687.3911569 | 1060.938969 | 0.625769373 | 0.013073539 |
| RAB30 | 192.3162362 | 296.5785257 | 0.625584418 | 0.043302973 |
| LRRFIP2 | 1323.213698 | 2040.871344 | 0.62521791 | 0.037833309 |
| TEFM | 296.6345383 | 457.3140591 | 0.624965567 | 0.022094247 |
| ATP6V0E2 | 1150.012894 | 1772.710387 | 0.62422406 | 0.007164733 |
| KIF2C | 3168.319329 | 4880.298215 | 0.623093093 | 0.024307167 |


| CGN | 3964.892395 | 6105.462586 | 0.622701682 | 0.000219811 |
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| TMEM237 | 1070.90104 | 1649.185491 | 0.622469846 | 0.004682025 |
| RAB23 | 635.773344 | 979.0368003 | 0.622449447 | 0.011906411 |
| RBM38 | 1214.98087 | 1870.298249 | 0.622166862 | 0.00900918 |
| BRMS1L | 201.9537407 | 310.7004604 | 0.621789482 | 0.042784623 |
| FIGNL1 | 1389.918915 | 2138.286982 | 0.621561374 | 0.001472192 |
| MST1R | 3940.676371 | 6062.506448 | 0.6213604 | 0.000672416 |
| HR | 676.6963086 | 1040.979133 | 0.62120404 | 0.033633049 |
| UBE2A | 1718.123249 | 2642.235568 | 0.621077732 | 0.001624991 |
| SLC41A1 | 1790.050333 | 2752.681504 | 0.620984555 | 0.002660823 |
| REXO5 | 595.3591409 | 915.9834487 | 0.62063735 | 0.026671116 |
| ESPL1 | 3397.283532 | 5223.583116 | 0.620522423 | 0.018150321 |
| TGFB1 | 2085.817884 | 3207.307305 | 0.620428177 | 0.002475011 |
| CREB3 | 1600.4529 | 2460.013094 | 0.620362309 | 0.025472645 |
| RAB5IF | 827.952718 | 1272.321893 | 0.619704325 | 0.045362246 |
| BTN2A2 | 900.7208924 | 1382.753484 | 0.618612136 | 0.000382857 |
| LIN52 | 491.1991595 | 754.102057 | 0.617917644 | 0.025250026 |
| GPX3 | 282.3221735 | 433.6561099 | 0.617269496 | 0.013013735 |
| RAP1GAP | 299.1639111 | 459.3809542 | 0.616399351 | 0.024767951 |
| MCM4 | 9973.596787 | 15287.82071 | 0.616161188 | 0.046223293 |
| CEP135 | 698.3174102 | 1070.134462 | 0.615958775 | 0.043482378 |
| KRT15 | 216.2594343 | 331.144751 | 0.615558191 | 0.017692645 |
| PXDC1 | 396.3639863 | 607.4549743 | 0.615450841 | 0.005135312 |
| MIEF2 | 813.7999116 | 1245.797353 | 0.614882379 | 0.007007097 |
| MTBP | 559.9875685 | 857.9580391 | 0.614768403 | 0.032337146 |
| OSCAR | 276.4708749 | 422.7650795 | 0.613502475 | 0.030338743 |
| SEC14L1 | 2981.58724 | 4561.114763 | 0.613337953 | 0.017021385 |
| LNPK | 1226.367607 | 1875.515021 | 0.612697791 | 0.004605514 |
| ABTB2 | 849.0413635 | 1296.26477 | 0.611101352 | 0.011949003 |
| ACOT7 | 2258.406752 | 3448.894009 | 0.610595403 | 0.035984658 |
| TNFAIP1 | 2164.795903 | 3302.169123 | 0.609228178 | 0.030473117 |
| PLA2G15 | 548.3346012 | 836.2793824 | 0.609018447 | 0.001427761 |
| DTYMK | 1998.814345 | 3046.731884 | 0.607793006 | 0.014243325 |
| BAX | 1679.400208 | 2558.777326 | 0.607217007 | 0.023996176 |
| NBPF14 | 541.6929369 | 825.9196344 | 0.606981594 | 0.011320554 |
| CHRNA3 | 122.0306361 | 185.659024 | 0.606879529 | 0.025601553 |
| STMN3 | 528.460505 | 805.1594267 | 0.606782819 | 0.001564011 |
| PPP1R13B | 1402.150191 | 2134.294247 | 0.606359007 | 0.000348986 |
| FANCM | 691.19003 | 1052.525105 | 0.605973601 | 0.017507623 |
| SSH3 | 1805.303203 | 2747.421622 | 0.605625776 | 0.002194977 |
| TRIM7 | 262.8606724 | 400.1833658 | 0.60538114 | 0.026893868 |
| RELL1 | 301.5701429 | 459.0572778 | 0.60487683 | 0.012753318 |
| ZFYVE19 | 1934.698365 | 2941.209695 | 0.60415938 | 0.00280912 |
| FOXD1 | 940.5439649 | 1427.842661 | 0.602583211 | 0.002923174 |
| UPF3B | 1407.257435 | 2135.993836 | 0.602301642 | 0.004890632 |
| PDGFA | 211.5765936 | 321.1874428 | 0.602192236 | 0.049562543 |
| ST3GAL4 | 337.0310151 | 511.3151885 | 0.602161259 | 0.021212033 |
| SUSD6 | 688.1650585 | 1043.941209 | 0.602005439 | 0.002605121 |
| RHEBL1 | 237.9222618 | 361.3533681 | 0.600385926 | 0.028249186 |
| SWAP70 | 2158.607594 | 3272.431494 | 0.60034474 | 0.015646666 |
| SLC9A5 | 365.2278464 | 553.3607677 | 0.599835555 | 0.024322767 |
| SLC39A8 | 289.0527414 | 438.2373512 | 0.599271395 | 0.0089634 |
| DMXL2 | 3864.379888 | 5853.271243 | 0.59905152 | 0.00984663 |
| CCDC14 | 4122.160825 | 6238.31037 | 0.59777756 | 0.001827993 |
| NAGK | 1221.638234 | 1848.73571 | 0.597753617 | 0.008449158 |
| SEZ6L2 | 1136.15011 | 1719.409491 | 0.597559588 | 0.030003385 |
| NFATC2IP | 2798.576006 | 4234.533299 | 0.597518078 | 0.000841966 |
| CCDC120 | 1313.526948 | 1986.481613 | 0.596985039 | 0.000582159 |
| XRCC1 | 950.4054402 | 1437.187266 | 0.596256603 | 0.001147273 |
| ABLIM2 | 245.0183722 | 370.2451112 | 0.595941244 | 0.01230447 |
| MAP3K12 | 637.7347979 | 963.8158767 | 0.594851895 | 0.022098963 |


| RPP30 | 973.2126772 | 1468.929774 | 0.594141168 | 0.04236052 |
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| MCM3 | 7534.489967 | 11370.25725 | 0.593613691 | 0.024953157 |
| MORN2 | 182.2221823 | 274.763242 | 0.5935796 | 0.028224073 |
| RRAS | 826.7481205 | 1247.568525 | 0.592873786 | 0.014564717 |
| ITGB1BP1 | 1320.91156 | 1991.551966 | 0.592296084 | 0.022269138 |
| USP35 | 553.343184 | 834.9690944 | 0.592281986 | 0.005503859 |
| SGK494 | 376.4402186 | 567.6059061 | 0.591964695 | 0.036749662 |
| USP37 | 1000.108733 | 1507.406761 | 0.591771311 | 0.013921095 |
| FSCN1 | 4283.020813 | 6454.513755 | 0.591573012 | 0.012887925 |
| EFNB2 | 280.7884872 | 423.2627714 | 0.589951907 | 0.020434881 |
| SELENOW | 1387.323371 | 2085.265015 | 0.587403824 | 0.009224856 |
| LIPH | 1269.502053 | 1908.049776 | 0.587297625 | 0.004345352 |
| MXD1 | 634.2303914 | 952.2253047 | 0.586353683 | 0.005568786 |
| RNF19B | 1155.551271 | 1735.222957 | 0.586242753 | 0.009943142 |
| EPHB3 | 715.6905112 | 1072.225376 | 0.583386564 | 0.011121453 |
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| GTSE1 | 2747.801474 | 4116.453165 | 0.583019168 | 0.046812629 |
| PSMB10 | 248.2843167 | 371.1174565 | 0.582447018 | 0.049872685 |
| NLRC5 | 753.1421476 | 1128.009087 | 0.581728001 | 0.012553048 |
| H2AFX | 6301.879819 | 9430.627833 | 0.581539958 | 0.005840302 |
| CEP72 | 851.2447348 | 1273.936767 | 0.581301441 | 0.035699184 |
| CNP | 3907.350733 | 5845.803389 | 0.581064328 | 0.001536229 |
| ATP10D | 214.7744359 | 321.431908 | 0.581054955 | 0.01778198 |
| DHFR | 5670.054475 | 8482.13368 | 0.581038795 | 0.013140118 |
| LACC1 | 188.357099 | 281.5411098 | 0.580590644 | 0.037076435 |
| JOSD1 | 3565.325916 | 5330.57882 | 0.580226287 | 0.005482029 |
| PARP3 | 681.8617252 | 1019.134851 | 0.579945544 | 0.005437792 |
| SH3TC1 | 583.2542094 | 871.3924245 | 0.578911513 | 0.027016174 |
| ZNF497 | 214.0993072 | 143.6629237 | -0.577512647 | 0.03727044 |
| RPL36A | 319.4486181 | 214.1798404 | -0.578131338 | 0.027999065 |
| SIDT2 | 1441.682192 | 966.2307728 | -0.578132408 | 0.003096465 |
| C19orf70 | 824.4480623 | 552.2580222 | -0.578208204 | 0.005123958 |
| CCDC28A | 651.6880123 | 436.7097624 | -0.578233256 | 0.0082581 |
| IGSF9B | 704.0286525 | 471.7565831 | -0.578319538 | 0.003347407 |
| PIKFYVE | 2910.038733 | 1948.391906 | -0.578710163 | 0.000660131 |
| DPYD | 322.1291728 | 215.6469689 | -0.578808883 | 0.037408577 |
| RNF170 | 1437.214518 | 962.4512618 | -0.578881988 | 0.00097318 |
| EIF1AY | 1165.816372 | 779.8364963 | -0.579934794 | 0.044225289 |
| HNF1B | 656.0680453 | 438.5749767 | -0.580153271 | 0.018856868 |
| SF3B5 | 2363.000359 | 1580.654329 | -0.580157833 | 0.014255666 |
| MORC4 | 5678.550372 | 3793.585599 | -0.582067228 | 0.005550071 |
| COPS2 | 4092.817051 | 2733.042412 | -0.582346318 | 0.022613804 |
| SERP1 | 6125.451677 | 4090.684778 | -0.582400502 | 0.009343012 |
| TBCA | 4147.467745 | 2769.744331 | -0.582403033 | 0.006242862 |
| KLHL28 | 748.0709185 | 499.0351051 | -0.582456964 | 0.011644023 |
| MTA1 | 7877.869639 | 5258.866442 | -0.583165889 | 0.010642271 |
| PHF3 | 5616.752036 | 3747.168185 | -0.583977523 | 0.0023203 |
| RAB40C | 1639.612502 | 1093.432675 | -0.584848416 | 0.03727044 |
| DENND4C | 4460.491443 | 2973.412017 | -0.585127447 | 0.001755732 |
| DNAJC19 | 1283.333951 | 855.2341075 | -0.58513618 | 0.013096715 |
| 08-Mar | 1464.218874 | 975.747428 | -0.586007266 | 0.000926745 |
| HEXIM1 | 8296.758896 | 5525.128767 | -0.586638715 | 0.001894737 |
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| RPL28 | 16579.06957 | 11034.92039 | -0.587256344 | 0.000604291 |
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| PPFIBP2 | 1262.587629 | 840.4391854 | -0.588002744 | 0.022444496 |
| WDR19 | 1041.778294 | 693.4237782 | -0.58845828 | 0.003780787 |
| THEM4 | 563.0526832 | 374.4901397 | -0.58869273 | 0.003116227 |
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| SLC25A23 | 3064.759888 | 2036.507534 | -0.58990288 | 0.002555035 |
| ZNF18 | 385.595266 | 256.7399165 | -0.590058147 | 0.024913127 |


| AKAP7 | 275.4678187 | 182.9929788 | -0.590146193 | 0.041326708 |
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| NIPAL2 | 669.7276221 | 444.252475 | -0.590447971 | 0.034294919 |
| TJP3 | 5341.153112 | 3547.098654 | -0.590757061 | 0.017163001 |
| VDAC1 | 10833.32654 | 7193.155468 | -0.590803569 | 0.005511118 |
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| LRP5 | 8081.616857 | 5364.777724 | -0.591225396 | 0.013609849 |
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| TSPO | 3629.159816 | 2408.796491 | -0.591568456 | 0.001948011 |
| FBXL4 | 1139.954848 | 756.7626301 | -0.591674339 | 0.001375772 |
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| ATP8B1 | 4052.117779 | 2687.928839 | -0.592048431 | 0.009918336 |
| TRMT10C | 1204.935504 | 799.0336354 | -0.592216244 | 0.02264014 |
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| STBD1 | 193.194167 | 127.937157 | -0.59231671 | 0.039993827 |
| GSTO2 | 2186.177041 | 1449.843028 | -0.592531783 | 0.001073191 |
| KIAA1328 | 192.4709904 | 127.7370718 | -0.59305726 | 0.048827418 |
| ESRP1 | 1936.253889 | 1283.212038 | -0.593549085 | 0.008670917 |
| RNF141 | 1602.57328 | 1062.040543 | -0.593764422 | 0.00213068 |
| LARP1B | 2274.998632 | 1506.658327 | -0.594115621 | 0.011204583 |
| LPCAT1 | 5261.288387 | 3485.269828 | -0.594331892 | 0.024245841 |
| QARS | 7422.203728 | 4916.448666 | -0.594344737 | 0.000195488 |
| MUT | 1918.050081 | 1270.130939 | -0.594958568 | 0.000552008 |
| HIBADH | 2421.679232 | 1601.940446 | -0.596630417 | 0.008585088 |
| DNAAF5 | 1533.709998 | 1014.278542 | -0.59687974 | 0.026446572 |
| PRKAB2 | 1446.466804 | 956.5549841 | -0.596988472 | 0.003167164 |
| SDHD | 1791.466228 | 1183.819427 | -0.597343344 | 0.00507921 |
| GLS | 4278.986518 | 2825.497638 | -0.598448357 | 0.009043174 |
| SORD | 1177.533382 | 777.3043056 | -0.598975243 | 0.023451765 |
| DCBLD1 | 2497.338459 | 1647.19926 | -0.600011254 | 0.004092733 |
| RABL2B | 827.1407141 | 545.7926041 | -0.600292094 | 0.005382319 |
| NMD3 | 2943.405941 | 1941.042147 | -0.600431884 | 0.030794037 |
| MRPL23 | 1033.718922 | 681.891672 | -0.600673338 | 0.002048445 |
| CREB3L2 | 4444.385294 | 2929.701571 | -0.601369042 | 0.001155473 |
| LRRC41 | 5247.872437 | 3458.741826 | -0.601611874 | 0.000135521 |
| FAM114A2 | 659.7308971 | 434.8452823 | -0.601726889 | 0.002315099 |
| HAX1 | 3922.020457 | 2582.544718 | -0.602751883 | 0.004034681 |
| SFPQ | 22598.53173 | 14876.06567 | -0.603187143 | 0.000642864 |
| PLD2 | 1605.302781 | 1056.676888 | -0.603653545 | 0.009541478 |
| PHF14 | 1156.188085 | 760.1926991 | -0.6040311 | 0.019500745 |
| DHX35 | 684.4389275 | 450.2760494 | -0.604248247 | 0.015665766 |
| ME2 | 4249.585878 | 2794.689116 | -0.604609286 | 0.029288712 |
| LGALS3BP | 22493.81737 | 14790.71094 | -0.604870762 | 0.017152915 |
| RASA1 | 1346.060782 | 884.0923181 | -0.60620699 | 0.000299302 |
| SFXN4 | 1580.485101 | 1038.015748 | -0.606310615 | 0.009141265 |
| SLC38A7 | 892.7075952 | 586.1627767 | -0.607067071 | 0.003327065 |
| SSR4 | 4056.606808 | 2662.500717 | -0.607402195 | 0.001351764 |
| STK40 | 2745.226872 | 1802.035743 | -0.607422346 | 0.008036752 |
| PLPP5 | 1725.099566 | 1132.285784 | -0.607596255 | 0.017383799 |
| WDR78 | 220.5342652 | 144.351605 | -0.60773008 | 0.048662965 |
| LTBR | 4663.08203 | 3059.774221 | -0.607834708 | 0.000376419 |
| SLC3A2 | 22087.72669 | 14481.02579 | -0.609048067 | 0.018986922 |
| CTDSP1 | 6355.087127 | 4166.286129 | -0.609143068 | 0.001277586 |
| CNIH1 | 4847.471076 | 3176.930507 | -0.609424336 | 0.004000203 |
| RPS21 | 9835.688027 | 6444.120272 | -0.610120027 | 0.001600262 |
| VPS41 | 2280.778295 | 1493.159168 | -0.610945637 | 0.000507151 |
| NUDT3 | 350.5678432 | 229.9444085 | -0.6117891 | 0.03727044 |
| ARL1 | 2729.409026 | 1785.75513 | -0.611973118 | 0.000176211 |
| GNPDA2 | 755.5705486 | 494.2449178 | -0.612106245 | 0.004241283 |
| PRDX1 | 12156.37713 | 7953.112031 | -0.61216817 | 0.04236052 |
| SIAE | 2283.556221 | 1494.338008 | -0.612226636 | 0.000410486 |
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| NDUFA10 | 5053.986413 | 3304.437369 | -0.613000183 | 0.000858471 |
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| POLR1C | 1029.368055 | 672.7347508 | -0.613052819 | 0.025747358 |
| FAM189B | 2280.863724 | 1491.675744 | -0.61306501 | 0.005806229 |
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| CEP120 | 1355.220984 | 885.9256763 | -0.613467961 | 0.002486081 |
| FANCF | 751.382251 | 490.8872199 | -0.613640026 | 0.006646808 |
| TNKS1BP1 | 5380.105945 | 3515.556819 | -0.614144295 | 0.002512657 |
| ZNF182 | 373.6263031 | 243.9471132 | -0.614321297 | 0.006603881 |
| THOC6 | 1548.83927 | 1010.86982 | -0.616254077 | 0.004301189 |
| C2CD5 | 3906.095596 | 2547.87269 | -0.616265125 | 0.000635594 |
| GATB | 1051.330758 | 685.613945 | -0.617002753 | 0.008730545 |
| TMEM256 | 279.4018713 | 182.4910981 | -0.617767647 | 0.026157866 |
| ZNF407 | 730.2424167 | 475.5470291 | -0.618591617 | 0.001251752 |
| KLF3 | 2295.087989 | 1494.416087 | -0.618765215 | 0.000363657 |
| ICE1 | 3089.093573 | 2011.032464 | -0.618977083 | 0.006662266 |
| CUL7 | 3082.016652 | 2007.290188 | -0.619030495 | 0.004046559 |
| CDK2AP2 | 2967.492706 | 1931.667434 | -0.619394878 | 0.002490361 |
| MT-ND3 | 35663.19058 | 23184.39945 | -0.621323823 | 0.012565035 |
| AJUBA | 11264.7963 | 7321.092103 | -0.621589543 | 0.006401584 |
| PEBP1 | 14301.45185 | 9294.314029 | -0.621783871 | 9.89E-05 |
| ZNF280D | 545.5299751 | 354.2175755 | -0.622242458 | 0.005265431 |
| ERP29 | 7235.824858 | 4699.452254 | -0.622823763 | 0.000977803 |
| SEPSECS | 1191.822723 | 773.5369612 | -0.622929895 | 0.00086075 |
| TYW3 | 1358.757952 | 881.5902493 | -0.623435792 | 0.044111129 |
| YIPF2 | 1580.535346 | 1025.965404 | -0.623642559 | 0.002562729 |
| FAM173A | 803.0656724 | 521.5279006 | -0.624290722 | 0.005774284 |
| TMEM241 | 675.8407498 | 438.5557796 | -0.624424111 | 0.026731937 |
| CASK | 2916.990772 | 1891.730059 | -0.624960029 | 0.000153737 |
| ESRRA | 2797.479075 | 1813.056969 | -0.625680925 | 0.000346532 |
| KLF5 | 7734.274126 | 5010.904767 | -0.626003642 | 0.002678917 |
| RSBN1 | 948.3943912 | 614.0508986 | -0.626499909 | 0.000635618 |
| EIF3K | 3893.278976 | 2521.41798 | -0.626656545 | 0.042453164 |
| GABPB2 | 1327.879706 | 859.7617643 | -0.626695552 | 0.002229283 |
| FAM160B1 | 1357.493742 | 878.8798646 | -0.626955185 | 0.000414195 |
| PDIA6 | 13992.1905 | 9059.400446 | -0.627180761 | 0.000246459 |
| C17orf75 | 1042.843677 | 674.8808962 | -0.62739038 | 0.001467319 |
| SMIM19 | 795.4873585 | 515.235158 | -0.627435479 | 0.002331038 |
| CBR4 | 1045.90865 | 676.6765084 | -0.6275925 | 0.000602277 |
| CANX | 65961.93393 | 42679.11106 | -0.628095953 | 8.12E-05 |
| ARL2 | 906.5066955 | 586.4369939 | -0.628106465 | 0.006159801 |
| MT-CO1 | 476182.3521 | 308065.116 | -0.628278862 | 0.010788809 |
| RPS15 | 25699.98819 | 16622.231 | -0.628652391 | 0.000352412 |
| LIPA | 2889.802217 | 1868.09135 | -0.62960236 | 0.000132766 |
| B4GALT2 | 1906.777228 | 1231.919358 | -0.63014875 | 0.024796561 |
| SSR1 | 9268.610077 | 5987.219376 | -0.630427723 | 0.001133248 |
| NSMCE1 | 1380.456125 | 891.9346759 | -0.63073373 | 0.001209163 |
| ZNF703 | 4061.57495 | 2622.903854 | -0.630808509 | $7.86 \mathrm{E}-05$ |
| PSD3 | 1047.153557 | 676.4419864 | -0.631091137 | 0.015092025 |
| AMPD2 | 1635.456459 | 1056.12473 | -0.631197295 | 0.000748308 |
| EIF3A | 29980.4294 | 19353.2906 | -0.63140335 | 0.006291888 |
| TRUB2 | 2244.543972 | 1448.483086 | -0.631751245 | 0.000272035 |
| SPCS3 | 6127.162756 | 3953.769805 | -0.631876838 | 0.0023339 |
| TRAF7 | 3304.330411 | 2132.013593 | -0.632272472 | 7.77E-05 |
| DUSP16 | 3299.239346 | 2126.727438 | -0.633432131 | 0.001109585 |
| PRRC1 | 3585.47828 | 2311.207883 | -0.633613657 | 0.00011404 |
| MAF1 | 2948.487875 | 1899.901715 | -0.634347303 | 0.000270167 |
| PSRC1 | 1470.338608 | 947.6543374 | -0.63446287 | 0.015493553 |
| ZNF783 | 908.9770117 | 585.1003449 | -0.634733799 | 0.01050065 |
| ZNF449 | 434.0781312 | 279.9403487 | -0.634751999 | 0.039287954 |


| ATXN1 | 1882.461173 | 1212.219158 | -0.63480204 | 0.0025651 |
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| FAM107B | 1466.72109 | 944.2600081 | -0.635523111 | 0.01421468 |
| SLC27A1 | 1260.882137 | 811.3340284 | -0.636621041 | 0.047353282 |
| FAM174A | 488.3790702 | 313.7387936 | -0.636894411 | 0.019159792 |
| TMEM39A | 1678.724408 | 1079.146398 | -0.637164539 | 0.000474798 |
| MRPL16 | 2411.406586 | 1550.5603 | -0.637266944 | 0.019690959 |
| FAHD2A | 1384.596285 | 890.3808753 | -0.637375795 | 0.000239081 |
| GCFC2 | 877.2800047 | 563.7436868 | -0.637549075 | 0.003004983 |
| TEF | 1716.14821 | 1103.200903 | -0.637704177 | 0.004470299 |
| ZFP64 | 907.1362057 | 583.2429787 | -0.637737768 | 0.013836062 |
| RABL2A | 627.8264592 | 403.4837334 | -0.637879792 | 0.047309627 |
| CFAP69 | 228.6183667 | 147.2014865 | -0.638147185 | 0.026899304 |
| PFAS | 3160.720339 | 2030.531458 | -0.638311653 | 0.048561411 |
| SEC61B | 2562.21104 | 1644.674947 | -0.639594156 | 0.003080067 |
| FUBP1 | 6787.229835 | 4356.440314 | -0.639664913 | 0.000134773 |
| SH3RF3 | 204.1076825 | 131.099746 | -0.640044322 | 0.024767565 |
| TMEM50B | 2086.618235 | 1338.91102 | -0.64021276 | 0.03933786 |
| ZNF16 | 476.6451269 | 305.1037977 | -0.641675645 | 0.009448307 |
| CGREF1 | 1413.802756 | 906.737497 | -0.641794717 | 0.006466085 |
| PTPN4 | 1398.723432 | 896.4908371 | -0.641905616 | 0.000252983 |
| NDUFS4 | 1149.908462 | 736.9138108 | -0.642226126 | 0.001615086 |
| LRRC27 | 412.9303282 | 264.8366258 | -0.642253881 | 0.032917991 |
| SP4 | 767.6524563 | 491.5990028 | -0.642267912 | 0.002545121 |
| PIGA | 634.2217478 | 406.0185278 | -0.642683382 | 0.006931373 |
| ZDHHC17 | 1648.286443 | 1055.073694 | -0.643367134 | 0.000279951 |
| SMYD5 | 1298.229994 | 830.8885684 | -0.643747117 | 0.024987289 |
| PLEC | 33725.98779 | 21583.37701 | -0.643979772 | 0.000521614 |
| AVL9 | 4008.241337 | 2563.96951 | -0.644390793 | $8.80 \mathrm{E}-05$ |
| MAP3K4 | 1374.440196 | 878.6708954 | -0.645308997 | 0.000177102 |
| ZBTB24 | 829.6319043 | 530.0369328 | -0.64578013 | 0.031259427 |
| GPRIN2 | 989.664711 | 632.5747752 | -0.645863051 | 0.007583826 |
| DNAJB11 | 3616.554966 | 2311.250079 | -0.645899682 | 0.001215488 |
| CDADC1 | 333.1843967 | 212.5592299 | -0.647541056 | 0.006252022 |
| TMED10 | 9869.876625 | 6299.842876 | -0.647764229 | 0.000291414 |
| NDUFS2 | 3210.230775 | 2049.227743 | -0.647814494 | 0.002782037 |
| SLC18B1 | 857.8132725 | 547.4762853 | -0.648505548 | 0.00063564 |
| TXN | 8383.15766 | 5345.614147 | -0.649122249 | 0.041576733 |
| TPP1 | 2222.147783 | 1417.180704 | -0.649227857 | 0.023255346 |
| NTPCR | 922.6897627 | 588.6633528 | -0.649601761 | 0.001371604 |
| MYB | 617.2425083 | 393.2753721 | -0.650271474 | 0.028658155 |
| KLHL9 | 2758.209098 | 1757.452574 | -0.650284233 | 0.000147792 |
| ALKBH2 | 534.4309684 | 340.3065721 | -0.650971461 | 0.012682976 |
| PATJ | 5457.861801 | 3474.985749 | -0.651224453 | 0.000835233 |
| RPS5 | 23441.22323 | 14919.64626 | -0.651807469 | $5.35 \mathrm{E}-05$ |
| PIGO | 2930.262181 | 1865.195411 | -0.651866658 | 0.000106178 |
| MT-CO3 | 177444.0005 | 112928.2899 | -0.651957683 | 0.022813421 |
| PAM | 4058.867075 | 2582.069695 | -0.652427586 | 0.002433236 |
| EXOSC7 | 963.5738752 | 613.1368765 | -0.652440066 | 0.000645922 |
| H6PD | 7178.478743 | 4564.907437 | -0.653225716 | 0.003856838 |
| ARL14EP | 843.1282727 | 535.5563036 | -0.653297857 | 0.024956662 |
| KIAA1109 | 4334.824638 | 2755.560825 | -0.653474931 | 0.000322199 |
| ZNF330 | 1121.309486 | 712.4100449 | -0.653945003 | 0.021228882 |
| SNX13 | 2271.730211 | 1442.835773 | -0.654462435 | 0.000489942 |
| DMAC1 | 947.0233278 | 601.3495551 | -0.655021254 | 0.020510467 |
| MMS19 | 4225.755809 | 2683.081195 | -0.655395613 | $2.62 \mathrm{E}-05$ |
| SMIM8 | 317.9524278 | 201.506244 | -0.656185383 | 0.005137801 |
| FXR1 | 8597.879419 | 5453.818302 | -0.656667006 | $7.94 \mathrm{E}-05$ |
| LARP1 | 24082.413 | 15275.9238 | -0.656729787 | 0.001092137 |
| DYNC2LI1 | 608.3088657 | 386.1051624 | -0.656913309 | 0.003116227 |
| ADCY7 | 2784.27099 | 1764.907699 | -0.657757027 | 0.035045769 |
| DNAJC3 | 5212.580079 | 3303.357159 | -0.657972864 | 0.005859852 |


| LRRC34 | 335.0293513 | 211.8527838 | -0.65830803 | 0.026886725 |
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| CLDN12 | 1927.744604 | 1221.644234 | -0.658339489 | 0.000347888 |
| HDHD5 | 2836.267556 | 1796.820295 | -0.658594485 | 0.003320713 |
| PECR | 511.3973921 | 324.2475144 | -0.659270141 | 0.037408577 |
| TRMT1L | 1456.668868 | 921.7985764 | -0.659694246 | 0.00042629 |
| MGAT5 | 5009.263887 | 3170.418695 | -0.659915326 | 0.00015687 |
| FZD4 | 352.1087099 | 223.0530083 | -0.660078645 | 0.01428913 |
| SLC25A26 | 706.271699 | 446.7759539 | -0.660218064 | 0.001010854 |
| CCDC163 | 357.8027061 | 226.5083665 | -0.660535737 | 0.005338624 |
| TTC8 | 986.8074049 | 623.9441532 | -0.661816832 | 0.00055148 |
| FRMD4B | 1653.907715 | 1045.356983 | -0.661845942 | 0.012329975 |
| MAP2K5 | 805.2612097 | 508.8688558 | -0.66213526 | 0.000396325 |
| STXBP4 | 418.5946782 | 264.1892304 | -0.66250555 | 0.004299746 |
| TSFM | 889.7900659 | 561.6179398 | -0.663659587 | 0.006168795 |
| WDYHV1 | 431.7849099 | 272.7298681 | -0.663729809 | 0.006933496 |
| SPRY2 | 506.9665505 | 319.581695 | -0.66416013 | 0.005126358 |
| ESD | 2924.677646 | 1844.899672 | -0.664639392 | $5.37 \mathrm{E}-05$ |
| UST | 1359.994973 | 857.8396266 | -0.664805994 | 0.000222653 |
| CHPF | 7244.091355 | 4568.899436 | -0.665005387 | 0.000739558 |
| HBP1 | 1466.842464 | 925.2690263 | -0.665062642 | 0.00228514 |
| P4HB | 28834.30642 | 18181.54211 | -0.66533413 | 0.000814148 |
| ZNF239 | 492.9204987 | 310.6777924 | -0.665462374 | 0.020025525 |
| RPLP0 | 81578.37098 | 51381.36248 | -0.666942736 | 6.52E-06 |
| EFNA3 | 181.943333 | 114.655857 | -0.667179134 | 0.040685551 |
| TBC1D8B | 737.7202975 | 464.7621625 | -0.667214099 | 0.003325815 |
| LRRC23 | 411.6598154 | 259.4556786 | -0.667417889 | 0.007227531 |
| RAPGEFL1 | 1204.749775 | 758.7826304 | -0.667536852 | 0.017755717 |
| MCCC2 | 5587.324222 | 3515.534942 | -0.668417634 | 0.005550186 |
| PDK1 | 1110.212494 | 697.9445718 | -0.668433278 | 0.012572585 |
| MBNL3 | 1443.737248 | 907.9862657 | -0.668680848 | 8.12E-05 |
| GAPDH | 82691.04149 | 52017.33298 | -0.668732236 | 0.001172689 |
| TXNRD1 | 23271.02787 | 14635.60245 | -0.669073896 | 0.022365114 |
| SPATA7 | 322.2806566 | 202.9033832 | -0.669200347 | 0.011083884 |
| ANKRD16 | 405.6038786 | 254.6694349 | -0.670616377 | 0.027715166 |
| SLC12A2 | 6359.094658 | 3993.792368 | -0.670846849 | 0.027926948 |
| TANGO6 | 796.4046645 | 500.0142828 | -0.671450981 | 0.021297038 |
| ALDH5A1 | 2491.431737 | 1564.308498 | -0.671488999 | $7.29 \mathrm{E}-05$ |
| STK17B | 2875.081553 | 1804.691836 | -0.672001198 | 0.000363669 |
| CALR | 37860.1713 | 23756.9995 | -0.672354414 | 0.008130848 |
| ADGRA3 | 2662.254286 | 1670.256553 | -0.67245667 | 0.000273416 |
| USO1 | 5947.447825 | 3731.42866 | -0.672529112 | 0.000156931 |
| ALCAM | 1911.547182 | 1199.034247 | -0.67288261 | 0.000272091 |
| ALDH3A2 | 5225.577133 | 3277.874145 | -0.673025922 | 0.006528018 |
| SLC39A6 | 4205.674701 | 2637.441284 | -0.673100051 | 0.001132918 |
| PRPF40B | 544.9800849 | 342.2246471 | -0.673232085 | 0.031431335 |
| FOXA1 | 1833.755506 | 1149.260296 | -0.673957776 | 0.000127078 |
| MGMT | 825.3190373 | 517.5299941 | -0.674144307 | 0.001577077 |
| ARFGEF3 | 1492.548753 | 934.8950147 | -0.674674556 | 0.00046547 |
| MPST | 3787.501232 | 2371.539379 | -0.675566336 | $4.95 \mathrm{E}-05$ |
| DNPH1 | 3083.07226 | 1929.786239 | -0.676463996 | 0.003282591 |
| CHMP6 | 570.0205756 | 356.9171581 | -0.676539918 | 0.00398256 |
| ST6GALNAC4 | 1273.444211 | 796.4797861 | -0.677283502 | 0.001809059 |
| RPL17 | 760.1370795 | 475.0370782 | -0.677491863 | 0.010371632 |
| LRPPRC | 17144.97636 | 10719.35198 | -0.677525139 | 0.022770125 |
| FGFRL1 | 13052.4355 | 8161.175917 | -0.677543977 | 0.000383955 |
| ZXDA | 347.5058853 | 216.7173448 | -0.677744236 | 0.007868595 |
| CRYL1 | 1082.353318 | 676.9820501 | -0.677818294 | 0.03678778 |
| PWP1 | 1502.643939 | 938.6876076 | -0.678180201 | 0.022072888 |
| CBX4 | 3647.723647 | 2279.416167 | -0.678263293 | 0.005844145 |
| OSGEPL1 | 388.6171917 | 243.0977435 | -0.678471071 | 0.011505366 |
| PLGRKT | 323.0732154 | 201.8644797 | -0.679093155 | 0.018630514 |


| RNF41 | 2594.937902 | 1620.34294 | -0.679114933 | 0.027267334 |
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| FRA10AC1 | 1377.025721 | 859.8842004 | -0.679174437 | 7.49E-05 |
| DFFB | 648.6754954 | 405.1721526 | -0.679559104 | 0.001745234 |
| FECH | 3080.702748 | 1923.127319 | -0.67993443 | 0.000326986 |
| TGDS | 845.9141246 | 527.9865191 | -0.68015114 | 0.005503335 |
| APOOL | 1379.944714 | 860.6701616 | -0.680837737 | 0.000205914 |
| GATD3B | 1254.774711 | 783.0890999 | -0.681199339 | 0.000862978 |
| TXNRD3 | 887.3022475 | 553.650976 | -0.681506912 | 0.003566926 |
| TMCO4 | 1210.842788 | 754.8578431 | -0.682134812 | 0.000184988 |
| SINHCAF | 5462.496938 | 3404.017686 | -0.682213871 | 0.001379267 |
| CFAP97 | 5243.636171 | 3262.389942 | -0.6844734 | 0.008772908 |
| MFSD9 | 870.7701366 | 541.2182479 | -0.685460548 | 0.000980545 |
| GMPPA | 2068.181489 | 1285.729747 | -0.686193751 | 0.001201052 |
| KANK1 | 2923.466698 | 1816.22019 | -0.6869158 | $3.74 \mathrm{E}-05$ |
| PACRGL | 508.6896675 | 315.6448014 | -0.687669654 | 0.010624088 |
| KYAT3 | 2728.77922 | 1693.573294 | -0.687972348 | $4.66 \mathrm{E}-05$ |
| PTEN | 5604.254571 | 3477.05486 | -0.688617731 | 0.000127078 |
| MOSPD2 | 1179.687068 | 731.7250312 | -0.688812664 | 5.46E-05 |
| ATF2 | 2322.353669 | 1440.539488 | -0.688891867 | 0.000979114 |
| JMJD8 | 685.342452 | 425.6258267 | -0.689197682 | 0.003097715 |
| ALG2 | 1678.349498 | 1040.183172 | -0.689820143 | 0.002105682 |
| DBP | 1683.782288 | 1043.447131 | -0.69078165 | 0.046812629 |
| PEX5 | 1384.934671 | 857.4636424 | -0.691432813 | 0.007174059 |
| COG5 | 1979.719309 | 1225.740492 | -0.69155246 | $1.22 \mathrm{E}-05$ |
| ARL15 | 456.2747457 | 282.2059287 | -0.691554203 | 0.000997242 |
| BTBD8 | 534.466925 | 331.1067901 | -0.69181739 | 0.01289821 |
| ZFP69B | 142.6977944 | 88.32302132 | -0.692217815 | 0.021592578 |
| C1orf43 | 6102.434819 | 3774.534467 | -0.693019652 | $2.64 \mathrm{E}-05$ |
| ALG3 | 1543.745446 | 954.7701081 | -0.6931029 | 0.005322926 |
| DISC1 | 159.4891974 | 99.05379707 | -0.693167464 | 0.046307937 |
| NAT8L | 1301.154562 | 804.6865268 | -0.693171864 | 0.001546888 |
| MBD5 | 746.1511495 | 461.7341461 | -0.693845079 | 0.002111279 |
| DECR1 | 1621.485594 | 1002.554116 | -0.694087482 | 0.000451059 |
| MCF2L | 1514.173868 | 935.769174 | -0.694440917 | 0.01890543 |
| WDR82 | 10390.08374 | 6419.052272 | -0.694754294 | 4.22E-05 |
| HSDL1 | 1123.410457 | 694.3819617 | -0.694845104 | 0.00147899 |
| OGFRL1 | 2113.807356 | 1305.303229 | -0.695201625 | 0.000399798 |
| QTRT1 | 1727.323548 | 1066.268164 | -0.695808232 | 0.002645577 |
| MTIF3 | 1027.345584 | 634.5981667 | -0.695885852 | 0.000257711 |
| GALNT7 | 3147.527304 | 1942.966506 | -0.695973182 | 0.00053248 |
| DDOST | 11151.11639 | 6882.779544 | -0.696105517 | 3.45E-05 |
| TMEM105 | 227.3977438 | 140.1995947 | -0.696156891 | 0.03507121 |
| EIF2S2 | 8455.537022 | 5216.127212 | -0.696825985 | 0.005252591 |
| APBB2 | 11826.7526 | 7295.606987 | -0.69695629 | 8.92E-05 |
| CDCA7 | 2358.358031 | 1453.701137 | -0.698112002 | 0.015493553 |
| COPG2 | 2207.783972 | 1360.705078 | -0.698222898 | 0.000445902 |
| TAZ | 931.1118986 | 574.1800296 | -0.698541596 | 0.048790035 |
| PIM3 | 3956.068495 | 2436.687117 | -0.699146843 | 0.001591042 |
| CNKSR3 | 810.9130588 | 498.7564344 | -0.69965687 | 0.001051303 |
| SERGEF | 314.0320196 | 193.4021166 | -0.700243741 | 0.005375258 |
| ACACA | 9352.37828 | 5755.478371 | -0.700527071 | 0.000862978 |
| PHLDB2 | 2999.850965 | 1845.138218 | -0.700842891 | 0.010036374 |
| RBCK1 | 8038.155092 | 4945.304129 | -0.700929175 | 0.003635844 |
| MDM4 | 2384.292848 | 1466.655579 | -0.701183788 | 0.000774851 |
| ZBTB45 | 1715.993925 | 1055.841279 | -0.701357184 | 0.001538355 |
| PTER | 2357.988214 | 1448.532408 | -0.702507278 | 0.002315099 |
| STAT6 | 6274.913444 | 3855.496116 | -0.702817881 | 0.00298601 |
| RPS19 | 25876.27022 | 15888.64057 | -0.703644301 | $6.71 \mathrm{E}-06$ |
| RPL35 | 18346.94533 | 11258.9628 | -0.704469803 | 0.000106648 |
| JMY | 3410.255922 | 2091.58341 | -0.705444923 | 4.33E-05 |
| TPRG1L | 1012.622277 | 620.9537901 | -0.705696963 | 0.000121034 |


| HID1 | 2931.92957 | 1797.972229 | -0.705709141 | 0.017317234 |
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| GALNT6 | 2115.566831 | 1296.527867 | -0.705847063 | 8.72E-05 |
| NMRK1 | 989.5518546 | 606.9810096 | -0.705918964 | 0.00234085 |
| H1FX | 3877.055668 | 2376.69212 | -0.70617568 | 0.000604291 |
| IFT43 | 619.7289688 | 379.8807086 | -0.706278202 | 0.000511678 |
| DUSP18 | 228.2046692 | 139.9256157 | -0.706489021 | 0.040797762 |
| GOLPH3L | 1697.835414 | 1039.221428 | -0.7087262 | $7.77 \mathrm{E}-05$ |
| CTSD | 3737.166585 | 2287.027349 | -0.708753362 | 0.01014965 |
| PODXL | 7510.809103 | 4594.713901 | -0.709051979 | 0.000262961 |
| MRPS17 | 242.5969738 | 147.719186 | -0.711376648 | 0.027224852 |
| C3orf58 | 367.9661949 | 224.3064295 | -0.712350383 | 0.005972728 |
| TBCK | 665.7157034 | 406.3036443 | -0.712369404 | 0.015519509 |
| FAM86B1 | 253.7318178 | 154.6038595 | -0.713015089 | 0.038483653 |
| PMM2 | 887.0901086 | 540.8035882 | -0.713300164 | 0.015115362 |
| HSP90AB1 | 70241.14784 | 42810.10121 | -0.714362919 | 0.015476315 |
| BTN3A1 | 665.9382825 | 406.1644794 | -0.714447941 | 0.034221818 |
| GNL3 | 5113.001164 | 3115.562764 | -0.71458522 | 0.046007386 |
| IMPDH2 | 8763.67124 | 5338.553661 | -0.714995304 | 0.003312365 |
| SMPDL3B | 1320.118841 | 803.8475963 | -0.715424679 | $3.84 \mathrm{E}-05$ |
| CAMKK1 | 915.0907255 | 557.4572941 | -0.716347057 | 0.001374907 |
| PTPRK | 2279.206243 | 1386.306476 | -0.716749604 | 0.000106648 |
| ASIC1 | 1986.458829 | 1209.121807 | -0.716759246 | 0.003159276 |
| AP1AR | 1975.990661 | 1201.928157 | -0.716943288 | 0.003715764 |
| HDAC4 | 1259.01794 | 764.8999999 | -0.718332653 | 0.000121473 |
| WDR36 | 3033.718271 | 1842.72696 | -0.718941468 | 0.017021454 |
| CCNB1IP1 | 1934.617058 | 1174.270134 | -0.719740386 | 0.009860959 |
| SH3BGRL | 1300.091292 | 789.3550651 | -0.720155971 | 0.041529433 |
| TCF25 | 4811.179204 | 2919.662376 | -0.7207876 | 0.009352914 |
| ZSCAN2 | 277.0412406 | 168.3575068 | -0.721261368 | 0.004138726 |
| TMEM268 | 873.3879508 | 529.5200009 | -0.722079997 | 0.000351287 |
| TRIM59 | 850.625 | 515.8078652 | -0.722091907 | 0.000416486 |
| CRAT | 4714.783286 | 2858.584359 | -0.722173281 | 0.003737687 |
| H1F0 | 6063.270837 | 3674.522037 | -0.7224546 | 6.23E-06 |
| VPS35L | 3232.640084 | 1958.843489 | -0.722849263 | 3.45E-06 |
| SYF2 | 2116.847546 | 1282.0751 | -0.722882241 | 0.00035398 |
| SRPRA | 6852.364944 | 4151.066064 | -0.723140274 | 0.000604291 |
| TBC1D16 | 3715.008943 | 2250.228984 | -0.723623444 | $3.04 \mathrm{E}-05$ |
| LYPD6B | 129.9191217 | 78.82017656 | -0.723928458 | 0.037408577 |
| GRB14 | 195.4668423 | 118.4694509 | -0.724146944 | 0.010077388 |
| RPLP2 | 22111.25228 | 13383.39663 | -0.724346048 | 0.000122649 |
| RIDA | 532.1288967 | 321.962151 | -0.724844596 | 0.025528176 |
| MYO5B | 8980.852069 | 5433.699359 | -0.72497666 | 0.000179709 |
| MRPL45 | 2308.252165 | 1394.730484 | -0.726328324 | 0.005139367 |
| AKR1A1 | 4683.616226 | 2831.419561 | -0.726407658 | 0.00571189 |
| TRMT10A | 453.0587982 | 273.4496414 | -0.726567757 | 0.017496413 |
| RPL11 | 24525.09894 | 14794.91255 | -0.729149555 | $1.27 \mathrm{E}-06$ |
| CHID1 | 2044.360976 | 1233.623366 | -0.729370213 | 0.004878931 |
| ZNF460 | 615.2244505 | 371.4462315 | -0.729893397 | 0.001357687 |
| SNX29 | 766.6982711 | 462.578513 | -0.730583989 | 0.000716677 |
| WNT16 | 226.1054638 | 135.9317987 | -0.730814408 | 0.049367104 |
| SRP72 | 7198.955308 | 4337.206188 | -0.730928746 | 0.00313915 |
| COX7C | 7422.120654 | 4471.865532 | -0.730929274 | 8.16E-07 |
| ARID3A | 1041.645844 | 627.0266442 | -0.731202924 | 0.043436118 |
| RPS28 | 13351.75314 | 8042.959275 | -0.731301868 | $2.50 \mathrm{E}-06$ |
| PGLS | 2214.303998 | 1332.977548 | -0.73201974 | 0.000345485 |
| ELP2 | 3091.44608 | 1859.920131 | -0.732710381 | 0.000565114 |
| ZBTB37 | 1483.153993 | 892.0548353 | -0.732855956 | $2.60 \mathrm{E}-05$ |
| TBC1D22A | 1386.521695 | 834.4031601 | -0.733454619 | 0.000218997 |
| INVS | 1171.255032 | 704.3514294 | -0.733566293 | 2.86E-05 |
| PCCB | 2897.921851 | 1742.551268 | -0.733874036 | 0.012418645 |
| MRPL15 | 1307.190735 | 785.7962288 | -0.733978267 | 0.016907215 |


| ZIC2 | 2225.945459 | 1338.14049 | -0.734124237 | 0.00098755 |
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| KDM1B | 1624.812402 | 976.5314701 | -0.734722149 | $2.46 \mathrm{E}-05$ |
| RABL3 | 924.7842408 | 555.5410354 | -0.735237408 | 0.006636636 |
| RPS27A | 22514.64423 | 13518.87561 | -0.735867262 | 0.000375514 |
| PELI1 | 3064.567318 | 1839.297008 | -0.736515135 | 1.83E-06 |
| ULK4 | 241.254164 | 144.652345 | -0.73722101 | 0.021193758 |
| WDR5B | 450.0132692 | 270.2101977 | -0.737288643 | 0.001530377 |
| DUS4L | 479.9791209 | 287.5724629 | -0.737568068 | 0.003384847 |
| TSEN2 | 521.1202685 | 312.27413 | -0.737716845 | 0.012505056 |
| RPL37A | 21745.6068 | 13036.56922 | -0.738207338 | $6.52 \mathrm{E}-06$ |
| TMEM250 | 2526.124514 | 1514.620845 | -0.738368301 | 7.29E-05 |
| TCEAL8 | 1360.34577 | 815.2196395 | -0.738486445 | $7.96 \mathrm{E}-05$ |
| GOLGA7B | 176.3902452 | 105.6287771 | -0.738939324 | 0.038388794 |
| ENC1 | 23681.12629 | 14172.96543 | -0.740581887 | 0.000119969 |
| ATPAF1 | 3675.521956 | 2199.413415 | -0.740677273 | $1.96 \mathrm{E}-06$ |
| MT-CYB | 88182.23425 | 52772.51561 | -0.74071085 | 7.82E-06 |
| AKNA | 1033.226174 | 618.2380013 | -0.740938793 | 0.000354758 |
| NR2F2 | 10576.23413 | 6328.030724 | -0.741038308 | $7.10 \mathrm{E}-05$ |
| NIPSNAP1 | 5267.918797 | 3150.530265 | -0.741866564 | 0.000234018 |
| WDR18 | 2806.256637 | 1677.949542 | -0.7419724 | 0.001550174 |
| ABAT | 818.2205386 | 488.6142182 | -0.742885232 | 0.000273416 |
| G2E3 | 1790.176686 | 1069.495697 | -0.743258705 | 0.003630268 |
| TXNL1 | 2595.665455 | 1549.730647 | -0.74377511 | 0.000631528 |
| SATB1 | 947.5146229 | 565.3829058 | -0.744737124 | 0.026984067 |
| HNRNPH2 | 3344.804075 | 1996.045428 | -0.744943771 | $5.38 \mathrm{E}-05$ |
| MBTD1 | 1000.009603 | 596.7065864 | -0.745123309 | 0.000115973 |
| MPND | 498.16592 | 297.6440284 | -0.745446966 | 0.025824337 |
| CMAS | 2792.762003 | 1665.60293 | -0.745570931 | 0.000605905 |
| ZNF775 | 257.0769315 | 153.5084003 | -0.746897879 | 0.009113473 |
| DHODH | 522.7000419 | 311.6168551 | -0.74707199 | 0.005820792 |
| FRK | 505.1024179 | 300.8754818 | -0.748579932 | 0.011054536 |
| IRS1 | 3337.333245 | 1986.390481 | -0.74871792 | 0.0023306 |
| VIL1 | 4239.117339 | 2522.018165 | -0.749171125 | 0.001019156 |
| COQ3 | 419.2666558 | 249.4846524 | -0.750321729 | 0.020318371 |
| CASP4 | 1354.331505 | 803.7775836 | -0.751825643 | 0.001876022 |
| NAT10 | 3456.956109 | 2052.033485 | -0.752299306 | 0.006968142 |
| GRPEL2 | 2189.919146 | 1299.463097 | -0.752492983 | 0.000858304 |
| MRPL30 | 1369.601469 | 812.1923838 | -0.75343923 | $1.44 \mathrm{E}-05$ |
| LPCAT2 | 1518.054465 | 899.3148905 | -0.754803288 | 0.001907386 |
| RPL39 | 9481.567996 | 5617.353645 | -0.755311666 | $1.27 \mathrm{E}-06$ |
| GXYLT2 | 854.8451176 | 506.7452698 | -0.755431082 | 0.009457452 |
| CCDC167 | 320.4193804 | 190.0382446 | -0.756484422 | 0.012356627 |
| POLR1D | 5255.667989 | 3110.251994 | -0.756606511 | $2.99 \mathrm{E}-05$ |
| POLL | 1627.367942 | 962.7951377 | -0.757313455 | 0.000142568 |
| AP1S1 | 4637.32189 | 2742.951061 | -0.757881689 | 0.00022618 |
| CAMK2D | 3038.171056 | 1795.129447 | -0.759174786 | 8.76E-05 |
| TAF1 | 3503.264375 | 2069.402032 | -0.759323801 | $1.81 \mathrm{E}-05$ |
| RNF144B | 168.4997751 | 99.77153901 | -0.75960821 | 0.023451765 |
| UTP25 | 1114.115698 | 657.3393569 | -0.760418908 | 0.013876871 |
| MECR | 812.4487542 | 479.7006708 | -0.76099032 | 0.000204204 |
| ICK | 1148.425341 | 677.9213405 | -0.761022313 | $1.52 \mathrm{E}-05$ |
| EMC2 | 1339.941774 | 790.6168734 | -0.761272494 | 6.89E-05 |
| SOCS7 | 3768.606463 | 2223.03027 | -0.761326004 | $3.74 \mathrm{E}-06$ |
| ZNF717 | 714.5874841 | 421.6093913 | -0.761675138 | 0.001436337 |
| POLI | 1016.622026 | 599.6611658 | -0.761686747 | 0.001897921 |
| BTF3 | 18580.17485 | 10957.53584 | -0.761811964 | $3.11 \mathrm{E}-05$ |
| SCLY | 285.0204719 | 168.028808 | -0.762264465 | 0.002368003 |
| CHMP2A | 3821.532927 | 2253.483404 | -0.762385884 | 0.000404341 |
| NPDC1 | 4145.334001 | 2443.293357 | -0.762826304 | 0.015907484 |
| EFNA1 | 2588.81595 | 1525.535864 | -0.762976726 | 0.005458123 |
| CLOCK | 4520.636716 | 2662.679209 | -0.763469482 | 0.000104056 |


| TFPI | 594.1864933 | 350.0435689 | -0.763659326 | 0.046951444 |
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| FTH1 | 35772.93771 | 21051.60081 | -0.764956114 | $2.56 \mathrm{E}-06$ |
| KDELR1 | 16769.39161 | 9866.803749 | -0.765223145 | $2.76 \mathrm{E}-05$ |
| 01-Mar | 1792.668438 | 1054.110239 | -0.766025433 | 0.000141515 |
| BTBD11 | 123.1670478 | 72.8325548 | -0.76637819 | 0.041125317 |
| MFSD14A | 172.4392014 | 101.4384417 | -0.766446661 | 0.016211213 |
| ARMC10 | 1927.999412 | 1133.32058 | -0.766504179 | 0.000153575 |
| FKTN | 1479.82462 | 869.4865286 | -0.76664242 | $3.58 \mathrm{E}-05$ |
| CCDC171 | 169.9411158 | 99.73307171 | -0.767216235 | 0.006195453 |
| RABGGTB | 2873.760575 | 1686.973842 | -0.768438636 | 0.001303082 |
| TRIM31 | 171.9152426 | 101.0916477 | -0.76853182 | 0.016382018 |
| BBC3 | 1784.343747 | 1047.733138 | -0.768694582 | 0.010406023 |
| G6PC3 | 1898.921351 | 1114.763177 | -0.768697421 | 0.00423353 |
| KCTD15 | 2408.274519 | 1413.26938 | -0.768710614 | 0.000323519 |
| ZNF33B | 1946.33178 | 1141.409342 | -0.769378744 | 0.000604391 |
| BTBD9 | 904.4113223 | 530.6606611 | -0.769687564 | 0.000227596 |
| DYNC2H1 | 512.3692138 | 300.5973834 | -0.769757899 | 0.002946171 |
| L3MBTL3 | 296.9990857 | 174.3823749 | -0.770466054 | 0.004072437 |
| ALDH1L1 | 2812.485408 | 1648.588232 | -0.771016904 | 0.028484885 |
| DNAJC10 | 4808.832392 | 2817.166171 | -0.771309522 | 0.004036166 |
| USP6NL | 3911.368302 | 2289.075359 | -0.772798725 | 1.19E-06 |
| NUDT12 | 644.9111742 | 377.2223693 | -0.772971481 | 0.000372322 |
| MMP15 | 6113.426768 | 3577.177858 | -0.773349625 | 0.004502776 |
| GDI2 | 11789.71524 | 6895.295002 | -0.77376488 | 4.11E-06 |
| DCAF4 | 765.033647 | 447.0485201 | -0.774821049 | 0.000460786 |
| TTC14 | 2376.15036 | 1388.236771 | -0.775484127 | 0.000101311 |
| CBWD6 | 236.5534075 | 138.1445551 | -0.775651336 | 0.015850422 |
| UFM1 | 2158.965119 | 1260.379442 | -0.77594342 | 0.004944239 |
| SRSF8 | 2338.736471 | 1365.244258 | -0.776033746 | 0.000332052 |
| LYRM9 | 359.2018876 | 209.8855516 | -0.776369864 | 0.010206715 |
| CLCN3 | 6225.099212 | 3634.820512 | -0.77639979 | 3.45E-05 |
| RSL1D1 | 7420.231387 | 4328.076085 | -0.777582643 | 0.024832029 |
| TATDN1 | 682.5027823 | 397.6704543 | -0.777779199 | 0.035664212 |
| HSD17B8 | 318.4804745 | 186.2110321 | -0.777965018 | 0.044164039 |
| ATF6B | 3515.431088 | 2049.410945 | -0.778796003 | 4.05E-06 |
| HDDC3 | 286.6292456 | 167.1572963 | -0.779321042 | 0.000531435 |
| TTPA | 163.0414623 | 95.11261861 | -0.77997479 | 0.022067989 |
| METRN | 1567.89394 | 913.1849526 | -0.780454905 | 0.025238749 |
| PYGB | 7070.689744 | 4115.722441 | -0.780694379 | 0.000392023 |
| SCG5 | 790.5819561 | 459.9368366 | -0.781588705 | 0.039891455 |
| TNS3 | 8368.920212 | 4864.727815 | -0.782636038 | 0.00060373 |
| UBXN6 | 4112.606116 | 2390.957978 | -0.782644611 | 0.001187704 |
| RPS12 | 18824.61576 | 10936.56818 | -0.783484508 | $2.62 \mathrm{E}-06$ |
| SMPD2 | 362.7143991 | 210.5298761 | -0.783606995 | 0.000404603 |
| METRNL | 2366.317461 | 1374.808209 | -0.783730205 | 9.53E-05 |
| DPYSL3 | 752.2586543 | 437.3821683 | -0.784015233 | 0.017949482 |
| TFRC | 7498.126089 | 4353.745413 | -0.784312886 | 0.000645922 |
| SLC35D2 | 351.3944852 | 204.2892693 | -0.785497732 | 0.000728708 |
| MCRIP2 | 1873.089171 | 1086.634674 | -0.786340535 | 0.000411538 |
| ACOT1 | 177.4986282 | 102.6553115 | -0.78634543 | 0.01039623 |
| FAR2 | 1020.33317 | 591.3758257 | -0.786816468 | 0.012354782 |
| TCEANC | 99.10611144 | 57.44362634 | -0.786844471 | 0.024903101 |
| NARS2 | 957.3887193 | 554.629306 | -0.787343402 | 0.015032919 |
| DVL1 | 5356.547572 | 3102.994369 | -0.78783445 | $7.40 \mathrm{E}-06$ |
| RHBDL1 | 887.8657212 | 514.2628066 | -0.788272894 | 0.037649489 |
| TXNDC12 | 571.686189 | 330.5475755 | -0.789453433 | 0.000442358 |
| WIPI1 | 806.3539459 | 466.1409115 | -0.789775911 | 0.000163193 |
| TMEM101 | 1513.647956 | 875.9759389 | -0.789813714 | $3.24 \mathrm{E}-05$ |
| CPNE3 | 4624.940389 | 2671.313934 | -0.791670891 | 0.000205256 |
| SQSTM1 | 12149.66818 | 7016.513257 | -0.792086025 | 5.13E-05 |
| DYRK2 | 1953.244789 | 1127.960396 | -0.79212127 | 6.27E-06 |


| TIGD6 | 192.5620443 | 111.3401931 | -0.792158312 | 0.004657136 |
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| ERLEC1 | 2457.734659 | 1418.868154 | -0.792699457 | 5.35E-05 |
| GPR135 | 212.2310516 | 122.9015714 | -0.792939406 | 0.006183852 |
| MARCKS | 3207.797822 | 1850.951378 | -0.793172689 | $4.29 \mathrm{E}-07$ |
| MT-ATP8 | 2810.144074 | 1621.453876 | -0.793690357 | $6.50 \mathrm{E}-06$ |
| RPS26 | 11612.36491 | 6698.19159 | -0.793769444 | 4.33E-05 |
| ATP5F1A | 22203.69688 | 12805.49543 | -0.79403293 | 0.000103481 |
| TMEM120A | 1364.19432 | 786.9351489 | -0.794076619 | $8.25 \mathrm{E}-06$ |
| CTSC | 1027.249846 | 592.5883447 | -0.794162969 | 0.005135312 |
| LMBR1L | 966.1655552 | 557.1013846 | -0.795229305 | 0.013017161 |
| PLXDC2 | 169.3707091 | 97.79831775 | -0.7960208 | 0.04185087 |
| UBE2J1 | 4148.131792 | 2388.193004 | -0.796359497 | 0.000378784 |
| RPS27 | 20610.22071 | 11858.69363 | -0.79744738 | $1.91 \mathrm{E}-05$ |
| COX18 | 738.6670366 | 424.6925772 | -0.798541279 | 0.003675068 |
| CTIF | 1684.889841 | 968.9613316 | -0.798551614 | 0.00041766 |
| ECSIT | 1086.303397 | 624.1217287 | -0.798805229 | 0.015292282 |
| SMIM26 | 524.6082225 | 301.2959709 | -0.79925223 | 0.002891554 |
| TRIQK | 385.9741388 | 221.6320066 | -0.799768406 | 0.001754053 |
| ZNF254 | 705.2442746 | 404.7895481 | -0.800001728 | $1.14 \mathrm{E}-05$ |
| SHROOM3 | 10826.43003 | 6216.490604 | -0.800277709 | 0.000809041 |
| TMED7 | 4306.183784 | 2472.09441 | -0.800485779 | 3.99E-06 |
| VPS51 | 3684.678212 | 2114.337531 | -0.80138782 | 7.27E-07 |
| BTBD3 | 989.5152483 | 567.9312462 | -0.801481959 | 0.000400139 |
| BET1 | 878.9602929 | 503.7304314 | -0.802122154 | 0.000148422 |
| COMMD8 | 694.2756439 | 398.0037789 | -0.802381785 | 0.000997653 |
| PRR22 | 221.9549116 | 126.8837977 | -0.80241301 | 0.028438175 |
| NUDT16 | 2029.995657 | 1163.688546 | -0.80255037 | $3.51 \mathrm{E}-06$ |
| PUS1 | 1756.03922 | 1006.034484 | -0.803202107 | 0.033153739 |
| SIL1 | 1816.535108 | 1040.489048 | -0.804621107 | 7.89E-05 |
| TOM1L1 | 2870.799078 | 1642.751159 | -0.805132642 | 4.49E-07 |
| PPA2 | 2816.066931 | 1611.300459 | -0.805363164 | 0.001067853 |
| CYP4V2 | 1093.428448 | 625.4316769 | -0.805913291 | 0.00173054 |
| TWF2 | 1553.917946 | 888.9493155 | -0.806171049 | $4.51 \mathrm{E}-06$ |
| NT5DC1 | 1432.995922 | 819.0657348 | -0.806256202 | $1.51 \mathrm{E}-05$ |
| NHP2 | 1925.915108 | 1101.357806 | -0.806277137 | 0.003812453 |
| FAM206A | 847.2856324 | 484.2313811 | -0.806658076 | 0.000334312 |
| TMEM126A | 558.4882383 | 319.2662578 | -0.8075163 | 0.002072214 |
| SECISBP2 | 3087.466533 | 1763.69138 | -0.807673418 | $3.31 \mathrm{E}-07$ |
| USP25 | 3184.152113 | 1819.015298 | -0.807900991 | 4.95E-06 |
| FBXO32 | 282.4942034 | 161.671916 | -0.807941428 | 0.020434881 |
| TXNDC15 | 1929.150289 | 1101.887805 | -0.808174614 | 0.000463021 |
| ELMO3 | 1934.901286 | 1105.515707 | -0.808234989 | 0.00191109 |
| ZNF333 | 544.3937232 | 310.9490255 | -0.80906334 | 0.00187987 |
| ARL4C | 2633.103322 | 1502.102881 | -0.809670155 | 3.36E-05 |
| CCDC191 | 355.7714545 | 203.0711091 | -0.809899861 | 0.033241479 |
| TMEM164 | 1141.794791 | 651.3765249 | -0.810605056 | $3.07 \mathrm{E}-05$ |
| COBLL1 | 2076.515978 | 1182.810259 | -0.811345124 | $2.00 \mathrm{E}-05$ |
| MLST8 | 3006.317505 | 1713.282184 | -0.811493079 | $4.30 \mathrm{E}-07$ |
| OAF | 1166.257647 | 664.857791 | -0.811512262 | $7.17 \mathrm{E}-06$ |
| SP5 | 2355.846015 | 1342.508481 | -0.811569468 | $1.31 \mathrm{E}-05$ |
| C7orf50 | 2753.060325 | 1568.457389 | -0.812187861 | 0.003327779 |
| MIPEP | 830.6438423 | 472.5675248 | -0.813410284 | 0.042809269 |
| NR1D2 | 4603.546915 | 2618.724082 | -0.813675515 | 7.99E-06 |
| TNS4 | 2015.251837 | 1146.760399 | -0.813844853 | 0.009978128 |
| SLC25A15 | 660.5476757 | 375.4469336 | -0.814909677 | 0.008797395 |
| CLNS1A | 2830.803354 | 1608.785215 | -0.815091043 | $7.60 \mathrm{E}-05$ |
| SLC19A2 | 1207.896069 | 686.2346718 | -0.815330035 | $2.74 \mathrm{E}-05$ |
| C8orf82 | 1679.862242 | 955.0736449 | -0.815361805 | 0.0022916 |
| FASN | 36439.41164 | 20706.11667 | -0.815476286 | 0.005774284 |
| SEC23A | 4671.943636 | 2654.373925 | -0.815638096 | 8.39E-07 |
| MRPL12 | 500.120775 | 284.2036842 | -0.815999663 | 0.028076247 |


| C1orf116 | 3189.894712 | 1808.88291 | -0.818820896 | 0.00026736 |
| :---: | :---: | :---: | :---: | :---: |
| MT-ATP6 | 115504.9851 | 65472.7513 | -0.818996391 | 0.000240901 |
| RPL27 | 17280.56426 | 9794.346005 | -0.819103331 | $5.84 \mathrm{E}-06$ |
| TMCC3 | 660.5878548 | 374.1692463 | -0.82010032 | 0.00024703 |
| LDHB | 1732.026516 | 980.2582127 | -0.820947686 | 0.002700576 |
| CLDN7 | 14438.52648 | 8169.950846 | -0.821622753 | $7.56 \mathrm{E}-05$ |
| B3GALT6 | 1367.313597 | 773.751923 | -0.822057854 | 0.000875879 |
| THNSL1 | 1004.445457 | 567.7807056 | -0.822208361 | 0.000133879 |
| NIPSNAP2 | 2483.890008 | 1403.063375 | -0.824179307 | 7.07E-07 |
| LARGE1 | 920.0846625 | 519.6735717 | -0.825343374 | $6.27 \mathrm{E}-06$ |
| BCAT2 | 3415.762291 | 1927.90988 | -0.825355709 | 8.33E-07 |
| HELB | 543.554859 | 307.058186 | -0.825548087 | 0.000159585 |
| CLDN4 | 18864.84593 | 10643.39937 | -0.82581985 | 0.000144835 |
| KCNAB2 | 1459.142449 | 823.0418438 | -0.826306464 | $1.46 \mathrm{E}-05$ |
| ANP32B | 11332.67366 | 6384.805225 | -0.827711221 | 5.59E-06 |
| PPFIBP1 | 7157.066812 | 4024.452834 | -0.830399372 | 7.01E-07 |
| R3HDM2 | 1967.816991 | 1105.612665 | -0.8317978 | $2.64 \mathrm{E}-05$ |
| FAM129A | 892.3113506 | 501.0786569 | -0.83217668 | 0.00069105 |
| FBXO30 | 1456.952161 | 817.7983075 | -0.832240405 | 0.000134067 |
| RPL6 | 40119.47128 | 22523.03103 | -0.832879976 | $2.23 \mathrm{E}-05$ |
| ZBED3 | 1593.216573 | 893.6370247 | -0.833701028 | $1.48 \mathrm{E}-05$ |
| GTPBP6 | 4164.844229 | 2335.69124 | -0.834454908 | $1.06 \mathrm{E}-05$ |
| TMA16 | 1163.550344 | 652.0366843 | -0.834969133 | 0.010503722 |
| TPO | 172.9099634 | 96.77212641 | -0.835724546 | 0.013755925 |
| PDE4D | 276.9199005 | 154.7705796 | -0.836344142 | 0.001359253 |
| DNAJC24 | 573.1851931 | 320.6995149 | -0.837070337 | 0.000228184 |
| TSPAN31 | 1011.431952 | 565.6823024 | -0.838807791 | 0.000259566 |
| LTA4H | 3445.129991 | 1925.821058 | -0.839120521 | 5.02E-06 |
| ACVR2B | 1798.865377 | 1005.412422 | -0.839335215 | $2.23 \mathrm{E}-05$ |
| TMEM42 | 930.0496027 | 520.0691034 | -0.839346861 | $6.56 \mathrm{E}-05$ |
| RCN1 | 5658.141998 | 3162.008249 | -0.839471162 | 2.24E-07 |
| MYDGF | 3116.517622 | 1741.350377 | -0.839906086 | $1.20 \mathrm{E}-05$ |
| THADA | 1093.892718 | 610.8289906 | -0.839943928 | 0.00036016 |
| ABRAXAS1 | 447.4684158 | 249.838365 | -0.840245693 | 0.000116158 |
| C16orf58 | 1959.381489 | 1094.391408 | -0.840771992 | 0.000133902 |
| VPS13B | 1748.295398 | 975.5468133 | -0.841724527 | $4.86 \mathrm{E}-07$ |
| ZC3H6 | 1201.838781 | 670.4938343 | -0.842276969 | 0.000275921 |
| DBT | 1818.29607 | 1013.247566 | -0.843136273 | $2.49 \mathrm{E}-07$ |
| MMP24OS | 1747.513368 | 974.4023818 | -0.843461057 | $2.99 \mathrm{E}-05$ |
| CA12 | 153.3533149 | 85.46193996 | -0.84396141 | 0.006633538 |
| CARM1 | 6212.727989 | 3460.708442 | -0.844083768 | $1.50 \mathrm{E}-06$ |
| KCTD18 | 975.3288853 | 543.201144 | -0.84452107 | 7.13E-07 |
| FZD7 | 2544.478986 | 1416.304226 | -0.84504134 | 0.00083184 |
| GNPDA1 | 2201.613697 | 1225.30751 | -0.845957672 | $3.68 \mathrm{E}-06$ |
| C12orf60 | 77.04615195 | 42.78857322 | -0.846071503 | 0.031694247 |
| PODXL2 | 2071.999635 | 1153.073421 | -0.846265631 | $1.05 \mathrm{E}-05$ |
| BOP1 | 3915.421936 | 2177.989085 | -0.846547633 | $2.10 \mathrm{E}-05$ |
| SLC10A7 | 415.8142424 | 231.4339172 | -0.846924026 | 0.000358495 |
| GAS7 | 210.3820445 | 116.8474773 | -0.846928477 | 0.010686701 |
| RPS15A | 3100.053684 | 1722.906264 | -0.847304379 | $1.60 \mathrm{E}-08$ |
| TEX52 | 104.5103394 | 58.03086556 | -0.847371147 | 0.028886188 |
| SLC7A7 | 3589.824037 | 1994.92563 | -0.847462866 | $4.01 \mathrm{E}-05$ |
| NUAK2 | 1913.457038 | 1062.52305 | -0.847935384 | $3.48 \mathrm{E}-05$ |
| ENOX2 | 579.6088888 | 321.446721 | -0.849776202 | 0.004140623 |
| FSIP2 | 243.6089998 | 134.9063519 | -0.84980481 | 0.035767377 |
| FAM13A | 836.446695 | 464.3196436 | -0.849887701 | 4.22E-05 |
| CCDC113 | 824.1070169 | 456.9586492 | -0.850331787 | $3.48 \mathrm{E}-05$ |
| NADK2 | 1708.914925 | 947.7069192 | -0.850797862 | 0.000797262 |
| IKBKB | 2100.336657 | 1163.426337 | -0.852761137 | 0.000352412 |
| SUMF2 | 5339.91087 | 2955.190083 | -0.853781929 | 0.000511678 |
| KRT18 | 45649.87941 | 25258.40893 | -0.853823111 | 0.001095242 |


| HS1BP3 | 1467.297864 | 812.395977 | -0.853884686 | 0.000184265 |
| :---: | :---: | :---: | :---: | :---: |
| MRPL3 | 4764.823371 | 2634.739701 | -0.854601405 | 0.020106022 |
| OXSM | 620.5363391 | 343.0237437 | -0.855123365 | 3.72E-05 |
| SLC1A4 | 4197.740634 | 2319.889813 | -0.855457788 | 0.000234344 |
| LIMS1 | 6780.326791 | 3746.016515 | -0.855739598 | 0.00011009 |
| JDP2 | 1707.702026 | 943.2670035 | -0.856222594 | 0.000184504 |
| SSR3 | 7632.886319 | 4215.275168 | -0.856484404 | 0.001908054 |
| TMEM168 | 908.4036727 | 501.5439133 | -0.856718746 | $4.71 \mathrm{E}-07$ |
| TKFC | 3394.293361 | 1874.692069 | -0.856898603 | $4.00 \mathrm{E}-06$ |
| CAT | 2780.11641 | 1534.003541 | -0.857858688 | $5.11 \mathrm{E}-05$ |
| 01-Mar | 234.6762175 | 129.2795036 | -0.858675077 | 0.000577904 |
| FOXO4 | 601.7380996 | 332.0729248 | -0.858927595 | 0.003025644 |
| ZBTB12 | 456.1665992 | 251.5526885 | -0.859063292 | 0.000301478 |
| RPL21 | 18981.21671 | 10460.62536 | -0.859541072 | $5.75 \mathrm{E}-08$ |
| TRIM27 | 4025.662403 | 2218.451348 | -0.859553087 | $1.48 \mathrm{E}-06$ |
| TSPAN1 | 1678.573035 | 925.352913 | -0.859572395 | 0.031442323 |
| TFB2M | 924.0203209 | 508.8214281 | -0.859830679 | 0.003507069 |
| MRPS27 | 5966.835532 | 3283.214829 | -0.861736002 | 0.000278672 |
| RPS29 | 7045.67806 | 3876.810758 | -0.861884708 | $1.21 \mathrm{E}-08$ |
| RIN2 | 352.3354705 | 194.0419216 | -0.862103288 | 0.001558947 |
| APEX1 | 8513.418747 | 4683.060157 | -0.862189275 | $1.54 \mathrm{E}-06$ |
| GAL3ST2 | 708.5581187 | 389.8235379 | -0.862308616 | 0.000503228 |
| ALG14 | 358.1933036 | 196.618416 | -0.863173371 | 0.000876323 |
| RNF44 | 3719.805977 | 2043.894495 | -0.864039701 | $1.03 \mathrm{E}-05$ |
| SH3BP4 | 11656.65445 | 6401.227383 | -0.864688361 | $1.53 \mathrm{E}-08$ |
| LARS | 6618.187824 | 3633.308976 | -0.865105027 | $1.28 \mathrm{E}-08$ |
| PRKAG1 | 1424.967459 | 782.3867201 | -0.865372291 | $6.18 \mathrm{E}-07$ |
| THBS3 | 764.4850056 | 419.6908932 | -0.865400003 | 0.030698722 |
| FUK | 2069.911442 | 1136.085985 | -0.86607925 | 0.001315539 |
| TRIB2 | 169.8839384 | 93.64881869 | -0.866768837 | 0.011514262 |
| WDR12 | 2078.774951 | 1139.483862 | -0.867140596 | 0.005304853 |
| MAMDC4 | 1086.563636 | 595.8842727 | -0.867575487 | 0.012743751 |
| ADPRM | 231.3477514 | 126.2698207 | -0.868297534 | 0.014674856 |
| KCNIP4 | 80.45134642 | 43.87850709 | -0.869204779 | 0.024518463 |
| DUOX1 | 222.761991 | 121.8670752 | -0.869575228 | 0.010605642 |
| MAN2A1 | 4027.384372 | 2201.545184 | -0.871042801 | $2.74 \mathrm{E}-06$ |
| TRAPPC9 | 1444.59086 | 790.0938867 | -0.871515853 | $2.69 \mathrm{E}-05$ |
| PPARA | 3266.000813 | 1785.188614 | -0.871584914 | $6.25 \mathrm{E}-05$ |
| ARSJ | 429.4560934 | 234.5393215 | -0.871937891 | 0.001309652 |
| EIF2S3 | 12917.3934 | 7056.282432 | -0.872238387 | $2.01 \mathrm{E}-06$ |
| ACP6 | 974.8803104 | 532.7028925 | -0.873180638 | $4.48 \mathrm{E}-06$ |
| ICA1 | 2162.365249 | 1180.310461 | -0.873725685 | $1.44 \mathrm{E}-06$ |
| ZFP36L1 | 4274.500608 | 2331.13442 | -0.874426305 | 0.000337382 |
| CHCHD10 | 3172.325264 | 1729.195928 | -0.875389498 | 0.001057948 |
| RNF125 | 752.7787495 | 410.060672 | -0.876461224 | 7.04E-05 |
| ARMC2 | 108.6193373 | 59.20536713 | -0.87648083 | 0.01051131 |
| PEX12 | 332.9845331 | 181.1444898 | -0.876606034 | 0.000163807 |
| TRAP1 | 5392.361077 | 2935.440199 | -0.877273923 | 0.002108166 |
| NKD1 | 5145.018752 | 2800.046577 | -0.877901211 | 3.93E-06 |
| PTMA | 69509.65371 | 37813.00713 | -0.878337283 | $7.45 \mathrm{E}-05$ |
| MIA2 | 2394.178193 | 1300.268696 | -0.880810126 | $1.77 \mathrm{E}-05$ |
| LGALS3 | 12941.8607 | 7020.210292 | -0.882516353 | 4.96E-05 |
| INSIG1 | 10062.49543 | 5458.085009 | -0.882645708 | 0.010208821 |
| SLC38A10 | 7054.210842 | 3825.725718 | -0.8828648 | 0.007872807 |
| HSPA9 | 23796.02015 | 12900.88657 | -0.883228421 | 0.000248415 |
| LDAH | 1487.063145 | 804.9350189 | -0.885109085 | 5.63E-08 |
| RBMX | 13065.26084 | 7070.285196 | -0.885793192 | $1.44 \mathrm{E}-07$ |
| NARS | 12166.93475 | 6581.014152 | -0.886530456 | $6.89 \mathrm{E}-05$ |
| PDSS2 | 697.3067107 | 377.1962304 | -0.886823317 | $1.31 \mathrm{E}-05$ |
| HINT3 | 1786.010207 | 964.7061911 | -0.888446202 | $6.10 \mathrm{E}-08$ |
| IARS2 | 7374.85029 | 3983.177966 | -0.888729837 | 4.33E-05 |


| ZNF397 | 1691.652011 | 913.8080646 | -0.888934402 | 6.43E-05 |
| :---: | :---: | :---: | :---: | :---: |
| SBSPON | 1293.962778 | 698.4791897 | -0.889217216 | 0.032719032 |
| TGFBR3 | 2198.964044 | 1187.214769 | -0.889462697 | $3.98 \mathrm{E}-05$ |
| TMEM135 | 1576.936084 | 851.6045984 | -0.889765198 | $1.38 \mathrm{E}-05$ |
| DTD2 | 500.498516 | 270.4148555 | -0.889896441 | 0.000229993 |
| HOXA9 | 1685.223593 | 908.4686416 | -0.890997371 | $1.44 \mathrm{E}-06$ |
| CPEB2 | 294.2587527 | 158.2810877 | -0.891549696 | 0.00076599 |
| ZNF524 | 803.6578214 | 432.7151314 | -0.892013093 | $1.15 \mathrm{E}-05$ |
| MEX3A | 519.2004043 | 279.7179261 | -0.892977816 | $1.79 \mathrm{E}-05$ |
| AIMP2 | 1233.826084 | 663.9866457 | -0.893102601 | 0.015122458 |
| EXOC4 | 3836.537984 | 2064.795327 | -0.893976259 | $9.95 \mathrm{E}-07$ |
| SMPDL3A | 533.8457091 | 287.0630948 | -0.894722649 | 0.000394059 |
| FAAH2 | 345.7265745 | 186.2597894 | -0.894775358 | 0.000760558 |
| RPL9 | 21517.66272 | 11569.45861 | -0.895206788 | 5.93E-10 |
| TWNK | 1257.374728 | 675.2392405 | -0.896293494 | 0.015335718 |
| PDK4 | 77.15251487 | 41.33930184 | -0.896444662 | 0.03110619 |
| PEX7 | 392.4841373 | 211.1765037 | -0.896831489 | 0.00060373 |
| MT-ND2 | 98046.51633 | 52657.16016 | -0.896850101 | 7.53E-06 |
| GNPAT | 2171.662657 | 1166.160349 | -0.897057624 | $1.07 \mathrm{E}-08$ |
| UVSSA | 2758.249609 | 1481.302143 | -0.897297737 | 0.000317425 |
| SOX4 | 2425.398537 | 1302.108457 | -0.897379299 | $5.66 \mathrm{E}-06$ |
| RPL30 | 10636.98473 | 5705.359239 | -0.898734144 | $1.90 \mathrm{E}-08$ |
| TBX3 | 4153.889114 | 2227.324306 | -0.89932186 | 0.000133866 |
| ZBTB22 | 988.3865377 | 529.4168616 | -0.90173053 | 4.19E-06 |
| LIG3 | 2227.420265 | 1192.229036 | -0.901784767 | 0.000442019 |
| EIF4A2 | 20764.37551 | 11109.4329 | -0.90229605 | 1.13E-09 |
| RPS13 | 15223.92257 | 8144.229547 | -0.902446244 | 2.02E-07 |
| GPAM | 1107.556645 | 592.1261256 | -0.902914152 | 5.02E-06 |
| ZNF485 | 166.214066 | 88.76477253 | -0.90323944 | 0.005884054 |
| TOP1MT | 1137.523805 | 607.6868232 | -0.9038124 | $6.20 \mathrm{E}-06$ |
| ATP6AP1L | 581.965182 | 310.91032 | -0.905022343 | 0.001311704 |
| CDKN1B | 4731.526222 | 2526.69748 | -0.905055551 | $2.81 \mathrm{E}-07$ |
| NUS1 | 4017.962563 | 2144.982859 | -0.905355684 | 4.72E-06 |
| TFAP4 | 1619.81718 | 864.2378544 | -0.90635491 | 9.17E-07 |
| FBXL17 | 1279.624715 | 681.6995309 | -0.907974823 | 8.90E-05 |
| KLHL24 | 1708.493813 | 910.3243707 | -0.908679785 | 0.003639426 |
| NR1D1 | 726.2931565 | 386.7230104 | -0.908963276 | 0.000785658 |
| RPSA | 53926.93676 | 28707.23853 | -0.909579394 | $1.00 \mathrm{E}-04$ |
| CLDN3 | 4379.026323 | 2330.966577 | -0.909839285 | 0.000154513 |
| EIF1 | 17537.95821 | 9333.043887 | -0.910001052 | 0.000406583 |
| ZFAND1 | 2422.140485 | 1286.962778 | -0.911791139 | 1.89E-05 |
| RPL19 | 39156.12699 | 20788.5065 | -0.913443481 | 8.35E-09 |
| TXNDC5 | 848.8061965 | 450.7385067 | -0.913537409 | 0.000392672 |
| MAN1A1 | 1684.117362 | 894.0112851 | -0.914490535 | $1.07 \mathrm{E}-06$ |
| SLC39A10 | 1523.943031 | 808.7711156 | -0.914562795 | 0.000451977 |
| LAMA5 | 17069.42391 | 9048.86348 | -0.915638483 | 0.022444496 |
| ZNF165 | 840.9434649 | 445.6833632 | -0.916711251 | 0.000363559 |
| ATP5MC2 | 4646.548982 | 2460.896155 | -0.916944308 | 2.25E-09 |
| FUT2 | 2382.850762 | 1262.464719 | -0.917090118 | 9.46E-05 |
| SCNN1A | 11358.54064 | 6014.157592 | -0.917439235 | 0.003306689 |
| ZNF624 | 147.4860088 | 78.29399988 | -0.917552966 | 0.006110545 |
| RPS11 | 27426.63215 | 14515.47648 | -0.917993928 | $2.57 \mathrm{E}-10$ |
| EIF3L | 7824.957548 | 4140.811063 | -0.918041234 | $6.89 \mathrm{E}-08$ |
| SSR2 | 3988.256516 | 2109.937505 | -0.918343481 | $9.31 \mathrm{E}-06$ |
| ADAP1 | 1228.96488 | 650.6740792 | -0.918628149 | $7.90 \mathrm{E}-06$ |
| RPL24 | 19565.58595 | 10349.81375 | -0.918661937 | $4.99 \mathrm{E}-07$ |
| SUSD4 | 726.4923022 | 384.4296207 | -0.919244651 | 0.002919081 |
| PRF1 | 436.8940737 | 231.3079144 | -0.919819047 | 0.01803607 |
| NUDT18 | 560.4931841 | 296.5395625 | -0.920206878 | $1.98 \mathrm{E}-05$ |
| RPL41 | 19108.52941 | 10086.77532 | -0.921784031 | 6.13E-09 |
| ATP5F1D | 4709.37198 | 2484.487234 | -0.9225508 | 0.00013186 |


| BCKDHB | 1122.938983 | 592.3547291 | -0.923371848 | $2.76 \mathrm{E}-05$ |
| :---: | :---: | :---: | :---: | :---: |
| CRYZ | 1957.177143 | 1032.402367 | -0.923388039 | 5.83E-06 |
| CADPS2 | 620.2394137 | 327.2931234 | -0.923558725 | 8.63E-05 |
| MAPT | 624.0627312 | 329.1929109 | -0.923757415 | 0.015850422 |
| AMER1 | 500.9384826 | 263.5066236 | -0.925063144 | 0.003467993 |
| TOMM7 | 2059.766627 | 1084.762507 | -0.925730792 | $1.07 \mathrm{E}-06$ |
| IER5L | 2361.670504 | 1243.310497 | -0.926043799 | $3.16 \mathrm{E}-05$ |
| C10orf95 | 70.65518932 | 37.17098938 | -0.927710466 | 0.022795253 |
| MT-ND4 | 282840.873 | 148538.8389 | -0.929155315 | $2.15 \mathrm{E}-05$ |
| ASS1 | 13308.88241 | 6988.962989 | -0.929269713 | 3.09E-06 |
| RPS16 | 28330.13517 | 14871.2887 | -0.929821969 | $1.66 \mathrm{E}-10$ |
| NFS1 | 1037.303204 | 544.7907353 | -0.930145925 | 0.000345639 |
| NACA | 14227.21761 | 7463.602708 | -0.93063645 | $2.88 \mathrm{E}-07$ |
| SEL1L | 3867.359288 | 2028.664518 | -0.930735808 | $4.55 \mathrm{E}-06$ |
| EIF3F | 7319.711434 | 3839.352173 | -0.930781447 | $4.94 \mathrm{E}-09$ |
| ALDH1B1 | 3118.396227 | 1634.893024 | -0.931468076 | 0.021708284 |
| ZBTB41 | 1258.558464 | 658.7914147 | -0.933508917 | $2.48 \mathrm{E}-08$ |
| BZW2 | 2926.541124 | 1531.87592 | -0.933726313 | 0.002483712 |
| METTL15 | 1071.190262 | 560.175683 | -0.934381715 | $4.79 \mathrm{E}-06$ |
| SLC4A8 | 675.6363111 | 353.6938673 | -0.934606594 | 0.000589803 |
| RASL11A | 422.3211058 | 220.7378534 | -0.935678745 | 0.020025525 |
| RPL23A | 12315.37052 | 6434.966755 | -0.936443961 | $2.67 \mathrm{E}-10$ |
| MXI1 | 1811.702838 | 946.9031874 | -0.936448776 | 0.000288876 |
| WARS2 | 852.7840132 | 444.8477277 | -0.937427109 | 0.00108141 |
| TMEM150A | 407.076364 | 212.6140457 | -0.937803318 | 0.001021085 |
| ARID5B | 3186.352754 | 1663.030705 | -0.93791289 | 0.000160561 |
| KBTBD7 | 678.2793345 | 353.9632042 | -0.938637234 | 0.003537679 |
| KIZ | 745.9452721 | 389.5797676 | -0.938910158 | 0.000263866 |
| RGL1 | 130.556819 | 68.03382091 | -0.940015204 | 0.007868595 |
| EPHX2 | 777.7070104 | 405.3454572 | -0.940041566 | 0.000175649 |
| APBB3 | 1507.299429 | 785.8469759 | -0.940123884 | 0.011528893 |
| PPM1H | 2132.781233 | 1111.485388 | -0.940414452 | 1.95E-09 |
| MT1A | 129.7187606 | 67.63469923 | -0.9405488 | 0.026725551 |
| ZNF202 | 681.8465529 | 354.9051285 | -0.941271763 | 0.000268912 |
| CCNG1 | 4965.617894 | 2583.815838 | -0.942335169 | $9.45 \mathrm{E}-09$ |
| TPT1 | 28886.9842 | 15014.71075 | -0.944053481 | $1.70 \mathrm{E}-06$ |
| SLC7A1 | 12329.5199 | 6403.411654 | -0.94511729 | 0.000715233 |
| CXADR | 8003.268773 | 4155.756563 | -0.945426752 | 8.89E-09 |
| RIOX2 | 1307.593199 | 678.6681026 | -0.945618363 | 0.007032425 |
| VWA2 | 932.2449802 | 484.1646082 | -0.945865511 | 0.002582088 |
| LCN2 | 531.8206428 | 275.8682604 | -0.945918247 | 0.018714813 |
| SLC6A6 | 5278.663773 | 2738.864834 | -0.946398288 | $2.81 \mathrm{E}-07$ |
| C6orf120 | 1425.428451 | 738.9759804 | -0.947006405 | 1.25E-07 |
| CEBPB | 3493.283705 | 1811.214392 | -0.947399753 | $4.26 \mathrm{E}-05$ |
| FTL | 58295.58275 | 30225.68554 | -0.947640286 | $1.13 \mathrm{E}-05$ |
| MANEA | 822.1897657 | 425.8305538 | -0.948300416 | $3.46 \mathrm{E}-05$ |
| ALDH2 | 2774.069048 | 1437.821837 | -0.948741899 | $3.09 \mathrm{E}-07$ |
| MAGI2 | 82.65267864 | 42.94109889 | -0.949085592 | 0.046930719 |
| ENDOD1 | 2492.47552 | 1291.454404 | -0.949129686 | $1.09 \mathrm{E}-05$ |
| RPS4X | 23893.44302 | 12374.13519 | -0.949306701 | $7.94 \mathrm{E}-11$ |
| RPL38 | 8901.35039 | 4607.352563 | -0.950148626 | $1.09 \mathrm{E}-08$ |
| RPS7 | 20892.10143 | 10797.69635 | -0.952181301 | $1.01 \mathrm{E}-09$ |
| RPS3 | 42784.99151 | 22105.9383 | -0.952691979 | $3.23 \mathrm{E}-10$ |
| PABPC1 | 57808.54928 | 29855.75449 | -0.953246309 | $3.95 \mathrm{E}-05$ |
| TACC2 | 4103.640009 | 2119.023745 | -0.953666252 | $1.43 \mathrm{E}-09$ |
| AUH | 1129.037399 | 583.0116594 | -0.954622829 | $3.20 \mathrm{E}-07$ |
| TBC1D5 | 3595.510642 | 1855.247524 | -0.95496975 | $7.33 \mathrm{E}-08$ |
| MVP | 3684.723864 | 1901.172796 | -0.954986326 | $4.74 \mathrm{E}-05$ |
| DMD | 343.5237906 | 176.6290224 | -0.95509571 | 0.001200785 |
| GULP1 | 349.7260873 | 180.1285919 | -0.956189281 | 0.000155935 |
| CD55 | 2914.831419 | 1501.302377 | -0.956602306 | 3.35E-07 |


| EIF4EBP1 | 4020.10865 | 2071.773918 | -0.95666335 | $1.96 \mathrm{E}-06$ |
| :---: | :---: | :---: | :---: | :---: |
| RPL36 | 13108.02907 | 6754.086775 | -0.95669263 | 3.88E-09 |
| RPS9 | 26488.95278 | 13644.7618 | -0.957031889 | $4.40 \mathrm{E}-10$ |
| SREBF1 | 10684.56141 | 5502.493107 | -0.957518532 | 0.001387558 |
| HOXB7 | 2382.980992 | 1226.404915 | -0.958267146 | 0.00042268 |
| VPS28 | 1942.99633 | 999.6665157 | -0.959334339 | $6.15 \mathrm{E}-06$ |
| TMEM192 | 1756.135991 | 902.4445042 | -0.959973558 | 8.37E-05 |
| FAM151B | 60.41730003 | 31.15998153 | -0.961128547 | 0.028250243 |
| CDH17 | 2626.084611 | 1348.840403 | -0.961222386 | 0.017523473 |
| HOXA11 | 354.9795005 | 181.8693885 | -0.961573724 | 0.000569924 |
| TARBP1 | 2876.145795 | 1475.238327 | -0.963419562 | $4.03 \mathrm{E}-05$ |
| ACAT1 | 3335.890631 | 1710.371614 | -0.963847963 | $2.63 \mathrm{E}-05$ |
| NOTUM | 3015.081469 | 1544.038956 | -0.965668458 | 0.037237105 |
| FGFBP1 | 838.9691005 | 429.8331857 | -0.965942002 | 0.010053856 |
| ATP6V1E2 | 398.1889041 | 203.7810689 | -0.966872911 | $3.91 \mathrm{E}-06$ |
| NUDT4 | 4679.503024 | 2393.665964 | -0.967140688 | $2.63 \mathrm{E}-10$ |
| NPM3 | 1548.68293 | 791.7098376 | -0.967899713 | 0.00584105 |
| ARSD | 2713.896042 | 1386.922102 | -0.968469639 | 0.001047323 |
| PRSS23 | 3478.481837 | 1777.015999 | -0.969183907 | 0.000206877 |
| RPS2 | 103692.6667 | 52926.97661 | -0.970234349 | $2.33 \mathrm{E}-05$ |
| CDH12 | 103.0642945 | 52.76780837 | -0.970424088 | 0.039274028 |
| FURIN | 15570.45129 | 7946.067673 | -0.970534698 | 0.000309206 |
| PCDHB2 | 68.15805775 | 34.88072603 | -0.971107374 | 0.016230154 |
| AK8 | 64.738046 | 33.07436707 | -0.97222584 | 0.030826418 |
| ACOT13 | 793.2205545 | 404.0838501 | -0.974319925 | $2.09 \mathrm{E}-06$ |
| SESN2 | 2409.843107 | 1224.359778 | -0.976892388 | 0.000151361 |
| SGPP2 | 1070.213931 | 543.127078 | -0.97772018 | 7.85E-06 |
| TRPS1 | 557.0492434 | 282.6274074 | -0.978313991 | $2.63 \mathrm{E}-05$ |
| LTBP1 | 713.5118051 | 362.2757516 | -0.978431841 | 0.012325865 |
| PYCR3 | 1075.823925 | 546.3286211 | -0.979157914 | 0.000208016 |
| MT-ND4L | 66863.86645 | 33912.85336 | -0.979423072 | $3.58 \mathrm{E}-05$ |
| IRF2BP2 | 4737.515333 | 2401.590947 | -0.979954177 | $3.15 \mathrm{E}-05$ |
| RPS3A | 27064.50671 | 13714.57647 | -0.980692834 | $1.80 \mathrm{E}-12$ |
| OVGP1 | 76.32817713 | 38.76933872 | -0.981019174 | 0.04920273 |
| ASMTL | 1826.25593 | 925.0198925 | -0.98204055 | $1.42 \mathrm{E}-05$ |
| EDEM2 | 852.2511739 | 431.3479663 | -0.984193293 | $1.22 \mathrm{E}-05$ |
| NEK11 | 102.9512488 | 52.03977293 | -0.986024124 | 0.012015142 |
| ALKBH7 | 1500.873146 | 757.6242091 | -0.987143017 | $9.40 \mathrm{E}-08$ |
| USF3 | 1950.748606 | 983.8186435 | -0.98791223 | $8.45 \mathrm{E}-09$ |
| UGDH | 4862.880393 | 2448.634203 | -0.989833904 | $2.54 \mathrm{E}-05$ |
| CNTD2 | 365.1297483 | 184.1490277 | -0.989893235 | 0.005123958 |
| HK2 | 5329.545014 | 2681.17321 | -0.990992455 | 0.000102491 |
| ACADSB | 1620.797598 | 814.8971842 | -0.991516336 | 7.71E-10 |
| FAM117B | 967.6721609 | 486.78 | -0.992012904 | $4.61 \mathrm{E}-07$ |
| ERMARD | 1493.93477 | 750.0708226 | -0.99493939 | 0.000262961 |
| ISL2 | 237.6292469 | 119.4019292 | -0.995450958 | 0.000385427 |
| IBTK | 5205.437703 | 2605.346293 | -0.998528372 | $2.75 \mathrm{E}-07$ |
| EIF3M | 7720.394153 | 3862.066333 | -0.999140937 | 0.000177196 |
| FARS2 | 604.6976166 | 302.4055818 | -0.999925974 | $1.46 \mathrm{E}-05$ |
| PSD | 101.9391098 | 50.86304456 | -1.000451661 | 0.007169572 |
| TMEM144 | 502.1959379 | 251.3822363 | -1.000724035 | $1.20 \mathrm{E}-06$ |
| CREBRF | 1077.657994 | 538.5668838 | -1.001036771 | 0.000177023 |
| SLC2A13 | 361.2681648 | 180.4582503 | -1.002902145 | $1.84 \mathrm{E}-05$ |
| ME1 | 5334.611501 | 2659.583053 | -1.004121166 | $5.29 \mathrm{E}-10$ |
| KIAA1147 | 3683.800511 | 1835.59159 | -1.005033676 | $1.04 \mathrm{E}-08$ |
| AC007240.1 | 52.01883177 | 25.90307521 | -1.00589961 | 0.035954662 |
| RPL22 | 2828.47469 | 1406.785376 | -1.007152434 | $4.64 \mathrm{E}-08$ |
| ID2 | 14350.35961 | 7138.005928 | -1.007569032 | $2.43 \mathrm{E}-05$ |
| GSTA4 | 260.6313056 | 129.8118116 | -1.009274105 | 0.030571705 |
| SNCAIP | 250.4574717 | 124.3920861 | -1.010023586 | 0.004664638 |
| AARS | 14465.03253 | 7173.176712 | -1.011970781 | 5.43E-10 |


| SRI | 1208.235544 | 597.8665294 | -1.015012543 | $1.59 \mathrm{E}-06$ |
| :---: | :---: | :---: | :---: | :---: |
| VLDLR | 800.6399482 | 396.1331548 | -1.015020707 | $2.40 \mathrm{E}-05$ |
| PHPT1 | 2465.862719 | 1219.619586 | -1.016024833 | 0.000455135 |
| NSA2 | 3875.74697 | 1915.967905 | -1.016092383 | $1.91 \mathrm{E}-05$ |
| CYBB | 51.88787031 | 25.59776256 | -1.016115473 | 0.035064192 |
| ERICH2 | 483.9793206 | 239.5445331 | -1.017719644 | $3.77 \mathrm{E}-06$ |
| SBF2 | 2428.842117 | 1199.45705 | -1.018278397 | 2.22E-07 |
| EXOSC5 | 989.9970301 | 488.4578044 | -1.018361 | 0.007460619 |
| CCT6B | 104.4714212 | 51.38575038 | -1.018530739 | 0.021828045 |
| PKDCC | 203.0799263 | 100.3493947 | -1.019008756 | 0.001051303 |
| PPM1L | 346.5869035 | 171.1046257 | -1.01991852 | $2.12 \mathrm{E}-06$ |
| ERRFI1 | 7559.313587 | 3720.186295 | -1.02288217 | $2.64 \mathrm{E}-05$ |
| RPL8 | 59565.22021 | 29223.35587 | -1.027348902 | $1.26 \mathrm{E}-09$ |
| TSC22D3 | 1266.899487 | 621.4794408 | -1.02764982 | 0.000284361 |
| IRAK1BP1 | 413.2573736 | 202.591271 | -1.028380638 | $2.42 \mathrm{E}-06$ |
| EIF3H | 7184.163136 | 3519.953613 | -1.029153928 | 2.53E-09 |
| SLC33A1 | 1048.911562 | 513.4062003 | -1.030119725 | 4.01E-05 |
| RPL18 | 27834.96022 | 13627.17073 | -1.030393718 | $8.01 \mathrm{E}-11$ |
| SAMD12 | 959.3031731 | 469.4239283 | -1.031572443 | 1.42E-09 |
| UTP14A | 2028.234784 | 990.7059993 | -1.033099902 | 0.000948487 |
| TLR5 | 109.0141709 | 53.37271286 | -1.033636391 | 0.038483653 |
| MMAA | 169.0169323 | 82.2441283 | -1.033725082 | 0.000559626 |
| SLC38A1 | 17842.40567 | 8714.572041 | -1.033731547 | 4.35E-07 |
| FAM172A | 968.0544699 | 472.2929306 | -1.03399888 | $1.01 \mathrm{E}-07$ |
| KSR2 | 729.0145004 | 355.6481989 | -1.034272152 | $1.10 \mathrm{E}-07$ |
| RPL32 | 20717.13286 | 10111.48882 | -1.034788122 | 1.73E-08 |
| MTMR4 | 4867.148701 | 2373.735737 | -1.03602051 | $8.50 \mathrm{E}-10$ |
| EARS2 | 2400.253392 | 1169.671423 | -1.036892729 | 2.29E-06 |
| TMED3 | 2366.580982 | 1152.922751 | -1.03709387 | $1.70 \mathrm{E}-09$ |
| TSEN15 | 1610.985985 | 784.1413861 | -1.038109622 | 0.000541907 |
| MCTP2 | 787.4320563 | 383.7571883 | -1.038183765 | 4.32E-06 |
| LONRF1 | 2139.773091 | 1042.217228 | -1.038502288 | 1.92E-07 |
| HNRNPA1 | 55345.78327 | 26934.3431 | -1.039017473 | 1.87E-12 |
| SUMF1 | 1248.471466 | 607.0761818 | -1.040983649 | 3.05E-06 |
| LARGE2 | 1235.032583 | 600.1595491 | -1.041601575 | $2.19 \mathrm{E}-10$ |
| SLC19A1 | 1824.656719 | 886.4215356 | -1.042339324 | 1.87E-05 |
| STX3 | 7584.930475 | 3676.797485 | -1.044711375 | $6.11 \mathrm{E}-07$ |
| KCNAB1 | 80.31485136 | 38.87279261 | -1.047137827 | 0.030047724 |
| EEF1B2 | 10531.53595 | 5095.952566 | -1.047182762 | 5.25E-05 |
| BHLHA15 | 293.3687301 | 141.9027611 | -1.047818507 | 0.001973608 |
| RPL15 | 46315.52756 | 22398.24846 | -1.04811342 | $1.55 \mathrm{E}-13$ |
| ADAT2 | 725.148616 | 350.288315 | -1.048743056 | $1.40 \mathrm{E}-06$ |
| PSPH | 3044.103829 | 1471.258615 | -1.048930811 | $1.29 \mathrm{E}-08$ |
| PLA2G4A | 78.29691281 | 37.90383568 | -1.049278177 | 0.020948996 |
| BICRAL | 1309.08597 | 630.8970229 | -1.053228014 | $3.40 \mathrm{E}-11$ |
| CPS1 | 190.2199752 | 91.99747352 | -1.054460596 | 0.002080517 |
| DTD1 | 617.4630541 | 297.0068734 | -1.055411465 | $9.39 \mathrm{E}-05$ |
| E2F5 | 798.4135025 | 383.3544003 | -1.05726291 | $1.26 \mathrm{E}-08$ |
| BDKRB2 | 700.0343824 | 336.3444298 | -1.058358555 | 0.001230954 |
| NBAS | 2642.127723 | 1268.344623 | -1.058364345 | $2.89 \mathrm{E}-07$ |
| SLC7A2 | 2296.763817 | 1100.827199 | -1.060327777 | $1.46 \mathrm{E}-06$ |
| COX7A2L | 3706.555139 | 1776.670455 | -1.060616818 | $1.01 \mathrm{E}-09$ |
| PPP1R9A | 2190.60425 | 1049.629679 | -1.061713736 | 4.66E-09 |
| DIRAS2 | 86.04485092 | 41.09727852 | -1.062699369 | 0.019089529 |
| PKP1 | 334.1813749 | 160.2493362 | -1.063241505 | 0.02060621 |
| SLC16A13 | 1038.892284 | 497.5421094 | -1.063842156 | $2.84 \mathrm{E}-05$ |
| RPL13 | 52778.09713 | 25224.60247 | -1.065108724 | 1.13E-14 |
| L3HYPDH | 409.1453068 | 195.0372556 | -1.06668702 | $1.20 \mathrm{E}-05$ |
| PIP5K1B | 663.8606536 | 316.5758239 | -1.066979227 | 0.000503725 |
| EDEM1 | 4153.507144 | 1982.179658 | -1.067126134 | $1.90 \mathrm{E}-08$ |
| HSP90B1 | 67743.7673 | 32323.50393 | -1.067524619 | $1.30 \mathrm{E}-07$ |


| TECTA | 149.5739986 | 71.37981255 | -1.068106007 | 0.012477706 |
| :---: | :---: | :---: | :---: | :---: |
| OSTC | 3075.090123 | 1466.186216 | -1.068538252 | $3.21 \mathrm{E}-09$ |
| KIAA1614 | 67.20244457 | 32.04202487 | -1.069406128 | 0.01497375 |
| DNASE2 | 3115.627053 | 1484.383098 | -1.070106076 | $4.30 \mathrm{E}-09$ |
| CPVL | 642.2544238 | 306.1689859 | -1.07025749 | $2.84 \mathrm{E}-06$ |
| FAM189A1 | 220.7422279 | 105.4629439 | -1.071495116 | 0.000397729 |
| ARHGEF4 | 756.6895949 | 360.2053466 | -1.072778141 | 0.001318292 |
| TGIF1 | 4223.989024 | 2007.919037 | -1.072838122 | $2.45 \mathrm{E}-11$ |
| IDH1 | 7733.46907 | 3675.570935 | -1.073392607 | $5.27 \mathrm{E}-08$ |
| WDR3 | 1978.563704 | 939.8701494 | -1.073514957 | 0.000680883 |
| TSNARE1 | 766.8371057 | 364.0902235 | -1.075701936 | 0.000155316 |
| ZNRF3 | 6939.660982 | 3289.519209 | -1.076944158 | $1.66 \mathrm{E}-10$ |
| KLLN | 78.09690096 | 36.77296954 | -1.077019436 | 0.006920916 |
| VAMP4 | 492.7073401 | 233.3298466 | -1.077204205 | $1.35 \mathrm{E}-07$ |
| DNAH1 | 2643.800487 | 1252.928317 | -1.07734956 | 0.006614834 |
| DIAPH2 | 1314.281661 | 622.9096074 | -1.077419495 | $2.32 \mathrm{E}-08$ |
| BAMBI | 2638.509492 | 1250.02261 | -1.078063389 | $3.21 \mathrm{E}-07$ |
| RPUSD4 | 2030.608277 | 960.45246 | -1.079505898 | $1.09 \mathrm{E}-05$ |
| SLIT1 | 136.2273306 | 64.52790867 | -1.081157276 | 0.020827984 |
| GCLC | 1918.727358 | 906.9791063 | -1.081338403 | 0.000463193 |
| D2HGDH | 2155.091466 | 1016.872633 | -1.084057341 | 0.00161811 |
| CTSO | 170.6858335 | 80.30599941 | -1.085496388 | 0.025791977 |
| KBTBD3 | 174.9708964 | 82.47985852 | -1.08554804 | 0.000578821 |
| APRT | 3961.645886 | 1865.923685 | -1.086411851 | $3.16 \mathrm{E}-06$ |
| TAF1D | 4325.775923 | 2034.186759 | -1.088267286 | $1.79 \mathrm{E}-05$ |
| PEPD | 2166.746272 | 1019.10632 | -1.088765418 | 9.17E-10 |
| PTPRB | 179.7965831 | 84.37423289 | -1.091990427 | 0.001586423 |
| RPS6 | 42040.96092 | 19717.36107 | -1.092322431 | 3.67E-14 |
| SLC16A9 | 696.4364579 | 325.8820475 | -1.093508311 | $2.04 \mathrm{E}-05$ |
| PTPRG | 3469.837048 | 1625.805696 | -1.093608061 | $1.74 \mathrm{E}-10$ |
| TMEM106B | 3280.068389 | 1535.711554 | -1.094280961 | 1.03E-08 |
| GALC | 2051.221384 | 960.4430014 | -1.095168206 | $4.21 \mathrm{E}-08$ |
| NPM1 | 46076.56079 | 21545.56333 | -1.096612019 | $6.38 \mathrm{E}-05$ |
| MYADML2 | 109.9868998 | 51.42668266 | -1.09712785 | 0.023574286 |
| DISP1 | 337.373446 | 157.5676802 | -1.097180654 | 0.001659539 |
| COX20 | 320.2120809 | 149.7689615 | -1.097301208 | 0.0003721 |
| MTHFD1L | 3693.4724 | 1724.81355 | -1.098339467 | 0.002978575 |
| NUBPL | 560.3299756 | 261.604282 | -1.098510575 | $4.88 \mathrm{E}-08$ |
| RPL18A | 29054.23586 | 13559.41391 | -1.099445227 | 1.10E-13 |
| C14orf28 | 199.3276321 | 92.61355477 | -1.100722117 | $6.24 \mathrm{E}-05$ |
| GFPT1 | 11542.10836 | 5378.915567 | -1.101462573 | 2.33E-07 |
| TMEM231 | 494.0751992 | 229.5001888 | -1.104016475 | $2.08 \mathrm{E}-07$ |
| RBM43 | 643.2219689 | 299.1706378 | -1.104373107 | 0.000208016 |
| ATP2C2 | 2711.636658 | 1261.357711 | -1.104479746 | $9.35 \mathrm{E}-08$ |
| SPRY1 | 518.6829331 | 241.2795857 | -1.104628397 | 5.64E-05 |
| TPD52L1 | 2174.65975 | 1010.090099 | -1.105552565 | 4.23E-08 |
| ITPR2 | 3470.580617 | 1611.918784 | -1.106366119 | $1.83 \mathrm{E}-11$ |
| SMYD3 | 685.1002694 | 318.4907588 | -1.106492931 | 2.72E-09 |
| FKBP7 | 118.5405788 | 55.28365068 | -1.106851671 | 0.000746449 |
| DNAJB9 | 1617.761002 | 750.2737033 | -1.108604637 | 8.82E-06 |
| RGMB | 499.1187898 | 230.7252212 | -1.110759745 | 5.62E-07 |
| WARS | 6186.809506 | 2863.161349 | -1.11149201 | 0.000143618 |
| MRPL24 | 1617.749577 | 748.1870354 | -1.112621814 | $2.27 \mathrm{E}-05$ |
| EPM2A | 196.6091369 | 90.71908446 | -1.112823474 | $3.51 \mathrm{E}-05$ |
| S100A14 | 8387.944683 | 3877.415955 | -1.113385513 | $1.79 \mathrm{E}-08$ |
| SND1 | 10148.31369 | 4689.807185 | -1.113581312 | 5.57E-12 |
| TOMM20 | 10366.57642 | 4788.176465 | -1.114276876 | 1.10E-09 |
| COLQ | 108.1792519 | 49.80956622 | -1.115518355 | 0.014839319 |
| ADAMTS17 | 110.8115515 | 51.19183924 | -1.115652705 | 0.00437645 |
| HNRNPA1P48 | 194.2905171 | 89.5784775 | -1.119003955 | 1.49E-05 |
| RPS24 | 23507.87947 | 10819.96994 | -1.119440786 | $9.24 \mathrm{E}-16$ |


| IQCK | 138.1949523 | 63.3843072 | -1.119849576 | 0.000985126 |
| :---: | :---: | :---: | :---: | :---: |
| PHB2 | 9248.853666 | 4255.226166 | -1.119978201 | $1.00 \mathrm{E}-07$ |
| PTPN13 | 2505.533532 | 1152.787781 | -1.120193435 | 3.17E-11 |
| C12orf66 | 519.2726662 | 238.2811721 | -1.122469958 | 0.001560636 |
| CACNB2 | 160.3661683 | 73.7005956 | -1.122739884 | 0.002835117 |
| BMP4 | 13879.83077 | 6371.238614 | -1.123292957 | $8.40 \mathrm{E}-08$ |
| FAT1 | 116472.6818 | 53377.60624 | -1.125689274 | 5.23E-09 |
| RSAD1 | 1012.224339 | 464.2217187 | -1.12613524 | 5.97E-10 |
| ZNF169 | 551.7999585 | 252.4889255 | -1.127060287 | $8.18 \mathrm{E}-05$ |
| RPL35A | 17828.80425 | 8162.443867 | -1.127116033 | 5.33E-14 |
| ALDH6A1 | 2637.847202 | 1207.078044 | -1.128307686 | 1.05E-06 |
| COL5A2 | 374.4681174 | 171.1513516 | -1.130032596 | 0.001558965 |
| WDR35 | 507.9848805 | 231.5860556 | -1.132208592 | $9.85 \mathrm{E}-06$ |
| FRAS1 | 6876.755516 | 3133.510896 | -1.133734298 | $4.30 \mathrm{E}-06$ |
| AGA | 320.6761485 | 146.0001511 | -1.135793266 | $1.82 \mathrm{E}-05$ |
| RPS8 | 45861.81958 | 20854.49658 | -1.136934275 | $2.89 \mathrm{E}-15$ |
| HNF4G | 573.8836286 | 260.497017 | -1.137727014 | 5.04E-08 |
| GALK2 | 963.806934 | 437.9987259 | -1.138398565 | $1.46 \mathrm{E}-08$ |
| ID1 | 7353.6339 | 3336.074823 | -1.140413159 | 0.001248402 |
| FAM84B | 2807.435805 | 1271.728649 | -1.14203114 | $1.34 \mathrm{E}-07$ |
| RPL23 | 22181.42052 | 10027.23286 | -1.14538699 | 6.12E-13 |
| LMF1 | 662.5427562 | 299.7284627 | -1.145398262 | 0.010416382 |
| RFX3 | 880.7463629 | 397.2948979 | -1.147853788 | $2.52 \mathrm{E}-07$ |
| SPRYD3 | 1415.505077 | 638.6494262 | -1.148649531 | $1.66 \mathrm{E}-10$ |
| FPGT | 610.8913519 | 275.6729596 | -1.148662929 | $4.58 \mathrm{E}-08$ |
| DDX25 | 47.03125147 | 21.31079591 | -1.149139263 | 0.036749662 |
| GDPD1 | 200.3861721 | 90.49317139 | -1.153176192 | 0.000140578 |
| BCL2L14 | 219.8201888 | 98.80964289 | -1.154913169 | 0.001633237 |
| NPW | 39.03770042 | 17.43628169 | -1.15922365 | 0.037576487 |
| ZFP2 | 118.3578252 | 53.17197908 | -1.15959721 | 0.000742976 |
| EBPL | 1961.194422 | 877.6608374 | -1.160045996 | $9.68 \mathrm{E}-12$ |
| HSPD1 | 32861.36573 | 14702.54618 | -1.160313757 | $6.15 \mathrm{E}-05$ |
| TBC1D4 | 13274.99548 | 5929.005669 | -1.162878503 | 7.59E-09 |
| SLC38A2 | 12470.60323 | 5566.851668 | -1.163652163 | 4.27E-11 |
| IMPACT | 2090.175106 | 931.9900101 | -1.165060252 | $3.91 \mathrm{E}-12$ |
| MBLAC2 | 545.0870642 | 242.5596188 | -1.165843276 | $1.51 \mathrm{E}-05$ |
| RPL37 | 17731.5419 | 7890.624348 | -1.168182687 | $1.44 \mathrm{E}-11$ |
| CTTNBP2 | 125.3993532 | 56.00464846 | -1.170188514 | 0.002919081 |
| AJM1 | 1269.52143 | 563.7152389 | -1.171577057 | 0.001966944 |
| GCC2 | 5591.077843 | 2477.378276 | -1.174208672 | 2.52E-06 |
| VWA8 | 2269.786637 | 1005.530804 | -1.174553294 | $1.82 \mathrm{E}-13$ |
| CCDC149 | 601.582557 | 265.6783091 | -1.178634083 | $5.78 \mathrm{E}-07$ |
| IFT140 | 1719.270591 | 759.6695806 | -1.178973797 | 1.09E-06 |
| RPL27A | 37545.19279 | 16529.73534 | -1.18359422 | $9.57 \mathrm{E}-16$ |
| FBXO36 | 256.3856412 | 113.0350547 | -1.184664944 | 5.02E-05 |
| NLE1 | 1283.359492 | 563.0134673 | -1.187716108 | $4.19 \mathrm{E}-05$ |
| LEPR | 96.82186561 | 42.53939315 | -1.192561003 | 0.003558449 |
| HFE | 1161.639881 | 508.1627543 | -1.19367913 | $7.71 \mathrm{E}-05$ |
| GCNT1 | 840.4940355 | 366.6006295 | -1.197650645 | 1.03E-08 |
| SEMA6A | 125.5638477 | 54.86796556 | -1.198693566 | 0.000263866 |
| ITGA2 | 4975.305765 | 2164.935303 | -1.200131489 | 0.000300506 |
| RPS25 | 16682.16685 | 7260.257149 | -1.200226889 | $3.70 \mathrm{E}-17$ |
| RPS18 | 48634.8717 | 21164.61526 | -1.200356161 | $9.97 \mathrm{E}-16$ |
| ARSG | 326.7918046 | 142.1103175 | -1.202067288 | $6.98 \mathrm{E}-05$ |
| EDF1 | 6821.603017 | 2963.1636 | -1.203210348 | $1.34 \mathrm{E}-05$ |
| PLCH2 | 536.4668227 | 233.1688046 | -1.204130908 | 0.000854879 |
| ABHD14B | 2309.927637 | 1002.193144 | -1.204576263 | 9.65E-15 |
| RPS14 | 26923.52262 | 11671.74512 | -1.205849478 | $2.64 \mathrm{E}-12$ |
| DCHS1 | 34.05630538 | 14.8253863 | -1.207906806 | 0.038694335 |
| SYBU | 770.2815561 | 332.7223942 | -1.20987142 | $3.09 \mathrm{E}-11$ |
| KCNH8 | 88.78370282 | 38.41816384 | -1.210422645 | 0.025374895 |


| SERPINB1 | 9641.594767 | 4164.101291 | -1.211212464 | $4.39 \mathrm{E}-10$ |
| :---: | :---: | :---: | :---: | :---: |
| TMTC4 | 1338.653362 | 578.5866991 | -1.211736464 | $3.81 \mathrm{E}-08$ |
| PDIA4 | 27719.82962 | 11918.45913 | -1.217768483 | 4.35E-07 |
| PELI2 | 131.1759195 | 56.65888604 | -1.218472143 | 0.000353895 |
| FXYD4 | 117.4872405 | 50.59385332 | -1.218785507 | 0.034787107 |
| RFTN2 | 50.89040034 | 21.61163181 | -1.220790076 | 0.036676033 |
| PHYKPL | 4421.181787 | 1896.390067 | -1.221393417 | 0.000345094 |
| RPL31 | 20929.26561 | 8970.801004 | -1.222271097 | $2.55 \mathrm{E}-15$ |
| PBX1 | 948.5752778 | 406.492341 | -1.222827244 | 0.000746449 |
| N6AMT1 | 710.7749256 | 304.6329663 | -1.223180951 | $6.61 \mathrm{E}-09$ |
| CRELD2 | 4366.833062 | 1869.261577 | -1.224244713 | $6.29 \mathrm{E}-05$ |
| NAGLU | 1668.780915 | 712.9464792 | -1.227617218 | $3.30 \mathrm{E}-09$ |
| DDIT3 | 973.4576964 | 415.1371402 | -1.22871616 | 2.82E-05 |
| TARS | 10862.60526 | 4632.41805 | -1.229412168 | $3.46 \mathrm{E}-06$ |
| NOP53 | 8720.965125 | 3713.95415 | -1.231518783 | $4.64 \mathrm{E}-14$ |
| TCF4 | 89.62741369 | 38.32064578 | -1.231558496 | 0.012926486 |
| ANK3 | 2443.37155 | 1040.209067 | -1.232312915 | $6.48 \mathrm{E}-06$ |
| RPL5 | 34967.63624 | 14857.64993 | -1.234774234 | $2.20 \mathrm{E}-13$ |
| ETFDH | 615.3876768 | 261.6808594 | -1.23597309 | $6.45 \mathrm{E}-07$ |
| NQO1 | 41927.21478 | 17795.35558 | -1.236429141 | $1.51 \mathrm{E}-06$ |
| ANTXR2 | 167.4751057 | 71.14966091 | -1.238399463 | $1.29 \mathrm{E}-05$ |
| IARS | 19775.3997 | 8379.676528 | -1.23869827 | $4.06 \mathrm{E}-10$ |
| GALNT4 | 50.44507796 | 21.19113583 | -1.239971466 | 0.013935977 |
| SERINC5 | 11868.32619 | 5017.770228 | -1.242020535 | $1.35 \mathrm{E}-07$ |
| RPL34 | 13680.21938 | 5778.870115 | -1.243214527 | 7.27E-18 |
| RPL7 | 40682.94313 | 17165.57208 | -1.244889103 | $1.46 \mathrm{E}-17$ |
| RPL10 | 44998.81475 | 18981.07348 | -1.245323704 | $2.10 \mathrm{E}-16$ |
| SWT1 | 183.6148293 | 77.37090517 | -1.246881916 | 0.000109828 |
| DDN | 189.5946426 | 79.82101633 | -1.249547295 | 0.001363325 |
| RGS5 | 66.28151357 | 27.73291619 | -1.25365377 | 0.003974173 |
| LZTFL1 | 1428.273434 | 597.6745838 | -1.256613296 | 3.67E-10 |
| CHRM3 | 205.0693269 | 85.74388967 | -1.258450913 | 3.03E-06 |
| BABAM2 | 734.0494358 | 307.039538 | -1.259157714 | $3.52 \mathrm{E}-12$ |
| RPIA | 912.8693037 | 379.7888119 | -1.264880515 | 7.95E-07 |
| AREG | 1062.153647 | 441.2416637 | -1.266673492 | $5.10 \mathrm{E}-05$ |
| SLC9B2 | 617.4681196 | 256.3840926 | -1.267246088 | 2.15E-06 |
| GMDS | 1393.755777 | 578.2815875 | -1.268362292 | $1.11 \mathrm{E}-05$ |
| BDKRB1 | 45.49950854 | 19.12386736 | -1.268672376 | 0.042996152 |
| DPH5 | 572.4374002 | 237.0400098 | -1.272005041 | 5.58E-09 |
| RBM3 | 8978.534944 | 3716.330336 | -1.272409027 | 0.000267479 |
| TDRD3 | 1192.709097 | 493.3582555 | -1.27255301 | $1.08 \mathrm{E}-13$ |
| RPS6KA2 | 1353.44044 | 560.0737182 | -1.272815524 | $8.09 \mathrm{E}-11$ |
| IZUMO1 | 2260.082061 | 931.5332254 | -1.27968546 | 0.000217065 |
| SDF2L1 | 2423.370883 | 997.7671085 | -1.2806042 | $1.15 \mathrm{E}-07$ |
| STX8 | 550.2795794 | 226.4858904 | -1.28170981 | $3.26 \mathrm{E}-11$ |
| TTC39B | 2078.464813 | 853.1995692 | -1.284572303 | $2.81 \mathrm{E}-16$ |
| RPL14 | 25117.77314 | 10253.11399 | -1.292587037 | 6.23E-10 |
| SORBS2 | 501.1977443 | 204.427412 | -1.294394527 | 0.007161276 |
| RNF43 | 2444.296385 | 993.8905004 | -1.298738966 | $2.01 \mathrm{E}-06$ |
| HSPA13 | 4124.025475 | 1674.58209 | -1.300234757 | $1.45 \mathrm{E}-15$ |
| HYOU1 | 19378.33064 | 7843.538347 | -1.304870719 | $2.48 \mathrm{E}-08$ |
| FUT3 | 507.2739436 | 205.1115438 | -1.306432229 | $1.20 \mathrm{E}-05$ |
| RASIP1 | 3411.461523 | 1379.062309 | -1.307349852 | $6.72 \mathrm{E}-05$ |
| HAGHL | 1558.859918 | 629.5060254 | -1.309116234 | $5.76 \mathrm{E}-05$ |
| CCNB3 | 62.28162778 | 24.9917331 | -1.31458152 | 0.005417459 |
| CTH | 626.5910973 | 252.0238576 | -1.314950083 | 5.14E-10 |
| CARS | 4392.354413 | 1763.589882 | -1.316377543 | $2.77 \mathrm{E}-11$ |
| RACK1 | 55717.01239 | 22269.57165 | -1.323025353 | $1.51 \mathrm{E}-18$ |
| SLC6A20 | 784.4272039 | 313.4051221 | -1.323448652 | 0.000132266 |
| CCDC78 | 1198.361448 | 479.0404118 | -1.323633992 | 0.002385335 |
| HAPLN2 | 38.95283762 | 15.69445613 | -1.323899904 | 0.026671116 |


| RPL4 | 79294.51093 | 31660.80798 | -1.324513122 | $6.31 \mathrm{E}-21$ |
| :---: | :---: | :---: | :---: | :---: |
| DDR2 | 97.03230458 | 38.37746974 | -1.324981266 | 0.003094289 |
| NOA1 | 3019.752133 | 1204.546167 | -1.325495348 | $5.90 \mathrm{E}-14$ |
| HSD17B4 | 4820.548857 | 1922.326017 | -1.326657422 | $1.76 \mathrm{E}-09$ |
| PARD3B | 1051.776844 | 418.6170128 | -1.327574883 | $2.30 \mathrm{E}-09$ |
| CCDC121 | 190.8359714 | 76.08368524 | -1.329198477 | 0.000115633 |
| HOXB6 | 7719.114976 | 3053.639135 | -1.337898945 | 0.000693179 |
| STEAP3 | 1269.591009 | 502.1742157 | -1.338762601 | $1.74 \mathrm{E}-15$ |
| PPIB | 7773.325537 | 3072.99441 | -1.339098155 | $4.48 \mathrm{E}-14$ |
| TRDMT1 | 267.5479091 | 105.5479416 | -1.340179015 | $3.32 \mathrm{E}-08$ |
| SEMA3A | 1073.983863 | 423.8288015 | -1.341104755 | $2.24 \mathrm{E}-07$ |
| PITX2 | 4550.760337 | 1792.443609 | -1.344049465 | 5.47E-08 |
| AMN1 | 181.9615569 | 71.6864652 | -1.347539543 | $1.57 \mathrm{E}-06$ |
| RPL13A | 74664.25682 | 29331.85124 | -1.347967873 | $9.24 \mathrm{E}-16$ |
| SARS | 13043.96796 | 5123.370898 | -1.348144639 | $1.67 \mathrm{E}-11$ |
| MID1IP1 | 4207.73164 | 1653.146662 | -1.348233127 | $3.45 \mathrm{E}-15$ |
| HOXB9 | 17572.28197 | 6883.460982 | -1.352109932 | $1.70 \mathrm{E}-09$ |
| GRIK4 | 52.9353726 | 20.70364147 | -1.352411954 | 0.024676669 |
| MFSD3 | 1922.107062 | 752.193271 | -1.354326058 | $9.98 \mathrm{E}-05$ |
| ITPR1 | 207.2506401 | 81.06471992 | -1.355778606 | $1.06 \mathrm{E}-06$ |
| IGBP1 | 2120.762313 | 826.6952986 | -1.358922494 | $3.36 \mathrm{E}-13$ |
| SLC1A1 | 2185.483758 | 851.2006229 | -1.360413503 | $1.56 \mathrm{E}-06$ |
| COLGALT2 | 100.1226464 | 38.78130633 | -1.362305235 | 0.000503164 |
| PRSS12 | 196.4931879 | 76.54712528 | -1.364281308 | 0.014707421 |
| PHLDA1 | 5390.467966 | 2090.56896 | -1.366272942 | $3.53 \mathrm{E}-08$ |
| NT5C | 994.7711025 | 386.146356 | -1.366683825 | $1.10 \mathrm{E}-12$ |
| TMEM141 | 1394.7163 | 540.9478889 | -1.367328365 | $9.69 \mathrm{E}-14$ |
| RPS23 | 10423.76843 | 4034.52951 | -1.369277071 | $9.00 \mathrm{E}-12$ |
| ERO1B | 3323.377726 | 1285.481069 | -1.37035564 | $1.59 \mathrm{E}-08$ |
| RPL29 | 39724.67734 | 15342.44265 | -1.372516026 | $9.18 \mathrm{E}-21$ |
| HOXA13 | 1222.232545 | 471.3082543 | -1.375089144 | 2.43E-06 |
| UFSP1 | 99.17906022 | 38.19988387 | -1.378722904 | 0.002965787 |
| GGACT | 235.9714771 | 90.84669215 | -1.3806018 | $3.28 \mathrm{E}-06$ |
| HS3ST1 | 172.0781313 | 65.89756545 | -1.381980316 | $5.17 \mathrm{E}-06$ |
| COMMD10 | 563.2986454 | 215.9968038 | -1.383152754 | $4.68 \mathrm{E}-14$ |
| EIF2A | 5509.995323 | 2108.904497 | -1.38524046 | $1.77 \mathrm{E}-09$ |
| EEF2 | 154519.666 | 59040.41697 | -1.388002953 | $1.99 \mathrm{E}-12$ |
| NBEA | 210.3844796 | 80.27437789 | -1.388085576 | 6.53E-08 |
| TCP11L2 | 342.4202422 | 130.6777446 | -1.391346356 | 0.000250992 |
| HOXB5 | 2644.340045 | 1006.743026 | -1.393179298 | 0.000562979 |
| PRKG2 | 31.16093942 | 11.8222878 | -1.393281729 | 0.041059731 |
| MANF | 4822.816009 | 1830.948757 | -1.39751584 | $5.30 \mathrm{E}-11$ |
| SLC9B1 | 34.59707179 | 13.30320385 | -1.399546226 | 0.029978258 |
| SEMA3C | 169.6500912 | 64.03495483 | -1.400948317 | 0.003519107 |
| ALDH1L2 | 572.2326721 | 215.5296351 | -1.410644627 | $6.49 \mathrm{E}-05$ |
| MT1E | 5852.663137 | 2192.031281 | -1.416766992 | $2.44 \mathrm{E}-11$ |
| FAM84A | 105.8160145 | 39.4436834 | -1.418012224 | 0.005277898 |
| PCCA | 1077.323561 | 403.1067074 | -1.418831527 | 2.69E-09 |
| KCNJ5 | 787.2459308 | 294.2430292 | -1.420951955 | 6.23E-06 |
| TKT | 29880.20176 | 11136.63035 | -1.423851462 | $9.44 \mathrm{E}-13$ |
| RPL7A | 53292.08039 | 19825.40028 | -1.426560603 | $3.10 \mathrm{E}-23$ |
| BDNF | 141.4034112 | 52.57423134 | -1.426575846 | 0.000279487 |
| MUC5B | 29.16156825 | 10.79932916 | -1.427621753 | 0.025000102 |
| FNBP1 | 73.42597425 | 27.19029515 | -1.430088688 | 0.010751111 |
| NRXN3 | 216.6060896 | 80.12999172 | -1.430318679 | $7.80 \mathrm{E}-05$ |
| SEC24D | 3291.109793 | 1220.132491 | -1.431928676 | $3.01 \mathrm{E}-11$ |
| NOB1 | 3683.017178 | 1363.438925 | -1.4333229 | $3.97 \mathrm{E}-09$ |
| RNF187 | 9801.468844 | 3628.57515 | -1.433596474 | $1.57 \mathrm{E}-10$ |
| LENG9 | 444.0969553 | 164.0886586 | -1.433813964 | 4.02E-12 |
| ABCB1 | 10176.79999 | 3762.95121 | -1.435142202 | $1.39 \mathrm{E}-08$ |
| HOXB3 | 8407.266885 | 3107.105055 | -1.436134569 | $1.28 \mathrm{E}-05$ |


| KCNN2 | 93.57890817 | 34.49086882 | -1.437631877 | 7.09E-05 |
| :---: | :---: | :---: | :---: | :---: |
| EEF1A1 | 417855.477 | 153695.2675 | -1.442931014 | $1.63 \mathrm{E}-23$ |
| HSPA5 | 65003.43807 | 23893.24568 | -1.443937019 | $1.04 \mathrm{E}-11$ |
| GPT2 | 5792.843333 | 2125.720724 | -1.446306083 | $1.68 \mathrm{E}-19$ |
| CEMIP | 1025.050146 | 375.0471274 | -1.451034754 | $1.86 \mathrm{E}-06$ |
| NTHL1 | 562.235479 | 205.7609937 | -1.452412032 | 2.83E-10 |
| SLC22A11 | 191.7246491 | 69.93030299 | -1.459276465 | 0.004222129 |
| FTCDNL1 | 133.2081778 | 48.49292842 | -1.459494589 | 7.99E-06 |
| KLF9 | 2431.805438 | 884.5936832 | -1.459605985 | $3.72 \mathrm{E}-11$ |
| ADAM23 | 85.28501352 | 31.00374683 | -1.462988764 | 0.000692402 |
| ULBP1 | 1302.524493 | 469.7650779 | -1.471728696 | 7.05E-08 |
| PIF1 | 1065.480875 | 384.1920441 | -1.472775496 | $2.78 \mathrm{E}-11$ |
| KIAA0825 | 37.48430329 | 13.36560639 | -1.473041024 | 0.033425194 |
| RHBDD1 | 1404.437098 | 504.8764019 | -1.475466426 | 5.59E-15 |
| MYRIP | 134.9765934 | 48.16411059 | -1.484533564 | 0.001038987 |
| EPRS | 15694.0893 | 5600.075572 | -1.486616813 | $8.49 \mathrm{E}-11$ |
| TBL1X | 2276.093981 | 811.0253107 | -1.489550517 | 1.13E-15 |
| SHANK2 | 730.4844748 | 260.3031822 | -1.491526983 | $2.50 \mathrm{E}-11$ |
| SCART1 | 339.3659097 | 120.4432976 | -1.497199166 | $2.25 \mathrm{E}-05$ |
| CACNG4 | 647.4287093 | 229.3614112 | -1.497964216 | 0.001745234 |
| SLC38A8 | 45.90297413 | 16.06339223 | -1.498592858 | 0.014683263 |
| PRRX1 | 53.5650543 | 18.90087247 | -1.500288201 | 0.00156676 |
| CCDC146 | 62.27154413 | 21.95093502 | -1.503424253 | 0.006566588 |
| XBP1 | 8864.965968 | 3120.191704 | -1.506460124 | 5.61E-14 |
| IMMP2L | 204.1233408 | 71.89313482 | -1.507204149 | 4.76E-08 |
| LONP1 | 11109.03642 | 3901.859274 | -1.509694128 | 7.73E-15 |
| OMA1 | 792.74965 | 278.5451022 | -1.511115202 | $4.85 \mathrm{E}-10$ |
| KLF15 | 1123.960833 | 394.1507154 | -1.512513812 | $3.20 \mathrm{E}-16$ |
| INHBE | 96.23695554 | 33.89759783 | -1.512681557 | 0.003337945 |
| ARHGAP22 | 50.34409454 | 17.49387336 | -1.514422005 | 0.006147982 |
| TGFB3 | 1036.121295 | 361.6381238 | -1.518786988 | $1.07 \mathrm{E}-05$ |
| ZMAT1 | 368.3848445 | 128.5001037 | -1.52050969 | 0.002682149 |
| RPL12 | 34357.74468 | 11929.92992 | -1.52601629 | $1.26 \mathrm{E}-18$ |
| SPEF2 | 214.5915693 | 74.44296769 | -1.526149427 | $2.00 \mathrm{E}-05$ |
| SRGAP3 | 100.7896701 | 34.91706247 | -1.531377132 | 0.004305636 |
| KDM7A | 3596.668828 | 1242.132348 | -1.533643746 | $1.45 \mathrm{E}-12$ |
| AXIN2 | 13008.40369 | 4466.05331 | -1.542324001 | $3.10 \mathrm{E}-23$ |
| BCAS3 | 787.5363217 | 270.584021 | -1.543490998 | $1.24 \mathrm{E}-06$ |
| SCFD2 | 472.7343284 | 160.4825679 | -1.554699262 | $2.01 \mathrm{E}-06$ |
| THBS4 | 71.85107121 | 24.2118996 | -1.558309322 | 0.001506994 |
| OPN3 | 71.5546202 | 24.25998862 | -1.55835423 | 0.000454552 |
| MTHFD2 | 14739.14548 | 5000.716065 | -1.559369831 | $4.26 \mathrm{E}-22$ |
| METTL26 | 2246.685094 | 760.4028409 | -1.563773218 | 5.12E-06 |
| ZNF277 | 1112.797207 | 376.1510338 | -1.56431248 | $1.93 \mathrm{E}-16$ |
| HIST2H2AC | 46.80988781 | 15.80729358 | -1.566328871 | 0.002118774 |
| PRR15L | 4253.732468 | 1430.77509 | -1.571992759 | 0.034724831 |
| YARS | 11713.44312 | 3933.319281 | -1.574268667 | $6.40 \mathrm{E}-14$ |
| ZC3H12B | 364.5087224 | 122.3204368 | -1.575223517 | $1.10 \mathrm{E}-06$ |
| KLHL31 | 114.9067272 | 38.28217848 | -1.577020183 | 0.000491962 |
| MGAM | 69.68980647 | 23.40602315 | -1.578059307 | 0.027454607 |
| BEST1 | 133.9585832 | 44.67119501 | -1.583439247 | $3.42 \mathrm{E}-05$ |
| SLC43A1 | 2061.742029 | 687.4560646 | -1.584057332 | 8.95E-19 |
| RASGRF2 | 319.8536058 | 106.154067 | -1.587115691 | 2.89E-08 |
| URAD | 76.75948219 | 25.61877961 | -1.587176235 | 0.002196755 |
| SCD | 54291.30491 | 18037.98151 | -1.589729652 | $6.50 \mathrm{E}-08$ |
| SOX9 | 13216.05808 | 4376.879313 | -1.594413041 | $4.27 \mathrm{E}-11$ |
| FUT1 | 10306.46681 | 3411.041869 | -1.595489278 | $1.30 \mathrm{E}-09$ |
| MARS | 7542.479413 | 2491.511149 | -1.598002552 | $1.48 \mathrm{E}-13$ |
| HHAT | 41.22616455 | 13.63915528 | -1.605031204 | 0.007647632 |
| RSL24D1 | 5647.031245 | 1853.739911 | -1.606701364 | 1.35E-14 |
| EHF | 2486.496178 | 814.4210192 | -1.610394046 | $3.16 \mathrm{E}-13$ |


| ZNF581 | 1336.914207 | 436.665187 | -1.613218235 | 5.50E-14 |
| :---: | :---: | :---: | :---: | :---: |
| DHFR2 | 397.3960255 | 129.855877 | -1.614275863 | $1.01 \mathrm{E}-09$ |
| GNA14 | 31.64877026 | 10.44571245 | -1.618169641 | 0.02909543 |
| VSNL1 | 1552.662558 | 505.6626545 | -1.618854337 | $1.12 \mathrm{E}-16$ |
| ATP8A1 | 1874.893901 | 609.8756778 | -1.620119449 | $6.48 \mathrm{E}-07$ |
| PPIL6 | 47.51434867 | 15.3598447 | -1.621980612 | 0.001432343 |
| GTDC1 | 277.5398362 | 90.0328681 | -1.628970727 | $1.21 \mathrm{E}-11$ |
| EIF3E | 15785.32584 | 5086.390526 | -1.633706804 | $9.85 \mathrm{E}-17$ |
| RPL10A | 18968.83938 | 6110.688876 | -1.63416799 | 2.97E-25 |
| SHMT2 | 12675.1253 | 4065.038603 | -1.640662064 | $1.68 \mathrm{E}-19$ |
| OTUD7A | 21.58450498 | 6.981066605 | -1.641058708 | 0.032976651 |
| RPL3 | 87503.03285 | 28049.25885 | -1.641377712 | $9.50 \mathrm{E}-32$ |
| MT1X | 234.2703225 | 74.84335657 | -1.649469862 | 2.93E-06 |
| SLC1A5 | 17019.89548 | 5416.100743 | -1.651915441 | $3.82 \mathrm{E}-23$ |
| GRB10 | 3394.551403 | 1078.425212 | -1.654524649 | $6.38 \mathrm{E}-22$ |
| FRMD3 | 169.2171393 | 53.37874464 | -1.662907819 | 0.000408931 |
| AC004687.2 | 54.09573706 | 17.17190132 | -1.664517199 | 0.018755555 |
| HKDC1 | 34.08334489 | 10.80514591 | -1.670591 | 0.004916559 |
| FDXACB1 | 57.45204265 | 17.86271352 | -1.677028249 | 0.004738885 |
| SUCLG2 | 2785.94973 | 865.300455 | -1.686902401 | $6.84 \mathrm{E}-29$ |
| PIP5KL1 | 2250.888313 | 696.1470683 | -1.693859593 | $2.47 \mathrm{E}-06$ |
| MYO7B | 81.6744277 | 25.07034182 | -1.702551427 | 0.021247779 |
| ISPD | 81.49296584 | 25.05626649 | -1.705672705 | $4.81 \mathrm{E}-05$ |
| CAB39L | 3616.818817 | 1105.476611 | -1.709964453 | 8.71E-13 |
| ST8SIA1 | 76.01465145 | 23.03505213 | -1.715384735 | 0.022670909 |
| SULT1C3 | 62.43622792 | 19.14265761 | -1.715559601 | 0.007543092 |
| CR2 | 618.3124706 | 187.9572777 | -1.715565016 | $4.48 \mathrm{E}-06$ |
| RGS16 | 321.8662426 | 97.74376334 | -1.715771206 | 7.63E-09 |
| PRICKLE1 | 503.0780154 | 152.6844018 | -1.718507131 | 7.93E-12 |
| CBLB | 335.4057716 | 101.6416405 | -1.72019404 | 3.64E-14 |
| SEMA5A | 198.5880268 | 59.36660457 | -1.735129911 | 0.00083184 |
| SNTB1 | 3254.865514 | 976.8662734 | -1.736347943 | $1.58 \mathrm{E}-23$ |
| VEGFA | 7730.22258 | 2300.547333 | -1.748623839 | $4.48 \mathrm{E}-14$ |
| PHGDH | 17649.71583 | 5246.278174 | -1.750376953 | 3.19E-19 |
| TTN | 28.30514338 | 8.365804598 | -1.750515679 | 0.013364875 |
| SLC25A6 | 29001.53274 | 8611.309727 | -1.751879842 | 2.53E-27 |
| KCNJ8 | 2085.262019 | 618.1070487 | -1.754036296 | $1.70 \mathrm{E}-16$ |
| ATF4 | 33188.06856 | 9820.423908 | -1.756786168 | $5.01 \mathrm{E}-25$ |
| DPH6 | 369.9635759 | 109.6686946 | -1.75914094 | 5.96E-09 |
| PEMT | 655.1056845 | 193.3118975 | -1.761113188 | $1.64 \mathrm{E}-15$ |
| NR3C2 | 27.7114414 | 8.20722401 | -1.762341441 | 0.007857779 |
| DEPTOR | 140.5384731 | 41.49307156 | -1.762494012 | 1.53E-08 |
| TMTC2 | 432.3499429 | 127.5338962 | -1.763851805 | $4.21 \mathrm{E}-13$ |
| MACROD1 | 1550.736229 | 455.6168853 | -1.768485792 | 3.16E-14 |
| ITGA9 | 129.0143466 | 37.83327051 | -1.77274611 | 0.000381938 |
| TMEM232 | 17.33754884 | 5.111299234 | -1.773921624 | 0.048827418 |
| PYCR1 | 14990.14625 | 4321.447526 | -1.794608361 | $2.96 \mathrm{E}-26$ |
| SLC6A13 | 19.39489741 | 5.529449332 | -1.797067729 | 0.036353685 |
| EIF4B | 30528.9146 | 8778.455149 | -1.798086073 | $7.72 \mathrm{E}-29$ |
| KNDC1 | 930.3665993 | 263.6851067 | -1.819992345 | $6.09 \mathrm{E}-05$ |
| NTRK2 | 294.981307 | 83.54508945 | -1.823131346 | 8.54E-14 |
| CHST11 | 27.80868053 | 7.841973803 | -1.828498924 | 0.014262221 |
| GEMIN8 | 456.1465449 | 127.6349579 | -1.838461418 | $2.64 \mathrm{E}-15$ |
| ETS2 | 16914.43487 | 4727.378933 | -1.839174465 | $4.26 \mathrm{E}-15$ |
| PYROXD1 | 780.9604964 | 217.3088458 | -1.844315612 | 3.02E-26 |
| LHPP | 1152.838581 | 320.7777467 | -1.84794546 | $1.83 \mathrm{E}-14$ |
| SETDB2 | 4311.358659 | 1192.982238 | -1.853265192 | 4.89E-20 |
| HERPUD1 | 7305.537824 | 2021.505565 | -1.853669562 | $4.26 \mathrm{E}-15$ |
| GARS | 11788.0766 | 3260.44461 | -1.854091978 | 8.43E-15 |
| SPATA17 | 31.93494824 | 8.619557358 | -1.860505585 | 0.015628571 |
| PRDM16 | 217.7222693 | 60.14811573 | -1.862426088 | 2.29E-05 |


| DOCK4 | 132.6900549 | 36.3980976 | -1.874581369 | 2.19E-08 |
| :---: | :---: | :---: | :---: | :---: |
| MYO1H | 94.90136135 | 25.8794741 | -1.878903561 | 0.000858304 |
| MKX | 789.271329 | 213.9288867 | -1.881773417 | $1.99 \mathrm{E}-17$ |
| CCDC170 | 276.7124001 | 74.71091486 | -1.885099973 | 2.16E-13 |
| PRDM12 | 19.74867416 | 5.330942353 | -1.889927361 | 0.035624803 |
| ADRA2C | 1572.37524 | 424.6370309 | -1.88999625 | 8.39E-09 |
| TRIB3 | 9896.435899 | 2667.921114 | -1.891168727 | $9.18 \mathrm{E}-21$ |
| SUPT3H | 289.2729675 | 77.85248684 | -1.895224741 | 8.43E-15 |
| FGGY | 353.2650393 | 94.46283463 | -1.905427702 | $2.16 \mathrm{E}-07$ |
| HOXB8 | 4823.657466 | 1277.628508 | -1.916684725 | 0.005767794 |
| MYO1G | 19.03248865 | 5.069026955 | -1.917276001 | 0.023412113 |
| KIF21B | 701.3503904 | 185.6554376 | -1.921392421 | 8.92E-09 |
| MRVI1 | 19.96400086 | 5.251089572 | -1.922884463 | 0.034101257 |
| ASNS | 596.885385 | 157.2929104 | -1.924125991 | 1.17E-19 |
| GDF15 | 5543.048875 | 1459.478002 | -1.925686099 | $3.35 \mathrm{E}-11$ |
| PMFBP1 | 53.82583378 | 14.25334739 | -1.929855708 | 0.004701074 |
| SLC6A9 | 1841.622698 | 482.9156105 | -1.932259516 | 2.43E-19 |
| FOXQ1 | 5515.017171 | 1435.209274 | -1.942481007 | $3.49 \mathrm{E}-18$ |
| HIST3H2A | 181.8312882 | 47.04959287 | -1.946249903 | 6.83E-08 |
| NLRP6 | 182.7464962 | 47.58493808 | -1.946951788 | $4.64 \mathrm{E}-08$ |
| SLC7A5 | 34527.49705 | 8945.907643 | -1.948391178 | $1.95 \mathrm{E}-20$ |
| DLGAP1 | 25.93832161 | 6.530146868 | -1.95503962 | 0.0156424 |
| GLYCTK | 2236.491582 | 561.7551797 | -1.993879261 | $2.85 \mathrm{E}-13$ |
| SLC1A3 | 672.8947396 | 167.1797493 | -2.007635424 | $2.75 \mathrm{E}-13$ |
| DNAH7 | 33.16909672 | 8.331694958 | -2.007730371 | 0.002841148 |
| FBN1 | 21.80292431 | 5.471857664 | -2.018897302 | 0.049034508 |
| HOXB4 | 1893.969538 | 461.4364734 | -2.037602309 | $1.43 \mathrm{E}-09$ |
| XPOT | 10128.23275 | 2451.909564 | -2.046306142 | 1.02E-32 |
| SPTLC3 | 268.9301996 | 64.93093126 | -2.049459167 | 0.032636887 |
| BBS9 | 364.5614628 | 88.13009291 | -2.054406004 | $1.35 \mathrm{E}-14$ |
| CLYBL | 360.0465583 | 83.31570552 | -2.116857345 | 1.82E-07 |
| TUBE1 | 2064.140848 | 473.0421485 | -2.124639328 | 3.59E-31 |
| LRRN2 | 41.24327451 | 9.521396833 | -2.137654101 | 0.003886243 |
| ODAM | 37.09893699 | 8.370496374 | -2.140510089 | 0.008695314 |
| PIR | 241.2701305 | 54.70936182 | -2.143927826 | 5.82E-10 |
| PDGFRB | 67.959841 | 15.33858948 | -2.155658424 | 0.000311181 |
| RHOBTB1 | 68.08426793 | 15.22474614 | -2.161904138 | $2.44 \mathrm{E}-06$ |
| SUGCT | 53.05377416 | 11.99719367 | -2.16506698 | 0.000260195 |
| ADAMTS19 | 26.38509562 | 5.789018842 | -2.176628702 | 0.003116227 |
| C1QTNF3 | 38.55784995 | 8.492621434 | -2.188209445 | 0.000828577 |
| MYC | 4954.158709 | 1079.518235 | -2.197784725 | $1.87 \mathrm{E}-12$ |
| ASCL2 | 7629.396342 | 1595.178223 | -2.258047181 | $1.66 \mathrm{E}-12$ |
| SLC30A10 | 33.34092563 | 7.082055526 | -2.25854718 | 0.002578072 |
| ADM2 | 2263.446108 | 471.010095 | -2.265362436 | $1.68 \mathrm{E}-19$ |
| PRR4 | 14.99108374 | 3.117060915 | -2.2658568 | 0.02657364 |
| APCDD1 | 2906.255262 | 600.4363908 | -2.275746179 | $1.69 \mathrm{E}-09$ |
| TCP10L | 22.69796503 | 4.647405995 | -2.278346172 | 0.008057694 |
| CDH4 | 49.02962751 | 10.22259847 | -2.281341302 | 0.000160561 |
| TTLL1 | 307.5329342 | 63.31235573 | -2.281527023 | $1.16 \mathrm{E}-07$ |
| SLC39A11 | 943.1548349 | 193.1868543 | -2.290402965 | $1.77 \mathrm{E}-27$ |
| PSAT1 | 14231.41171 | 2839.740463 | -2.325064507 | $2.50 \mathrm{E}-25$ |
| LIX1 | 12.55177548 | 2.494587087 | -2.330640719 | 0.03373682 |
| CDX2 | 10357.58477 | 2045.026114 | -2.340600577 | $3.71 \mathrm{E}-09$ |
| KIF26B | 145.5005066 | 28.57268725 | -2.344813164 | $1.67 \mathrm{E}-11$ |
| GRIP1 | 227.6163172 | 44.70765054 | -2.345239881 | 2.43E-19 |
| ZNF521 | 15.53005505 | 2.952663576 | -2.355679922 | 0.022520266 |
| BEND6 | 55.20282247 | 10.65137618 | -2.35936442 | $4.38 \mathrm{E}-05$ |
| DUOXA1 | 17.8900399 | 3.522237512 | -2.363861728 | 0.009735185 |
| CPO | 21.5351596 | 3.919251471 | -2.42713523 | 0.008375866 |
| DOCK10 | 57.17305086 | 10.5585499 | -2.430559758 | 0.000189209 |
| CYP2E1 | 65.46564797 | 11.890388 | -2.459123623 | 8.69E-06 |


| KLHDC7B | 48.72195521 | 8.911896507 | -2.462520126 | 5.27E-05 |
| :---: | :---: | :---: | :---: | :---: |
| PTP4A3 | 309.2408962 | 53.96363796 | -2.518157273 | 1.03E-10 |
| FGF21 | 163.0903275 | 28.50099711 | -2.519052125 | $9.27 \mathrm{E}-12$ |
| RBMS3 | 81.99679847 | 13.8623652 | -2.556967567 | 0.001177026 |
| HGD | 43.44769936 | 7.491923899 | -2.557345559 | 0.001478039 |
| SETBP1 | 18.48668041 | 3.077134524 | -2.568754159 | 0.016016551 |
| AKAP6 | 95.69896778 | 16.21828693 | -2.574378828 | $2.88 \mathrm{E}-10$ |
| PCK2 | 12725.73495 | 2126.584299 | -2.581449636 | 6.49E-59 |
| CHAC1 | 2645.435285 | 441.6040685 | -2.581996608 | $4.26 \mathrm{E}-22$ |
| CPQ | 161.4336896 | 26.7945021 | -2.58883825 | $8.09 \mathrm{E}-11$ |
| BHMT | 28.5924648 | 4.769531055 | -2.595611155 | 0.000724927 |
| DMGDH | 180.6577179 | 28.48689863 | -2.665298676 | $1.34 \mathrm{E}-10$ |
| RP1L1 | 13.06485072 | 2.09522724 | -2.724731467 | 0.04401903 |
| MAML3 | 86.00803596 | 12.91334665 | -2.741395735 | $6.52 \mathrm{E}-10$ |
| XYLT1 | 125.308311 | 18.92536038 | -2.742936561 | $6.47 \mathrm{E}-07$ |
| FPGT-TNNI3K | 27.48862612 | 4.104784949 | -2.747587343 | 0.00076667 |
| MROH7 | 33.88512814 | 4.970383923 | -2.761972143 | 0.003923004 |
| RPL22L1 | 2711.866225 | 393.2421423 | -2.784838933 | $7.78 \mathrm{E}-19$ |
| SMOC2 | 32.310071 | 4.628615744 | -2.791669598 | 0.003365433 |
| UGT1A6 | 15.14060678 | 2.110546629 | -2.816972803 | 0.010779533 |
| EIF2S3B | 11.17119659 | 1.567925583 | -2.839416201 | 0.03013797 |
| ZBTB20 | 117.1097005 | 16.27700357 | -2.857258483 | $2.71 \mathrm{E}-09$ |
| CMA1 | 11.3736552 | 1.589061722 | -2.861700781 | 0.022775183 |
| HMCN1 | 27.48064576 | 3.723090379 | -2.874615565 | 0.006293414 |
| NDP | 152.5321404 | 20.12243404 | -2.916600534 | 0.007583826 |
| KIAA1024 | 45.2687129 | 5.955762069 | -2.928689447 | $2.94 \mathrm{E}-06$ |
| SLC8A1 | 34.16691016 | 4.488825406 | -2.945464773 | 0.000118058 |
| GIF | 22.68509694 | 3.000752605 | -2.950230503 | 0.025221904 |
| KCNQ1 | 1465.998937 | 187.1510741 | -2.971264131 | $2.26 \mathrm{E}-21$ |
| AC009119.2 | 17.26929841 | 2.152818908 | -2.992777764 | 0.004442468 |
| FAIM2 | 32.64055253 | 4.083648809 | -2.999463776 | 0.000318108 |
| CLDN2 | 5585.357067 | 697.0683164 | -3.002962334 | $1.73 \mathrm{E}-28$ |
| FREM1 | 22.55512482 | 2.735366345 | -3.017164935 | 0.005302599 |
| TMEM178A | 23.8202112 | 3.082951274 | -3.022147175 | 0.001712097 |
| CUBN | 17.71527246 | 2.152818908 | -3.023391289 | 0.014867696 |
| NUPR1 | 222.0892854 | 26.19876614 | -3.090342611 | 0.001153159 |
| EREG | 7823.943253 | 889.7602572 | -3.136167996 | $4.57 \mathrm{E}-37$ |
| GLDN | 128.7418425 | 14.69263362 | -3.143266049 | $3.68 \mathrm{E}-11$ |
| FHIT | 145.1199985 | 16.31939494 | -3.146634402 | $1.87 \mathrm{E}-12$ |
| FSTL1 | 14.09035533 | 1.567925583 | -3.167135957 | 0.015717831 |
| DDIT4 | 4132.167268 | 451.0983043 | -3.195907272 | $1.00 \mathrm{E}-43$ |
| CAPN14 | 15.17498077 | 1.692396531 | -3.225660575 | 0.012215627 |
| C1QTNF7 | 8.935490376 | 0.966587895 | -3.243059675 | 0.04051874 |
| MGAM2 | 12.89382757 | 1.329492213 | -3.326202452 | 0.022795155 |
| FAM78B | 39.43578072 | 3.821733412 | -3.385749965 | $2.84 \mathrm{E}-06$ |
| SLC7A11 | 6360.127558 | 602.5183358 | -3.399255402 | 8.22E-58 |
| CDH7 | 681.0633765 | 63.33705867 | -3.4266072 | 0.002162283 |
| CADPS | 436.7426599 | 38.97588925 | -3.497828545 | $3.77 \mathrm{E}-16$ |
| LURAP1L | 35.03391624 | 2.910391297 | -3.528849083 | $1.48 \mathrm{E}-05$ |
| EPHA3 | 7.825620525 | 0.664746106 | -3.618140887 | 0.047609907 |
| ALX4 | 7.886536459 | 0.664746106 | -3.639704418 | 0.043947051 |
| GABRA2 | 11.76294938 | 0.905525365 | -3.660758255 | 0.03482768 |
| ZNF610 | 8.371274662 | 0.643609967 | -3.725062022 | 0.047067057 |
| NAALADL2 | 167.1042659 | 12.19335476 | -3.789051099 | $1.34 \mathrm{E}-10$ |
| KLF8 | 18.45475318 | 1.247293544 | -3.880399124 | 0.002349458 |
| LAMA4 | 16.17669261 | 1.088712955 | -4.044282898 | 0.003656345 |
| RGS6 | 116.336995 | 7.004548633 | -4.065076332 | $1.50 \mathrm{E}-10$ |
| BHMT2 | 18.16938096 | 0.884389225 | -4.297946563 | 0.002056388 |
| ACTL8 | 12.3813982 | 0.643609967 | -4.310442531 | 0.010211899 |
| SULT1C4 | 6.848009664 | 0.301841788 | -4.33772438 | 0.037356329 |
| GABRA3 | 7.444804275 | 0.362904318 | -4.462076509 | 0.025012955 |


| PSD2 | 52.47488947 | 2.479267698 | -4.540426166 | $1.43 \mathrm{E}-08$ |
| :---: | :---: | :---: | :---: | :---: |
| ANK2 | 268.0090145 | 7.644687738 | -5.112749143 | $7.72 \mathrm{E}-29$ |
| PDE7B | 11.96361289 | 0.280705649 | -5.148255746 | 0.00298979 |
| EHD3 | 12.17095923 | 0.301841788 | -5.176027952 | 0.002567679 |
| SLC4A4 | 7.439916546 | 0 | -5.424800183 | 0.012477706 |
| SNX20 | 7.631793938 | 0 | -5.456104097 | 0.008244402 |
| SYCP2L | 7.888331558 | 0 | -5.505448358 | 0.005227054 |
| DCT | 14.56172788 | 0 | -6.393115603 | 0.00026736 |
| PRKN | 20.77841484 | 0 | -6.903645583 | $1.32 \mathrm{E}-05$ |

Table 9. Multiple testing for glycolysis-related genes

| DLD1 |  |  | HCT15 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Gene name | P value | FDR | Gene name | P value | FDR |
| HK2 | 0.0004 | 0.0064 | LDHB | 0.0007 | 0.0112 |
| PGK1 | 0.0005 | 0.004 | ENO3 | 0.0009 | 0.0072 |
| PFKL | 0.0011 | 0.005867 | ENO2 | 0.0017 | 0.009067 |
| ENO3 | 0.0076 | 0.0304 | PFKM | 0.0033 | 0.0132 |
| PFKP | 0.0138 | 0.04416 | GPI | 0.0048 | 0.01536 |
| ENO2 | 0.0171 | 0.0456 | PFKL | 0.0052 | 0.013867 |
| ALDOA | 0.0243 | 0.055543 | PGK1 | 0.0074 | 0.016914 |
| SLC16A1 | 0.036 | 0.072 | HK2 | 0.008 | 0.016 |
| PFKM | 0.0378 | 0.0672 | GAPDH | 0.0082 | 0.014578 |
| SLC2A1 | 0.0536 | 0.08576 | ENO1 | 0.0228 | 0.03648 |
| LDHA | 0.0673 | 0.097891 | LDHA | 0.1053 | 0.153164 |
| GAPDH | 0.0711 | 0.0948 | PGAM1 | 0.2052 | 0.2736 |
| GPI | 0.1337 | 0.164554 | ALDOA | 0.249 | 0.306462 |
| LDHB | 0.1953 | 0.2232 | SLC16A1 | 0.4192 | 0.479086 |
| PGAM1 | 0.2169 | 0.23136 | SLC2A1 | 0.4787 | 0.510613 |
| ENO1 | 0.477 | 0.477 | PFKP | 0.6251 | 0.6251 |

The total number of rejections of the null include both the number of false positives (FP) and true positives (TP). Simply put, FDR = FP / (FP + TP).

Table 10. Protein quantification of Mass Spectrometry analysis (Top 20)

|  | NTC abundance |  |  | TKO abundance |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Gene name | Repeat 1 | Repeat 2 | Repeat 3 | Repeat 1 | Repeat 2 | Repeat 3 | Fold <br> change | Student's <br> T-test p- <br> value |
| PRSS2 | 83.9 | 96.1 | 64.8 | 275.7 | 316.1 | 316 | 3.708333 | 0.000442 |
| GDF15 | 74.43333 | 72.5 | 63.3 | 147.9333 | 190.9333 | 160.2 | 2.37387 | 0.000682 |
| SERPINA1 | 74.46667 | 73.5 | 69.3 | 157.0333 | 151.6667 | 176.0667 | 2.231206 | $9.02 \mathrm{E}-05$ |
| LCN2 | 89.2 | 140.5 | 121.2 | 237.7 | 291.9 | 244.4 | 2.205757 | 0.005628 |
| VGF | 79.13333 | 98.63333 | 86.43333 | 174.1 | 201.5 | 182.9333 | 2.114055 | 0.000621 |
| SEMA3F | 58.6 | 47.7 | 40.8 | 72.5 | 98.9 | 135.1 | 2.083617 | 0.026585 |
| MUC5AC | 120.5333 | 116.8333 | 113.0333 | 218.5333 | 218.4667 | 273.0667 | 2.026446 | 0.000791 |
| CTSD | 106.8667 | 115.7667 | 93 | 206.9333 | 205.8 | 217.1333 | 1.995564 | 0.000466 |
| CTSL | 69.76667 | 77.56667 | 52.13333 | 112.9333 | 137.4 | 135.0667 | 1.932152 | 0.007616 |
| LGMN | 56.5 | 75.36667 | 59.43333 | 120.5 | 119.1 | 129.8333 | 1.931173 | 0.002005 |
| PRSS22 | 74.8 | 68.6 | 107.1 | 185.3 | 142.9 | 153.1 | 1.921357 | 0.013224 |
| PVR | 90.2 | 60.4 | 55.65 | 126.2 | 115.45 | 152.45 | 1.910788 | 0.017554 |
| PSAP | 59.9 | 72.96667 | 51.13333 | 106.4333 | 114.2333 | 125.1333 | 1.879348 | 0.004812 |
| PPIC | 108.2 | 109.2333 | 86.16667 | 186.8667 | 187.9333 | 194.0333 | 1.873628 | 0.001275 |
| NUCB1 | 78.4 | 86.03333 | 79.5 | 134.3333 | 152.5333 | 142.9 | 1.76182 | 0.000267 |
| SLC39A10 | 129.9 | 112.25 | 119.2 | 203.95 | 222.95 | 201.6 | 1.739311 | 0.000472 |
| ADAM9 | 97.5 | 63.3 | 76.76667 | 121.4667 | 147.0667 | 134.3333 | 1.695805 | 0.016694 |
| SUMF1 | 73.9 | 59.8 | 62.7 | 97.3 | 122.2 | 112.5 | 1.690428 | 0.004756 |
| LGALS3BP | 66.63333 | 59.33333 | 48.76667 | 91.13333 | 98.6 | 103.7667 | 1.679702 | 0.005974 |

Table 11. Univariate and multivariate analysis of clinicopathological factors for overall survival (OS)

| Univariate Analysis |  | Variables | Multivariate Analysis |  |
| :---: | :---: | :---: | :---: | :---: |
| OR (95\% CI) | $p$ |  | OR (95\% CI) | $p$ |
| 0.1374 to 0.5559 | 0.0003 | TXNIP | 0.1610 to 1.0010 | 0.0502 |
| 1.5545 to 6.0570 | 0.0012 | GDF15 | 0.6098 to 4.0023 | 0.3526 |
| 0.8804 to 3.0622 | 0.1189 | Gender |  |  |
| 0.8970 to 3.2307 | 0.1036 | Age |  |  |
| -1 to -1 | 0.9588 | T stage |  |  |
| 1.0166 to 3.5853 | 0.0443 | N stage | 0.4946 to 2.1334 | 0.9426 |
| 1.0497 to 11.1098 | 0.0413 | M stage | 0.5533 to 6.4868 | 0.309 |
| 0.9938 to 3.5046 | 0.0523 | Clinical stage |  |  |

Table 12. Single cell analysis for altered gene expression between primary colorectal cancer tissues and liver metastases ${ }^{582}$

| gene | avg_logFC | p_val_adj |
| :---: | :---: | :---: |
| TAC1 | 5.087790741 | $2.6 \mathrm{E}-182$ |
| GAPLINC | 4.295450138 | 0 |
| APCDD1 | 4.259525078 | $1.6 \mathrm{E}-137$ |
| LINC00176 | 4.076166748 | $4.9 \mathrm{E}-293$ |
| NR0B2 | 4.041507643 | $9 \mathrm{E}-131$ |
| CES1 | 3.945832044 | 0 |
| CEL | 3.339273393 | $6.4 \mathrm{E}-220$ |
| PTK7 | 3.236556587 | $1.6 \mathrm{E}-253$ |
| RP4-781K5.4 | 3.180150822 | $4.2 \mathrm{E}-137$ |
| PCSK1N | 3.156354474 | $1.6 \mathrm{E}-120$ |
| PLCB1 | 3.150034087 | $1.8 \mathrm{E}-106$ |
| EPDR1 | 3.144508853 | $4.5 \mathrm{E}-111$ |
| NOTUM | 2.947505656 | $9 \mathrm{E}-149$ |
| VAV3 | 2.843852695 | $4.1 \mathrm{E}-115$ |
| TEAD2 | 2.735146664 | $3 \mathrm{E}-106$ |
| LGR5 | 2.706176321 | $2.34 \mathrm{E}-92$ |
| AXIN2 | 2.674946216 | $1.5 \mathrm{E}-147$ |
| NKD1 | 2.573936247 | $6.4 \mathrm{E}-200$ |
| C8orf4 | 2.454778798 | $1.34 \mathrm{E}-74$ |
| RGMB | 2.421575647 | $2.76 \mathrm{E}-78$ |
| DAB2 | 2.396711512 | $4.3 \mathrm{E}-120$ |
| PROX1 | 2.30678142 | $6.74 \mathrm{E}-90$ |
| SESN1 | 2.288272094 | $8.66 \mathrm{E}-83$ |
| GDF15 | 2.282187723 | $1.5 \mathrm{E}-242$ |
| XXbac-BPG32J3.19 | 2.258926404 | $1.2 \mathrm{E}-122$ |
| QPRT | 2.182598235 | $4.5 \mathrm{E}-180$ |


| DPEP1 | 2.176475687 | $5.9 \mathrm{E}-237$ |
| :---: | :---: | :---: |
| ALDH1A1 | 2.17513563 | $7.64 \mathrm{E}-90$ |
| WDR72 | 2.174030306 | $1.69 \mathrm{E}-66$ |
| RARRES2 | 2.162834133 | $1.6 \mathrm{E}-116$ |
| ZNF503 | 2.131736857 | $9.2 \mathrm{E}-121$ |
| FN1 | 2.116309965 | $5.9 \mathrm{E}-101$ |
| CAPS | 2.094614275 | $1.1 \mathrm{E}-141$ |
| PTP4A3 | 2.092213853 | $1.33 \mathrm{E}-95$ |
| TSPAN12 | 2.091161983 | $4.87 \mathrm{E}-81$ |
| CLU | 2.022991552 | $1.7 \mathrm{E}-100$ |
| ASCL2 | 2.005777287 | $1.4 \mathrm{E}-256$ |

