Expression levels of blood microRNAs as biomarker of cognitive decline due to Alzheimer's Disease

Dr Angélique Sadlon

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Ageing Epidemiology (AGE) Research Unit
School of Public Health
Faculty of Medicine
Imperial College London

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Copyright declaration

Declaration of originality

I confirm that the work described in this thesis is my own work. Work from others is clearly indicated as such and appropriately referenced.

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Acronyms and abbreviations

AChEi	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
APP	Amyloid precursor protein
APPsα	Secreted amyloid precursor protein-α
APPsβ	Secreted amyloid precursor protein-β
Aβ	Amyloid β peptide
BACE1	β-site APP cleaving enzyme 1
CAIDE score	Cardiovascular Risk Factors, Aging, and Incidence of Dementia score
CNS	Central nervous system
CSF	Cerebrospinal fluid
DASH	Dietary Approaches to Stop Hypertension
ELISA	Enzyme linked immunosorbent assay
FDG	F-18 fluorodeoxyglucose
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GATK	Genome AnalysisToolkit
GWAS	Genome-wide association studies
IFN	Interferon
IL	Interleukin
LOAD	Late-Onset Alzheimer's disease
MAPK	Mitogen-activated protein kinases
MCI	Mild cognitive impairment
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
P-tau	Phosphorylated tau protein
PD	Parkinson's disease
PET	Positron emission tomography
preDIVA	Prevention of Dementia by Intensive Vascular Care
eQTL	Expression quantitative trait loci
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RNA	Ribonucleic acid
RT-qPCR	Real-time quantitative polymerase chain reaction
SCIENCe	Subjective Cognitive Impairment Cohort (SCIENCe)
SD	Standard deviation
SNP	Single nucleotide polymorphism
SPECT	Single-photon emission-computed tomography
SPRINT	Systolic Blood Pressure Intervention Trial
T-tau	Total tau
TF	Transcription factor
TGF	Transforming growth factor
TLR	Toll-like receptor
TREM	Triggering receptor expressed on myeloid cells

Abstract

Studies investigating differential miRNAs expression levels in patients with Alzheimer's disease (AD) abounded in the last decades and catalysed the interest towards miRNAs as novel non-invasive biomarkers of AD. Chapter 1 provides an overview of AD's pathogenesis, discusses the evolution of the disease's definition, and introduces miRNAs. In Chapter 2, a systematic review and a P-value based meta-analysis of 107 studies investigate miRNA expression levels in AD patients. This leads to a prioritisation of 25, 32 and 5 dysregulated miRNAs at study-wide significance in the brain, the blood and the cerebrospinal fluid (CSF) of AD patients, respectively. A pathway enrichment analysis for the top dysregulated miRNAs in the brain confirms their role in regulating biological functions implicated in AD. In Chapter 3, expression levels of the 32 dysregulated miRNAs in the blood and 6 top dysregulated miRNAs in the brain of AD patients, are assessed using real-time quantitative polymerase chain reaction in the blood of cognitively healthy individuals from the CHARIOT-PRO cohort. Low performers on the total Repeatable Battery for the Assessment of Neuropsychological Status scale show downregulation of six miRNAs (hsa-miR-128-3p, hsa-miR-144-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-29c-3p and hsa-miR-363-3p). Pathway enrichment analysis highlights involvement in pathways initiating early pathogenetic changes in AD. Finally, in chapter 4, whole-genome sequencing data from the Alzheimer's Disease Neuroimaging Initiative is used to perform an association analysis between polymorphisms within the six miRNAs' genes and CSF biomarkers of neurodegeneration. A functional annotation of significant variants highlights expression quantitative trait loci, location in enhancer regions and alterations in the binding sites of transcription factors regulating neuronal function. The association of variants located within the same miRNA gene with different markers of neurodegeneration reveals a positive correlation between members of the amyloid cascade and microglial activation in the CSF. The final chapter highlights the clinical relevance of these findings and discusses future perspectives.

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Related academic work

Publications

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Chapter 1: Introduction

1.1. Epidemiology

Dementia is a neurocognitive disorder defined by progressive memory loss and impaired cognitive ability, eventually leading to functional dependence [1]. Alzheimer's disease (AD) is the most frequent form of dementia [2]. Since the first case described by Alois Alzheimer in 1906, the number of individuals affected by AD has risen dramatically. According to large retrospective studies, the number of AD cases worldwide has considerably increased from 21.7 million individuals in 1990 to 46.8 million in 2015 [3]. Additionally, forecasting models suggest that more than 130 million people worldwide will be affected by dementia in 2050 [4]. These alarming rates put AD at the core of a global public health crisis. Indeed, in terms of years lived with disability, AD ranks in 4^{th} and 2^{nd} position in age groups 75-79 years and ≥ 80 years respectively, on top of chronic diseases such as ischemic heart disease, chronic obstructive pulmonary disease or diabetes [3]. Increased life expectancy in the years to come will impose a major burden upon societies, health professionals and caregivers.

1.2. Pathogenesis

Amyloid plaques and neurofibrillary tangles (NFT) are the classical neuropathological features of AD [5-9]. They were first described by Alois Alzheimer in a publication in 1906 "In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability. […] Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex" [10]. More than a century later, scientific advances have revealed a very complex interplay underlying the disease's pathogenesis, with some mechanisms not yet fully unveiled.

1.2.1. Amyloid plaques

The amyloid hypothesis is a dominant model in AD pathogenesis [11-13]. Amyloid plaques (also called senile plaques) are composed of highly aggregated amyloid β (Aβ) fibrils which are formed by Aβ peptides [14]. The formation of Aβ peptides starts with the cleavage of an amyloid precursor protein (APP) by a β-site APP cleaving enzyme 1 (BACE1). This leads to the production of APPsβ which is then cleaved by a γ-secretase to produce Aβ peptide [15-18]. The

latter, which consists of 38-42 amino acids is highly hydrophobic and aggregates easily to form Aβ fibrils. Another processing pathway, the "non-amyloidogenic pathway", results in the production of APPsα via an α-secretase (*Figure 1*) [19]. Interestingly, multiple studies have reported that neurons, compared to other cell lines such as fibroblasts or cardiac cells, show increased activity of BACE1 [20-22]. Increased BACE1 activity was reported in post-mortem AD brains compared to healthy controls [23, 24]. Similar results were reported when BACE1 activity was measured in the CSF of patients with mild cognitive impairment (MCI) and AD [25, 26]. Interestingly, APOE ε4 carriers with both AD and MCI showed increased CSF BACE1 activity compared to non-carriers [26].

Literature has provided opposing functions of APPsα and APPsβ [27]. APPsα has been linked to neuronal plasticity, neuroprotection and neuronal stem cell proliferation [28-31]. By contrast, APPsβ and Aβ have been linked to neuronal cell death, synaptic dysfunction and axonal pruning [32-39]. Moreover, in AD, reduced activity of the α secretase pathway has been described and decreased levels of APPsα were reported in *APP* mutation carriers, and in patients with sporadic AD [40, 41]. In a cross-sectional analysis of 96 individuals, increased levels of APPsα and APPsβ were reported in individuals with AD compared to healthy controls and non-AD [42]. In contrast, other studies have failed to show a statistically significant difference between AD and controls [43-45].

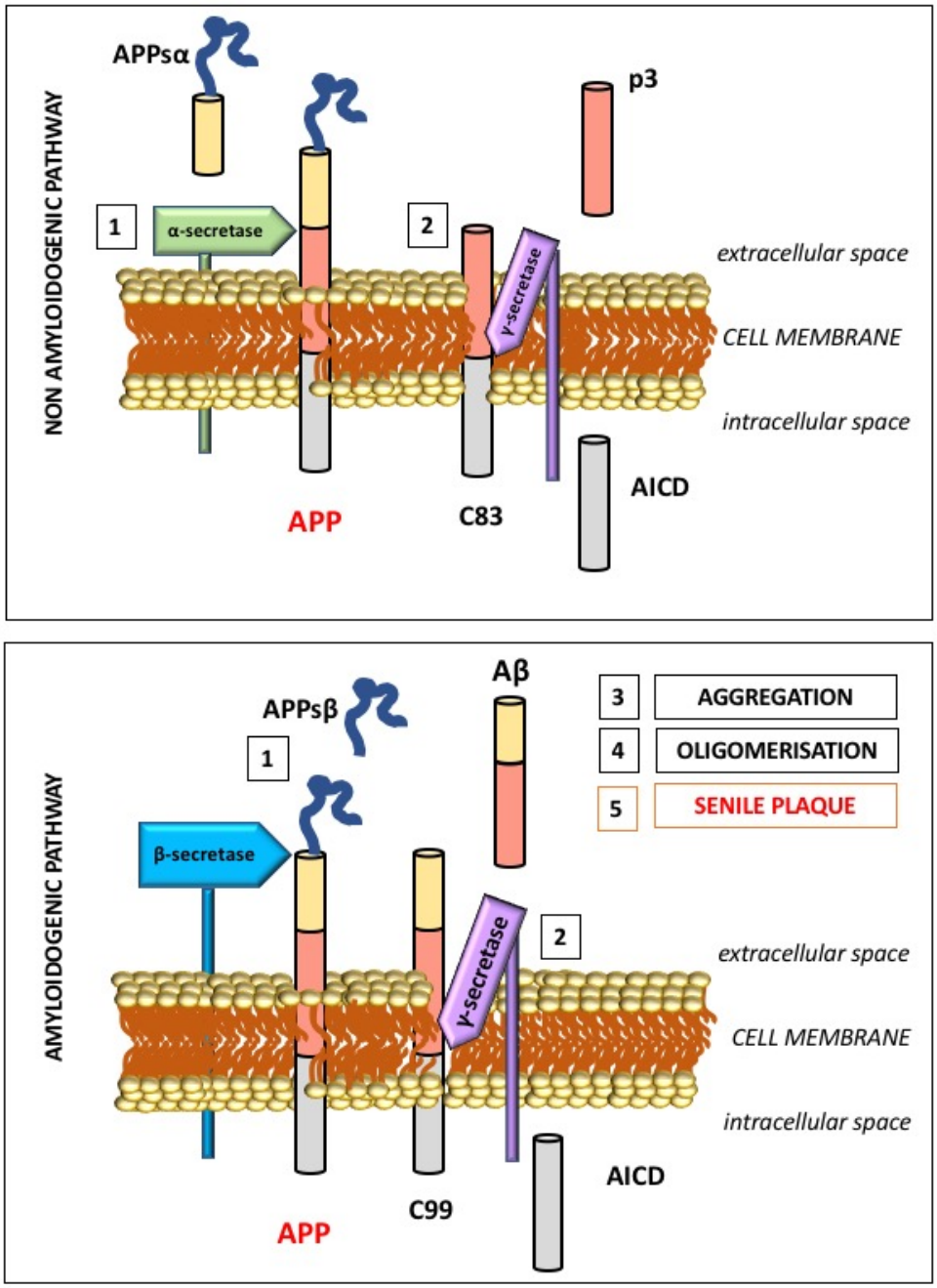
However, the role of the amyloid cascade in AD pathogenesis is not yet fully understood. For example, Aβ 40 and Aβ 42 have also been linked to neurotrophic functions [46, 47]. It is suggested that the effect of Aβ might be dose dependent as low levels of Aβ led to impaired presynaptic efficacy and high levels were associated with post-synaptic depression. Conversely, intermediate levels of Aβ stimulated presynaptic activity, hence highlighting the complex relationship between Aβ and neurons [48]. Moreover, numerous reports point toward dysfunctional Aβ clearance systems, which in parallel with increased production of Aβ, fuel early pathogenic changes associated with the disease [49].

1.2.2. Tau and neurofibrillary tangles

Tau protein is expressed in neurons as well as non-neuronal cells [50-52]. The highest concentration of tau protein is however found in distal portions of axons [53, 54]. By binding to microtubules, tau leads to their stabilisation and to the formation of a cytoskeleton involved in intracellular transport [55]. Multiple mechanisms such as aberrant phosphorylation or

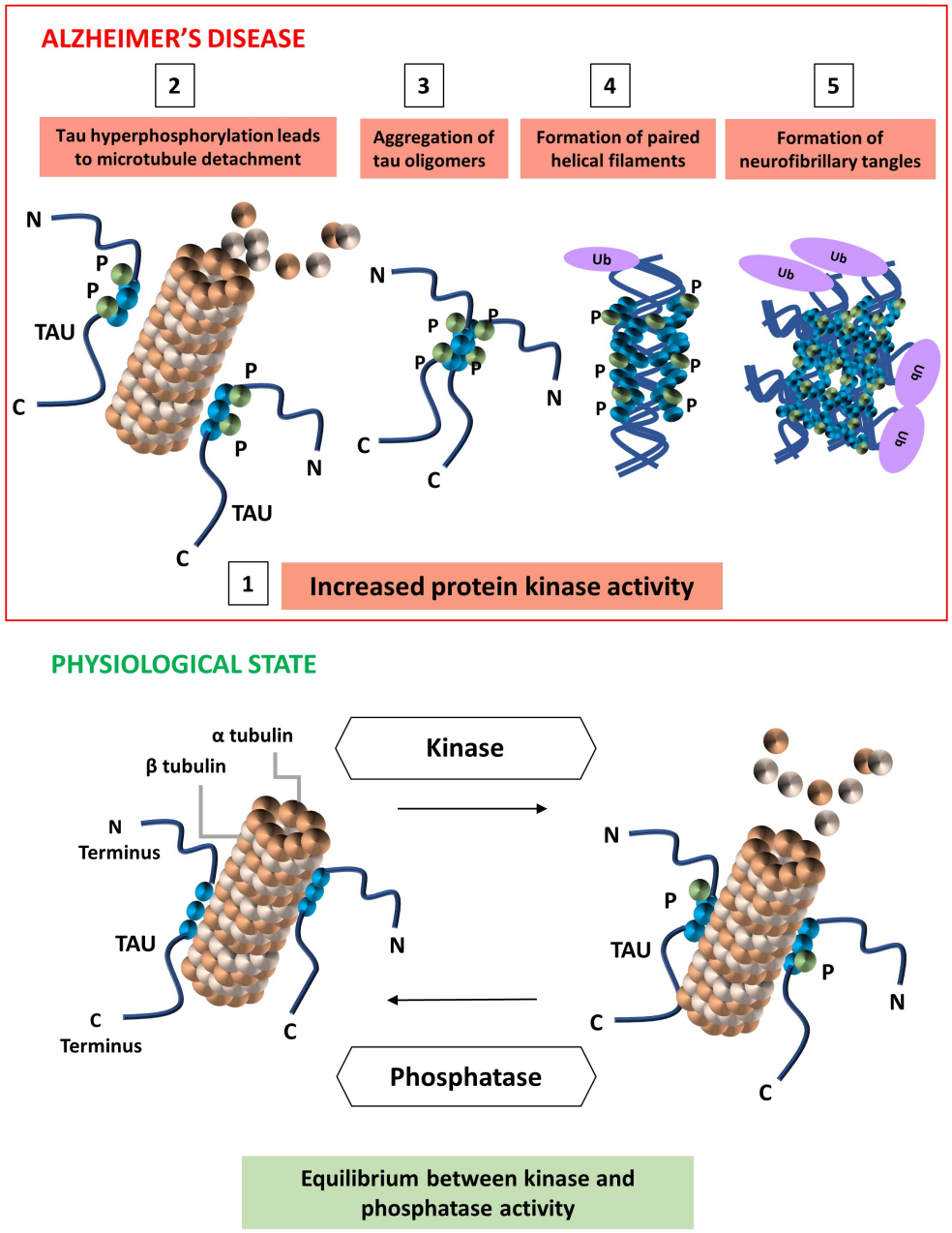
cis/trans transformation can modify tau at a post-translational level (reviewed in [56]). Once phosphorylated, tau shows decreased affinity for the microtubules and starts to detach from them, leading to their disintegration [57]. Newly soluble tau proteins are then subject to additional post-translational modifications, which induce a cascade of events: phosphorylated tau (P-tau) protein dimerisation forms tau dimers, which in turn assemble into tau oligomers. Then, aggregation of tau oligomers results in the formation of paired helical filaments, which eventually assemble into NFT (*Figure 2*) [58]. NFT severely impair axonal function by affecting axonal transport and degradation [59]. Numerous experimental studies have linked NFT to cognitive decline and memory impairment [60-62]. The importance of tau pathology in AD has been highlighted by Braak and Braak, who have described six distinct stages linking the gradual NFT deposition in various regions of the brain affected by AD to clinical symptoms [63, 64]. Interestingly, recent studies suggest that tau oligomers may in fact be the key player in tau-related AD pathogenesis. These small aggregates, once released in the extracellular space from NFT, can spread in a prion-like manner across different regions in the brain, where they lead to axonal and synaptic dysfunction [65-69].

Figure 1: APP processing pathway (modified based on [70, 71]).



Top panel: Non amyloidogenic pathway. APP is cleaved by an α secretase into APPsα and C83 (1) which is in turn cleaved into p3 and AICD by a γ secretase (2). **Bottom panel: amyloidogenic pathway.** APP is cleaved by the β secretase (BACE1) into APPsβ and C99 (1) which is in turn cleaved by a γ secretase into amyloid β (Aβ) and AICD (2). Aβ then undergoes a series of transformation leading to Aβ aggregation and oligomerisation (3 and 4) and the formation of senile plaques (5). *Abbreviations*: AICD= amyloid β precursor protein intracellular domain, APP: amyloid β precursor protein.

Figure 2: Tau hyperphosphorylation in Alzheimer's disease (modified based on [72]).



Under physiological conditions (bottom graph), there is an equilibrium between kinase and phosphatase activity on tau. In AD (upper graph), increased protein kinase activity leads to tau hyperphosphorylation (1 and 2). Phosphorylated tau detaches from the microtubules and then aggregates into tau oligomers (3). The latter forms paired helical filaments which assemble into neurofibrillary tangles (4 and 5).

1.2.3. Interaction between amyloid and tau in the AD pathogenesis

The roles of amyloid and tau pathology on AD have often been compared and contrasted, although evidence from experimental studies described the intricate relationship between tau and Aβ toxicity. In the presence of tau, *in vitro* and *in vivo* studies have shown that Aβ could lead to several pathways associated with AD neurodegeneration such as microtubule dysfunction, impaired long-term potentiation, and abnormal cell cycle re-entry [73-77]. In addition, injection of Aβ in a transgenic mouse model overexpressing tau resulted in a dramatic increase in the number of NFT at the injection site [78]. Similar results based on transgenic mice revealed that Aβ probably acts upstream of the tau induced-synaptic and neuronal loss [79-81]. These changes can be measured in the CSF as reported by a study on APP transgenic mice. Here, authors reported that increased Aβ deposits correlated with decreased levels of Aβ42 and t-tau in the CSF [82]. In contrast, a study in mice has challenged this hypothesis by showing that mice lacking tau had lower levels of amyloid plaques compared to mice expressing tau [83]. Current base of knowledge suggests that Aβ and tau may interact in a feedback loop manner, that eventually leads to neuronal loss [84]. Noteworthy, a dynamic relationship between tau and amyloid expression is noted over time. Indeed, in a longitudinal study of 1343 participants, abnormal tau positron emission tomography (PET) was preceded by abnormal amyloid PET suggesting that the latter is required to increase tau deposition [85]. In addition, a temporal change in tau site specific phosphorylation is noted. In individuals from the dominantly inherited AD, increase in p-tau$_{217}$ and p-tau$_{181}$ levels in the CSF was concomitant with Aβ deposition several decades before the onset of clinical symptoms. In the opposite, increase in T-tau (total tau) as measured on tau PET was measured several decades later and correlated with the onset of clinical symptoms [86].

1.2.4. Neurofilament

Neurofilaments are essential components of the neuron cytoskeleton where they participate in maintaining neuronal structure and regulate axonal growth and function. These proteins are composed of four subunits: light (NfL), medium, heavy and α-internexin. The most abundant subunit is the NfL which controls the properties of the other subunits [87]. Following neuronal injury, neurofilaments are released in the extracellular space and can then be measured in the blood or CSF [88]. Numerous studies report increased levels of NfL in the CSF and blood of AD patients [89]. Moreover, NfL correlated well with other hallmarks of AD in cross-sectional and

longitudinal studies and is increasingly regarded as a non-invasive biomarker of neurodegeneration in AD [90, 91].

1.2.5. Inflammation

Abundance of literature has suggested that inflammation might be a mediator in the intricate relationship between amyloid and tau in neurodegeneration. Whether as friend or foe in the pathogenesis of AD, interest in inflammation has waxed and waned in the last decades [92, 93]. Microglia, monocytes, macrophages and astrocytes have all been described as cellular mediators in the AD pathogenesis, in particular, microglia have been studied extensively (reviewed here: [94-101]). These macrophage-like glial cells have been associated with many functions in the central nervous system (CNS) such as mediation of adaptive and immune response, growth factor secretion, and regulation of cell apoptosis or synaptic function [102-105]. Recently, genetic studies have provided additional evidence for the role of microglia in AD. Variants within *TREM2* (triggering receptor expressed on myeloid cells 2), an essential microglia receptor, were reported to be associated with increased risk for AD [106-109]. Increased levels of a soluble variant of TREM2 (sTREM2) were reported in patients with MCI and early stages of AD [110, 111]. Patients with dominant AD mutations showed increased levels of sTREM2 in the CSF five years before the onset of symptoms, highlighting a possible role of neuroinflammation in early stages of the disease [112]. This was further confirmed by a recent study reporting positive correlation between sTREM2 and pro-inflammatory markers such as TNF-α, TNFR1, TNFR2, ICAM1, VCAM1 and IP-10 [113]. Moreover, the ability of microglial cells to adapt to the environment and change its metabolism and morphology from a resting state to an active state attracted further scientific interest to these cells [114]. For several years, microglial activation state was dichotomised into a M1 and M2 phenotype. Accumulating evidence suggested that microglia, in response to the signal from the environment, undergoes a series of transformations resulting in two different phenotypes: M1, with mainly pro-inflammatory activity and M2, with mainly anti-inflammatory activity (reviewed in [115, 116]). In this regard, experimental studies suggested that M1 microglia was predominant in the early phase of the disease characterised by neuronal injury and degeneration while M2 microglia was found at later stage of the disease where reparation is predominant [117]. Nevertheless, in recent years, this concept has been challenged [118]. It is now suggested that microglia, in response to external stimuli, abandon their physiological state

and homeostatic function for another state characterised by different gene expression profile such as the disease-associated microglia (DAM) state (reviewed here: [119]).

Several triggers of microglial activation have been described. Evidence from mouse models suggests that binding of Aβ to Toll-like receptor 4 (TLR4) on microglial cells, induces the release of proinflammatory cytokines and subsequent Aβ clearance [120, 121]. Noteworthy, in another experimental study, continuous stimulation of TLR4 by Aβ led to a signalling dysfunction of the receptor and to inappropriate inflammation activation [122].Recently other inflammation triggers such as tau oligomers, but also gut microbiota, have been described [123, 124]. Additionally, next to cellular mediators of inflammation, abundant literature has highlighted the importance of cytokines in AD pathogenesis (reviewed here [125]). While some of them might be beneficial for neuroprotection after neuronal injury, others may play a role in neurodegeneration.

Finally, results from recent imaging studies highlighting the presence of inflammation in absence of NFT or amyloid plaques have launched a debate on the temporality of inflammation in AD [126, 127]. It has also reinforced the idea that Aβ or tau oligomers may be the triggers of an inflammation process, which leads to amyloid plaques, NFT formation and eventually to neuronal loss.

1.2.6. The cholinergic hypothesis

The interest in the role of acetylcholine in AD has started in the early 1970's, when reduced cholinergic activity was described in AD brains [128, 129]. Studies on primates and healthy subjects showed how inhibition of cholinergic activity through scopolamine was associated with memory impairment and learning disability. Interestingly, the administration of a cholinergic agonist was able to reverse those effects [130-132]. These encouraging results led to the development and Food and Drug Administration (FDA) approval of acetylcholinesterase inhibitors (AChEI) in the 1990's [133, 134]. However, since then, several results have curbed down the enthusiasm for AChEIs as disease-modifying treatment in AD. First, although small improvements in cognition in patients under donepezil, an AChEI, were described, the long term effect in terms of disability and institutionalization was not different from patients under placebo [135]. Also, long term treatment with donepezil did not stop cognitive decline over

time, compared to placebo in a cohort of 205 AChEI-treated patients [136]. Second, studies have reported various responders to AChEI. Some studies have reported that patients with highest levels of medial lobe atrophy, show lowest response to AChEI in terms of improved cognitive function whereas APOE ε4 carriers showed a better response than non-carriers [137-140]. Third, there is still debate regarding the timing of the cholinergic depletion in the pathogenesis of AD. Indeed, some authors suggest it is an early event contributing to the development of the disease, while others consider it is a late stage event [129, 141-144]. In addition, the physiological loss of cholinergic neurons with age seems to be a confounding factor, when comparing the density in cholinergic neurons in patients with AD to age-matched healthy elderly [145-148]. Fourth, studies in rats show that depletion of cholinergic neurons was not associated with increased memory deficits [149, 150]. Finally, increasing evidence from the literature suggests that cholinergic loss may not be a trigger of neurodegeneration but a contributor to its severity via a synergetic action with other factors such as stroke, seizures and circadian dysfunction (reviewed here: [151]). In addition, some authors suggest that amyloid deposition induces a cholinergic loss, which eventually affects cognitive function through a system of feedback loops [152, 153]. Other authors consider that the role of the cholinergic system in AD may be explained by the loss of its neuroprotective effect following cholinergic depletion precipitated by the exposure to risk factors during lifetime [151].

1.2.7. Genetics and Alzheimer's disease

Development of genomic techniques has fostered our understanding of the underlying role of genomics in AD pathogenesis and unveiled a complex interplay between genes and pathologic pathways associated with AD. Mutations in different genes have uncovered genetic risk factors associated with AD (reviewed here: [154]). Early onset AD (EOAD), i.e. AD that begins before the age of 65, represents between 5% and 10% of all AD cases [155]. Three different genes which might be affected by mutations have been described: *APP*, presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) [156-158]. For the APP gene, the mechanisms leading to EOAD depend on the location of the mutation coding for the Aβ domain in the *APP* gene [156, 159-161]. *PSEN1* mutations are the most common mutation associated with AD [162-164]. However, in EOAD, *PSEN1* despite being autosomal dominant, shows incomplete penetrance. Moreover, several studies have reported that, among *PSEN1* mutation carriers, there is heterogeneity in the age of onset, rate of progression and severity of disease [165]. Similarly to *APP*, the location of the

mutation in the *PSEN1* gene can lead to different phenotypic traits [166]. Finally, *PSEN2* mutations are rare and show variable penetrance [165, 167].

The genetic factors associated with late onset AD (LOAD) or sporadic AD have attracted increased attention. Apolipoprotein is involved in lipid metabolism. Impaired function of a subtype of apolipoprotein, Apolipoprotein E (APOE), leads to an increase in cholesterol and triglycerides in plasma [168, 169]. Interestingly, experimental studies have reported that APOE is linked to Aβ42 clearance in the brain [170]. Three primary *APOE* alleles have been identified: ε2 (rs429358 -TT), ε3 (wild type-TC), and ε4 (rs7412-CC) among which the ε4 allele has been associated with LOAD [171]. According to some studies, APOE ε4 may be associated with up to 20% of total AD cases. Moreover, deposition of Aβ42 correlates with the number of ε4 alleles [172]. By contrast, ε2 decreases AD risk [173]. Interestingly, a gene variant of another apolipoprotein, clusterin, has shown protective effects in carriers, through increased Aβ clearance [174, 175]. Large genome-wide association studies (GWAS) have identified several variants in genes coding for other pathways involved in the pathogenesis of AD. Some show a protective effect (e.g. variants of the Phosphatidylinositol binding clathrin assembly protein (*PICALM*), Membrane-spanning 4 domains, subfamily A member 6A (*MS4A6A*) and *CD33*); other variants however increase the risk of AD (e.g. Bridging integrator 1 (*BIN1*), ATP-binding cassette, subfamily A (*ABC1*) member 7 (*ABCA7*), Complement component (3b/4b) receptor 1 (Knops blood group) (*CR1*), Membrane-spanning 4 domains, subfamily A member 4E (*MS4A4E*) and CD2-associated protein (*CD2AP*)) [176-180]. Recently, mutations in *TREM2*, a microglial receptor, have been described as a significant risk factor for LOAD [107]. In 2013, a meta-analysis of 4 GWAS grouping 74,046 individuals of European ancestry revealed additional loci involved in the amyloid cascade (SORL1, CASS4), inflammatory pathway (*HLA-DRB5-DRB1, INPP5D* and *MEF2C*), neuronal activity in the hippocampus (*PTK2B*), tau pathway (*FERMT2*) and axonal transport (*CELF1, NME8*) [181]. Recently, a meta-analysis of 455,258 individuals of European ancestry identified 9 additional novel loci (*ADAMTS4, HESX1, CLNK, CNTNAP2, ADAM10, APH1B, KAT8, ALPK2, and AC074212.3*) [182]. Similarly, a meta-analysis conducted by the International Genomics of Alzheimer's Project (IGAP) in 2019 confirmed *ADAM10* and highlighted four novel loci, *IQCK, WWOX, ACE and ADAMTS1* [183]. Undoubtedly, further meta-analysis of GWAS will expand this list in the next years. Moreover, mutations in mitochondrial genome – so called "mitochondrial cascade hypothesis"- have also been discussed as a risk factor for AD but further research on this topic is needed [184].

Epigenetics has attracted increased attention in the last decades. According to Jaenisch and Bird, epigenetics studies "the stable alterations in gene expression potential that arise during development and cell proliferation" [185]. The role of epigenetic mechanisms in the neural system has been widely described, like for example in memory and learning ability [186-191]. In addition, the role of epigenetics in AD risk factors such as aging, nutrition, diabetes mellitus, hypertension and obesity further underscores the potential role of epigenetics in the AD pathophysiology [192-198]. Two epigenetic modifications, DNA methylation and histone modification have been extensively investigated in AD and provide a novel perspective in the complexity of AD pathogenesis [199, 200]. So far, evidence can only point towards correlation between an epigenetic mechanism and phenotype in AD; hence, there is no information regarding the causal relationship between those modifications and the observed phenotype. Furthermore, it is worth mentioning that most of the epigenetic studies include multiple cell lines. However, epigenetic patterns might differ between different cells. This might be an important aspect in AD, where multiple cell types are involved in the pathogenesis. Ongoing research in epigenetics tries to address these yet to be fully understood mechanisms.

1.3. Alzheimer's disease: an evolving clinical entity

Parallel to our growing understanding of the pathological mechanisms underlying AD, increasing awareness regarding the heterogeneity of patients diagnosed with AD has led to multiple revisions of the diagnostic criteria of AD.

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) issued a set of criteria for the diagnosis of probable, possible and definite AD. Noteworthy, definite AD could only be attributed if the classical hallmarks of AD had been confirmed in post-mortem brain specimen [201]. Furthermore, the criteria required some other causes of dementia, such as Parkinson's disease (PD), multi-infarct dementia, neurosyphilis or Creutzfeldt-Jakob disease to be excluded first. Nearly a decade later, the International Classification of Diseases (ICD-10, 1992) and the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR, 1994) published their criteria for AD diagnosis [202, 203].

As with the 1984 criteria, diagnosis of AD was based on clinical symptoms, i.e. memory loss and impaired cognitive function in the absence of any other organic brain condition.

Later on, the NINCDS-ADRDA, ICD and APA definitions were continuously challenged by scientific advances in the field. Following the struggles of the first clinical trials of AChEI in patients with AD, the scientific community became increasingly aware of possible heterogeneity among patients diagnosed with AD dementia [204-206]. Indeed, accumulating evidence from several studies reported different degrees of cognitive impairment among patients diagnosed with AD dementia [207-211]. In addition, different rates of progression towards advanced stages of dementia were reported in longitudinal studies [212-216]. Also, several studies investigating the clinical neuropathological correlation between ante-mortem clinical diagnosis and post-mortem diagnosis, revealed the presence of pathological features non-related to AD such as Lewy bodies or microinfarcts. For some cases, the diagnosis of AD even had to be revised [217-219]. Moreover, in other studies, histopathological examination of brains from cognitively normal elderly individuals showed neuropathological processes related to AD [220-222]. Finally, studies in individuals with autosomal dominant AD identified biomarkers of neurodegeneration such as Aβ40/42, P-tau, T-tau in CSF as well as amyloid deposition on PET before the onset of symptoms, hence suggesting that clinical AD might be at the end of a continuum of neuropathological changes, which starts several years before the onset of the first symptoms [172, 223-225].

Consequently, empirical definitions and diagnostic criteria of AD were updated to accommodate scientific progress in the field. The International Working Group (IWG) (in 2007 and 2010) and then the NIA-AA (in 2011) published revisions suggesting a shift from AD as a single clinical entity towards AD as a clinical and neuropathological entity composed of three distinct clinical phases: preclinical, prodromal/ MCI and AD dementia [226-229]. While some differences between the two working groups recommendations were noted, they shared common features [230]. First, two phases of the disease were identified and defined: preclinical stage, i.e. before onset of symptoms and clinical stages, i.e. when symptoms are apparent. In addition, to reflect differences in cognitive impairment severity, clinical stages were further classified into mild cognitive impairment (prodromal AD in IWG) and AD dementia. Second, the role of biomarkers in the diagnosis of the disease was also introduced.

Both the IWG and NIA-AA included markers of AD pathology in their criteria to support the diagnosis of AD: *amyloid* – Aβ 1-42 if measured in the CSF or amyloid deposits if measured on PET, *tau* – measured in the CSF, *hippocampal atrophy* – measured in the magnetic resonance imaging (MRI)- and *hypoperfusion or hypometabolism* as measured on PET or single-photon emission-computed tomography (SPECT). For the IWG, the presence of at least one pathophysiological marker, i.e. amyloid or tau, was sufficient to diagnose preclinical stages of AD. The NIA-AA further divided preclinical stages of AD into three phases: stage 1 (no cognitive impairment, amyloid abnormal), stage 2 (no impairment-amyloid and injury marker abnormal) and stage 3 (subtle cognitive decline, amyloid and injury marker abnormal). It is important to emphasise that the definition of clinical stages was designed for routine clinical care whereas the criteria for preclinical stages aimed at providing researchers with a common language to identify and define participants taking part in clinical trials.

Since then, differing definitions of preclinical stages of AD have been suggested by different working groups [231, 232]. Also, an intense debate has started to rise regarding the biomarker temporality in AD. Indeed, several studies conducted in preclinical AD revealed the presence of neuronal damage in AD specific regions independently of Aβ deposition [233-236]. Hence, this directly challenged the NIA-AA 2011 recommendations advocatin the presence of amyloid in preclinical stages. As a result, Jack *et al.* put forward a novel classification based on biomarkers only: the *A/T/N classification*. Each category would reflect the underlying pathophysiological process it measures. ***A*** refers to amyloid pathology and fibrillary Aβ deposition which can be measured by high ligand retention on amyloid PET or low CSF Aβ 42. ***T*** refers to tau pathology as measured in CSF (p-tau) or tau PET. ***N*** refers to neurodegeneration or neuronal injury as measured via ^{18}F fluorodeoxyglucose (FDG)-PET hypometabolism, atrophy on structural MRI in regions characteristic of AD or CSF t-tau [237]. This novel classification would harmonise the definition of individuals in preclinical stages without relying on the presence of clinical symptoms. Also, temporality of biomarker was discarded in this classification.

A recent study investigating the prevalence of preclinical stages of AD in a population of healthy elderly individuals reported varying prevalence numbers depending on the diagnostic criteria used. Undoubtedly, these results highlight the need for harmonisation [238]. In April 2018, the NIA-AA issued novel recommendations aimed at researchers in the field of AD [239]. They integrate both a biomarker profile, as described in the A/T/N classification (eight different

biomarker profiles according to the presence or not of each marker A, T or N) and a clinical staging reflecting the level of cognitive impairment (cognitively unimpaired, mild cognitive impairment and dementia) (*Table 1*). In these recommendations, an individual meeting the criteria for the presence of amyloid (A+) in CSF or on PET imaging automatically belongs to the "*Alzheimer's Disease Continuum*". There, depending on the presence of additional biomarkers such as Tau (T+) or markers of neurodegeneration or neuronal injury (N+), individuals would be defined as Alzheimer's Disease (A+T+N+), Alzheimer's pathologic changes (A+T-N-) or Alzheimer's and concomitant non-AD pathologic change (A+T-N+). In contrast, individuals with negative amyloid markers are defined as "*non-Alzheimer's disease pathologic change*" (A-T+N+, A-T-N+, A-T+N-). This latter category is of particular importance as growing evidence suggests it is an essential contributor to the heterogeneity of the patients previously diagnosed with AD [235, 240-242].

Table 1: NIA-AA recommendations 2018 for syndromal cognitive staging combined with biomarkers (adapted from [239])

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	$A^- T^- (N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^- (N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ (N)^+$			
	$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non- Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with dementia
	$A^- T^+ (N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
	$A^- T^- (N)^+$			
	$A^- T^+ (N)^+$			

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment. NOTE: Formatting denotes three general biomarker "categories" based on biomarker profiles: those with normal AD biomarkers (no colour), those with non-AD pathologic change (dark grey) and those who are in the Alzheimer's continuum (light grey)

1.4. Preclinical stages: novel battlefield in Alzheimer's disease

While it is expected that these latest recommendations will be reviewed in the future, there is an undeniable shift in focus from clinical stages of AD to preclinical stages of AD.

Current gold standard for AD treatment relies on AChEI. Despite short-term improvement on cognitive function, these drugs do not prevent patients from progressing towards advanced stages of the disease [243, 244]. Major efforts and resources have been invested in the development of disease-modifying treatments for AD. From 2002 to 2012, 413 AD trials have been conducted. However, the failure rate of these trials was 99.6% and to date there are no approved disease-modifying therapies in AD [245]. Noteworthy, most of the trials focused on advanced stages of the disease where irreversible neuronal loss has already occurred. Targeting early phases of the disease would provide an unique opportunity to halt the progression towards irreversible neuronal damage [246-248]. The move is worth a try: recent forecasting models suggest that a delay of 1 year in the diagnosis of AD can significantly reduce the global disease burden [249].

Successful experience in early stage interventions and therapies in chronic conditions such as diabetes and hypertension should be used as stepping stones for preclinical AD interventions [250-253]. Yet, the prerequisite towards the development of intervention strategies in preclinical AD will depend on our capacity of identifying individuals in these stages. In AD, there are limitations associated with currently validated biomarkers in preclinical stages. Indeed, a study reported that the difference in amyloid β between brains of AD patients and brains of healthy controls was very small and approximated 5 mg. An increase of only 2-5% in amyloid deposition was sufficient enough to induce a shift to AD in healthy controls [206]. Therefore, these results imply that PET imaging should be specific enough to detect a slight change in amyloid deposition in healthy individuals. However, currently used thresholds in imaging techniques for amyloid detection such as ^{18}F amyloid PET or ^{11}C Pittsburgh compound often classify individuals with very sparse changes in amyloid deposition to "normal" [254-256]. However, post-mortem examination of cognitively unimpaired individuals showing subtle changes in neuropsychological testing revealed the presence of AD related neuropathological changes [257, 258]. Defining an appropriate cut-off is a challenging task as it will require that

the right balance is determined between sensitivity and specificity. Lowering the cut-off for preclinical stages could probably lead to the inclusion of normal individuals. In addition, there is also a need for harmonising current analytical methods used in biomarkers' measurements' which are highly heterogeneous [259].

Another major limitation with some of the current biomarkers is that their measurement relies on invasive methods, since a LP is required to sample CSF, or expose patients to potentially harmful ionising radiation e.g. for a PET scan. Moreover, these acquisition methods are often only available in highly specialised centres and may therefore be less accessible to the wide population. However, evidence collected from diverse population will be needed to help fine-tune biomarker-based detection. Nonetheless, this approach would undoubtedly impose a major financial burden upon health systems. This aspect is non-negligible considering the dramatic rise in healthcare-associated costs in developed countries [260-262].

Lessons learned from prevention program in other conditions such as cardiovascular diseases, show how a cost-effective prevention program in AD should rely on the capacity to identify individuals at risk with a possibly minimally invasive approach, cheap and easily implementable in the community [263].

Among the potential novel biomarkers in AD, miRNAs have attracted increased attention in the last decade.

1.5. miRNA: a small non-coding RNA that regulates gene expression at post-transcriptional level

MicroRNAs (miRNA) are single stranded ribonucleic acids (RNA) of ~18-22 nucleotides which regulate gene expression at post-transcriptional level [264]. MiRNAs were first described 30 years ago in the nematode *Caenorhabditis elegans*. At that time, it was shown that *lin-4*, a developmental regulator, coded for a regulatory RNA consisting of 22 nucleotides. Surprisingly at that time, this RNA was able to base pair with a mRNA involved in the developmental process of *C.elegans* and by this mean, could control the production of the encoded protein [265-267]. Since then, the number of identified miRNA genes has continuously grown. MiRBase, a biological database of miRNA sequences counts more than 2000 annotated miRNAs in humans [268]. *In vivo* and *in silico* studies have shown that a single miRNA is able to regulate the

expression of hundreds of genes suggesting that miRNAs could collectively regulate the expression of one third of the genes in the human genome [269-272].

1.5.1. miRNA biogenesis and target repression

The biogenesis of a miRNA consists of several steps that lead to the conversion of a primary miRNA into a mature miRNA of ~22 nucleotides length. Most miRNA families follow a canonical biogenesis pathway (*Figure 3*) [273]. miRNAs are transcribed from genes located along the genome. The majority of the genes coding for miRNA are non-coding genes, but some miRNAs can also be coded from introns of protein coding genes [274]. A miRNA gene is transcribed by RNA polymerase II and by RNA polymerase III (only a minor fraction) into a primary miRNA transcript (pri-miRNA) [275-277]. A 5' cap and a 3' poly-A tail are added to the transcript, similarly to other protein coding transcripts. Pri-miRNA then binds to a Drosha enzyme, which includes a RNA binding protein DGCR8 [278-281]. Current understanding suggests that DGCR8 is responsible for the identification of the cleavage site while Drosha controls the cleavage of pri-miRNA [282-284]. The product of pri-miRNA cleavage is a stem-loop precursor which is exported from the nucleus to the cytoplasm via Exportin 5 [285-287]. In the cytoplasm, Dicer, an endonuclease containing a RNA binding protein TRBP, releases the mature miRNA by cleaving the loop region of the miRNA precursor [288-291]. This mature miRNA consists of a duplex RNA (consisting of ~21 nucleotides in length, depending on the miRNA). Alternative pathways in the miRNA biogenesis have been described such as mirtron class of miRNAs, which derive from introns, and miRNA biogenesis that occurs independently of Dicer (reviewed here: [292]).

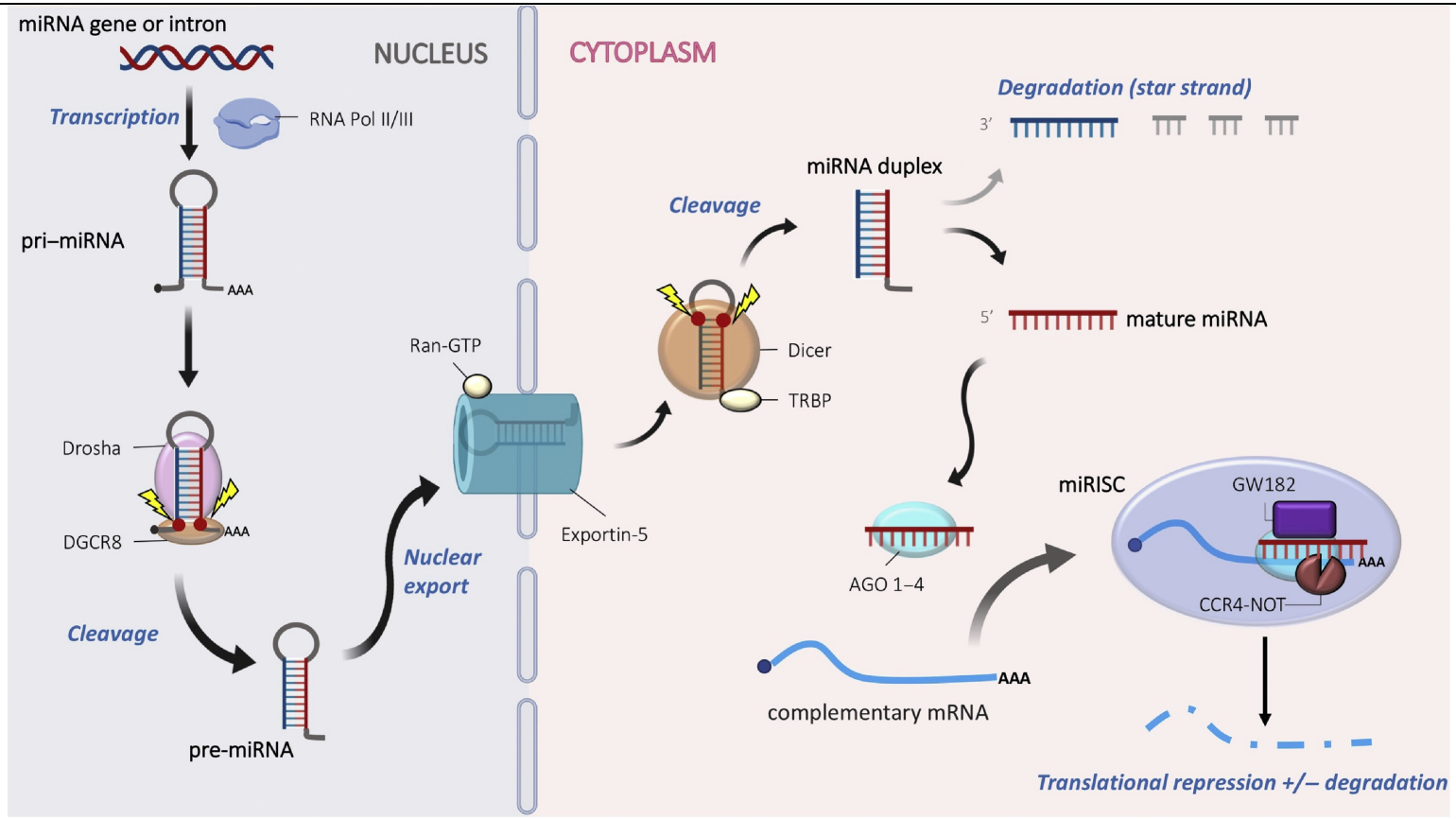
One strand (also called the guide strand) of the duplex RNA is then loaded on the RNA induced silencing complex (RISC) which is composed of Argonaute proteins (Ago 1-4 humans) [293, 294]. The other strand (also called star strand or passenger strand) is then either cleaved by Ago 2 and the nuclease complex C3PO or by other helicases [295-302]. If the 5'end of the stem loop is integrated, this strand will be referred to the "-5p" strand whereas if the 3' end of the stem loop is integrated, this strand will be referred to the "-3p" strand.

Finally, miRNA-RISC interacts with mRNA targets depending on the complementarity between the miRNA and the mRNA – in most cases within the 3'untranslated region [303, 304]. The 6-8 nucleotide seed sequence near the 5' terminus of the miRNA has been reported to be the most determinant factor defining the complementarity between miRNA and mRNA target [264].

Repression and degradation of the mRNA target can then occur through different mechanisms: if the miRNA's central region (also called seed region), is complementary to the target mRNA, cleavage can occur via Ago 2 and its endonuclease activity [305, 306]. If, however, this complementarity is absent, then cleavage occurs via GW182. Finally, degradation occurs via complexes such as CCR4-NOT and PAN2-PAN3 which stimulate deadenylation and mRNA degradation [307-309]

It has been shown that target repression does not necessarily involve mRNA degradation. [310-317]. In addition, some RISC independent target repression has been reported. For instance, in one study, miR-328 was not associated with RISC but with a translational regulator poly(rC)-binding protein hnRNP E2 which led to increased translation of the target mRNA c/EBPα [318]. However, compared to the canonical pathways, these pathways remain rare events [319].

Figure 3: Canonical miRNA processing pathway (adapted from [320])



Transcription of miRNA gene by RNA polymerase II/III (RNA Pol II/III) produces a primary miRNA (pri-miRNA) which is cleaved into a pre-miRNA by Drosha and DGR8. This is followed by transport into the cytoplasm via Exportin 5/Ran GTP. A micro-RNA duplex is then produced via cleavage of the pre-miRNA by Dicer/TRBP (TAR RNA binding protein). Only one strand of miRNA is kept (mature miRNA) while the other strand (star strand) is deleted. The complex Ago 1-4/ mature miRNA then binds to a complementary mRNA. The miRNA induced silencing complex (miRISC) represses translation of mRNA which is frequently degraded.

1.5.2. miRNA regulation

The expression of miRNA can be regulated at a transcriptional level [321-324]. For example, the presence of two miRNAs, miR-1 and miR-133 has been particularly reported in cardiac cells. Multiple lines of evidence have shown that their expression in cardiomyocyte is regulated by transcription factor such as SRF, MEF2 and MyoD [325-329]. Post-transcriptional regulation has also been described. For example, in experimental studies, let-7 maturation in embryonic cells is blocked by Lin28, a RNA binding protein that inhibits Drosha and Dicer [330-332]. In addition, recent studies have provided interesting results showing that, depending on the cellular environment, miRNA can induce an increase in target expression. For example, increased expression of TNF-α was reported after miRNA binding to the TNF-α mRNA during cell cycle arrest [333, 334]. Similarly, increased levels of miR-373 were associated with increased levels of their targeted mRNA E-cadherin [335].

1.6. Aims and objectives of this thesis

A wealth of data highlighting the critical role of miRNAs in regulating biological processes has been generated in recent decades (reviewed here: [336, 337]). In parallel, the number of studies reporting dysregulated miRNA expression in a wide range of diseases has also increased substantially, unveiling the potential of miRNAs as non-invasive biomarker of disease which could be used as a diagnostic, progression and therapeutic response marker [338]. While miRNAs have been extensively investigated in cancer research, their role as novel non-invasive biomarker in AD has attracted increasing attention, particularly for preclinical and prodromal stages of AD.

The primary aim of this thesis was to examine/study the relationship between early-stage cognitive decline and miRNA expression levels in blood.

The objectives were

1. To conduct a systematic review and meta-analysis of studies investigating miRNA dysregulation in the brain, blood and CSF of AD patients and prioritise a list of top dysregulated miRNA for each tissue (chapter 2).

2. To explore how the top dysregulated miRNAs in AD affect biological function in the brain by conducting a pathway enrichment analysis (chapter 2).
3. To investigate the expression levels of the previously top prioritised miRNAs in cognitive healthy individuals at various risk for developing cognitive impairment due to AD, using baseline real-time quantitative polymerase chain reaction (RT-qPCR) data from the CHARIOT PRO study (chapter 3).
4. To identify whether single nucleotide polymorphism (SNP) located within the genes coding for differentially expressed miRNAs in individuals showing early signs of cognitive decline, are associated with CSF biomarkers of neurodegeneration using whole genome sequencing data from ADNI (chapter 4).
5. To evaluate the functional consequences of these variants on mediators of AD pathogenesis (chapter 4).

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Chapter 2: Systematic review and meta-analysis of miRNA expression studies in Alzheimer's disease

All work presented in this chapter is my own unless otherwise indicated.

Related publication

Takousis P*, **Sadlon A***, Schulz J, Wohlers I, Dobricic V, Middleton L, Lill CM, Perneczky R, Bertram L. Differential expression of microRNAs in Alzheimer's disease brain, blood, and cerebrospinal fluid. Alzheimers Dement. 2019 Nov;15(11):1468-1477. doi: 10.1016/j.jalz.2019.06.4952. Epub 2019 Sep 5. PMID: 31495604.

*first shared author

2.1. Introduction

The first description of the role of miRNAs in *Caenorhabditis elegans* in 2003 was quickly followed by experimental studies revealing how miRNAs regulate critical processes in neuronal development. First evidence was provided in 2005 where a study in rat neuronal cells showed that neurite growth was stimulated by increased levels of miR-132, which itself was regulated by cAMP-response element binding protein (CREB), a key player in memory formation [1-3]. In the following year, Schratt et al described how miR-134, another brain specific miRNA, represses the expression of *LIMK1*, a protein kinase regulating dendritic spines formation in hippocampal neurons. Perhaps most strikingly, the authors proved that the injection of brain-derived neurotrophic factor (BNDF) counteracted the effect of miR-134 and increased the translation of the *LIMK1* mRNA [4]. Later, a feedback circuity between miRNAs and targeted genes was revealed: in dopaminergic neurons, Pitx3, a transcription factor regulating neurogenesis, induced the expression of miR-133b which then repressed the translation of the *PITX3* mRNA [5]. In parallel, animal studies found that, loss of function of genes coding for enzymes critical for miRNA maturation induced neuronal loss. For instance, altered neuronal architecture with synaptic and dendritic loss as well as neuronal apoptosis were noted in a mouse model with knockout of Dicer, an enzyme that catalyses maturation from pre-miRNA to miRNA by cutting the central hairpin [6, 7].

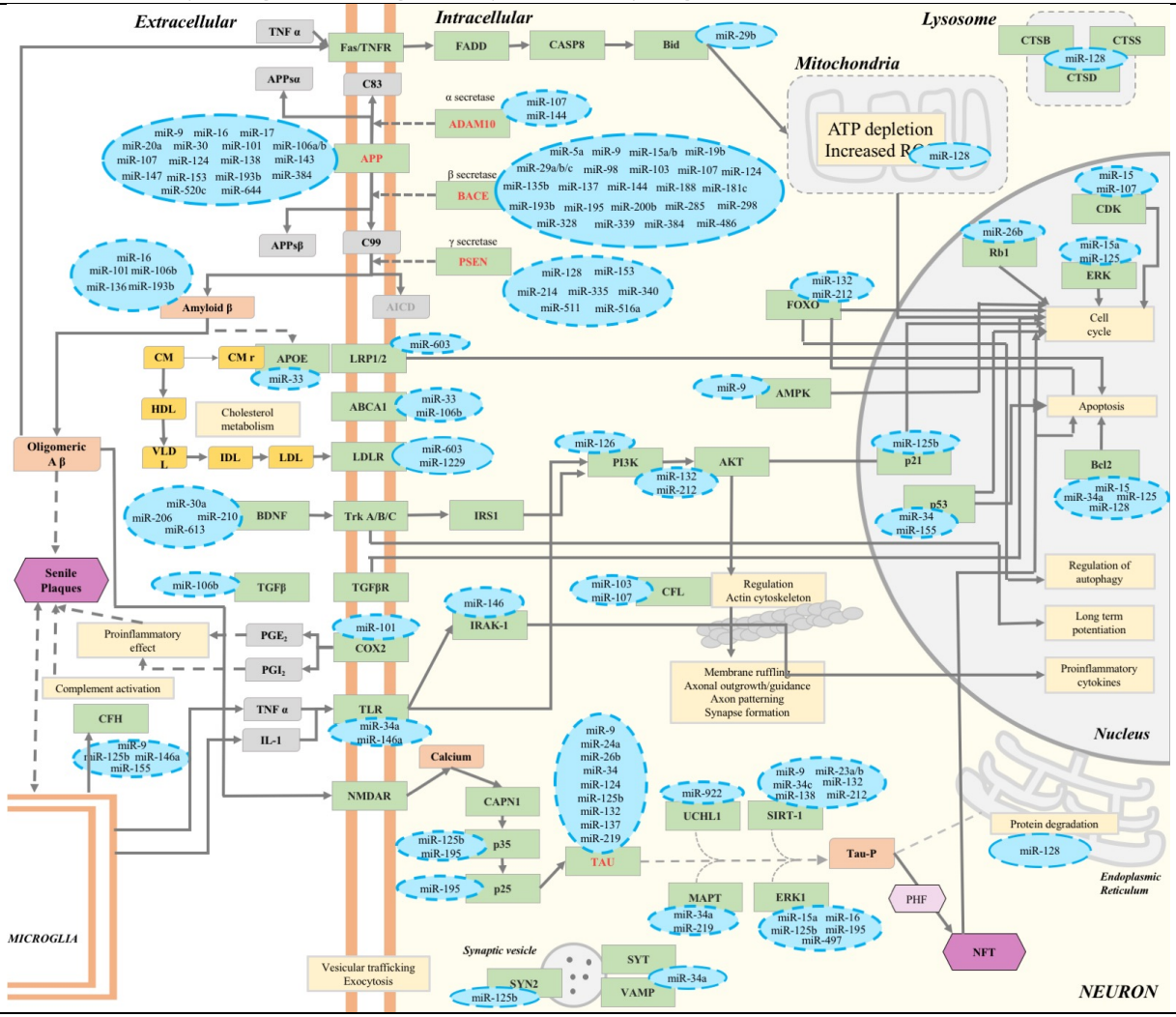
Mounting evidence on the role of miRNAs in maintaining and regulating brain function stimulated research on the effect of miRNAs on amyloid and tau metabolism. In human cortical cells, it was shown that miR-101 and miR-153 reduced the expression of amyloid protein levels [8, 9]. Reports also revealed how miRNAs can influence tau levels by altering the expression of proteins involved in tau degradation. For instance, in rat neuronal cells, miR-128a repressed the expression of *BAG2*, an essential chaperone for ubiquitin independent tau degradation [10]. Since these first descriptions, an exponential rise in studies investigating the role of miRNAs in AD pathogenesis has occurred and has highlighted their involvement in a large number of biological pathways, known to be altered in AD, including apoptotic signalling pathways, inflammatory signalling pathways as well as pathways involved in lipid metabolism (*Figure 1*) [11-19]. Since the early 2000's, the number of referenced miRNAs has dramatically increased; around 2000 confirmed human miRNAs are currently referenced in the latest

version of miRBase, a biological database referencing miRNA sequences and annotations [20]. In parallel, novel gene targets of miRNA are being described using *in-silico* approaches. These techniques use computational methods to predict a miRNA-gene pair based on seed sequences, site conservation, site accessibility, miRNA structure and energetic properties as well as expression analysis [21]. Additionally, recent years have seen the development of machine learning approaches which predict novel miRNA-disease associations [22, 23].

Following the accumulating evidence linking miRNAs to AD pathogenesis, studies conducted in humans, investigating dysregulation of one or several miRNAs in AD patients, were launched. The first study investigated the expression of 12 neuronal specific miRNAs in hippocampal tissues of AD cases and compared it to healthy controls [24]. Since then, a large number of studies have been conducted in different tissue types, using various miRNA quantification methods, from PCR and microarray analyses to next generation sequencing [25-116]. While these studies are valuable in unveiling the role of miRNAs in AD patients, they differ in terms of patient inclusion criteria, tissue type analysed, and methods used to assess the miRNAs expression levels. Moreover, only a few studies validated their findings using other cohorts. Some resources, such as the Human microRNA Disease Database (HMDD), attempt to summarise the evidence on miRNA dysregulation in AD patients, but show limitations as they do not apply a systematic review and do not take into account the sample size or the strength of dysregulation [117]. Yet, prioritising miRNAs among the long list of described dysregulated miRNAs in AD would be a very useful approach for identifying novel biomarkers and therapeutic targets in AD. Recently, P-value based meta-analyses of miRNA expression in diverse conditions such as prostate cancer, nasopharyngeal cancer, breast cancer or epilepsy have emerged as a novel approach combining results from various datasets and eventually providing a list of top differentially expressed miRNAs, for each respective condition [118-121]. Moreover, a recent P-value based meta-analysis for PD highlighted key dysregulated miRNAs in the brain, blood and CSF of PD patients.

In the next section, we aimed at performing a systematic review of original studies investigating miRNA expression in AD patients versus healthy controls using a P-value based meta-analysis. In a further step, I conducted an enrichment pathway analysis of the top prioritised miRNAs in the brain in order to decipher the role played by these miRNAs in biological pathways.

Figure 1: Biological pathways involved in AD pathogenesis targeted by miRNAs dysregulated in AD



MicroRNAs affect the expression of key mediators of AD pathogenesis involved in tau and APP metabolism, signalling pathways, apoptosis as well as mitochondrial and lysosomal function.

Abbreviations: **ABCA1** : ATP-binding cassette subfamily A member 1 , **ADAM10** : ADAM metallopeptidase domain 10, **AKT** : AKT serine/threonine kinase, **AMPK** : adenosine monophosphate-activated protein kinase, **APOE** : apolipoprotein E, **APP** : amyloid β precursor protein, **BACE** : β-secretase , **Bcl2** : B cell lymphoma 2, **BDNF** : brain-derived neurotrophic factor, **Bid** : BH3 interacting domain death agonist, **CAPN1** : calpain 1, **CASP8** : caspase 8, **CDK** : cyclin dependent kinase, **CFH** : complement factor H, **CFL** : cofilin, **COX2** : cyclooxygenase, **CTSB** : cathepsin B, **CTSD** : cathepsin D, **CTSS** : cathepsin S, **ERK** : mitogen-activated protein kinase 1, **ERK1** : mitogen-activated protein kinase 3, **FADD** : Fas associated via death domain, **FOXO** : forkhead box O, **IRAK-1** : interleukin-1 receptor-associated kinase 1, **IRS1** : insulin receptor substrate 1 , **LDLR**: low density lipoprotein receptor, **LRP1/2** : LDL receptor related protein 1/2, **MAPT** : microtubule associated protein tau, **NMDAR**: N-methyl-D-aspartate receptor, **PSEN** : presenilin 1, **Rb1** : retinoblastoma, **SIRT-1** : sirtuin 1, **SYN2** : synapsin II, **SYT** : synaptotagmin, **TGFβ** : transforming growth factor β, **TGFβR** : transforming growth factor β receptor, **TLR** : toll like receptor, **TNFR** : tumor necrosis factor receptor, **Trk A/B/C** : neurotrophic receptor tyrosine kinase 1/2/3, **UCHL1** : ubiquitin C-terminal hydrolase L1, **VAMP** : vesicle-associated membrane protein

2.2. Methods

2.2.1. Type of studies and participants

Studies comparing miRNA expression in AD patients versus healthy controls were included. We decided to exclude studies of patients with familial or monogenic AD. We did not exclude patients who were under anti-dementia therapy.

2.2.2. Literature search strategy

After defining the scope of our systematic review, we conducted an electronic search of Medline (in PubMed) from inception to 24.08.2018 using following search terms "(microRNA OR miRNA OR miR OR micro-RNA) AND Alzheimer*". Search was limited to full text original articles; conference abstracts were not considered. Language was limited to English.

2.2.3. Data extraction

Two reviewers (including myself) screened titles and abstracts independently. In the case of one study being included by one reviewer only, the full text article was assessed for eligibility by the other reviewer. Disagreements and doubts were resolved by consensus. Data extraction was undertaken independently by the two reviewers in an electronic data extraction form. The data items included were: PMID, first author name, institution, sample origin (country and city), number of cases and controls, analytical methods used, tissue type analysed (i.e. brain, CSF, blood), if applicable tissue subtype (i.e. serum, whole blood, peripheral blood mononuclear cells, lymphocytes and monocytes for blood samples or hippocampus, frontal cortex, temporal cortex, cerebellum, parietal cortex, entorhinal cortex, occipital cortex for brain samples), featured miRNAs (i.e. miRNAs which were highlighted by authors in the abstract), miRNA (as reported in the study), direction of dysregulation and P value (unadjusted P values for multiple testing if available and adjusted for age and gender if possible).

2.2.4. Data collection and cleaning

miRNA names were extracted as reported in the included studies. Included studies showed heterogenous ways of reporting the miRNA names. Therefore, we decided to add an additional column entry where all names were aligned to mature miRNA sequences in the miRBase format [20]. In cases where different miRNA names were attributed to the same miRNA mature

sequence (35/3813 entries), we grouped them under one common identifier. This concerned miRNAs hsa-miR-199a-3p/hsa-miR-199b-3p, hsa-miR-365a-3p/hsa-miR-365b-3p, hsa-miR-517a-3p/hsa-miR-517b-3p, hsa-miR-548c-5p/hsa-miR-548am-5p/hsa-miR-548aa-5p and hsa-miR-548aa/hsa-miR-548t-3p. In addition, this format was converted into a miRBase identifier "MIMAT". We excluded expired entries or non-miRNA sequences (e.g. fragments of vault RNA), which were not listed in miRBase.

An additional column identified sample overlap, i.e. samples where the same miRNA was investigated in identical donor groups (based on the origin of the samples, overlapping co-authors or references to previous studies). In this case, we only retained one data entry. Also, in some situations, several tissue subtypes were analysed and compared to the same healthy controls. As with the previous situation, we included only one data entry. Selection was based on two successive steps. First step consisted of keeping the entry with the highest number of subjects. If the number of subjects was identical, we proceeded to the second step where tissue subtype was prioritised. In brain samples, tissue subtypes were prioritised based on Braak staging [122, 123]. In the case of blood samples, we prioritised monocytes in favour of lymphocytes.

In some instances, only truncated P values were reported. We therefore applied a conservative conversion: "p ≥0.05" and "p ≥0.01" were converted to "p=0.5", "p <0.05" to "p=0.025", "p <0.01" to "p=0.005", "p <0.001" to "p=0.0005", "p <0.0001" to "p=0.00005", etc. When additional summary statistics were reported (e.g. mean, median, standard deviation or standard error for cases and controls), exact P values were calculated.

Stouffer's method was applied to conduct the meta-analysis. Briefly, this approach converts P values into signed z scores and combines them using the inverse variance weighting based on the sample size [124, 125]. All analyses were conducted in R Statistical Software (Foundation for Statistical Computing Vienna Austria) using a customized R script. Bonferroni correction for multiple comparisons was applied and a P value ≤ 1.08×10^{-4} was considered as statistically significant (α=0.05/number of entries= $0.05/461=1.08 \times 10^{-4}$).

2.2.5. Featured miRNAs

Studies decided to report some of the significant miRNAs in their abstract. Those miRNAs were identified and extracted. We then compared the study wide ($\alpha=1.08x10^{-4}$) or nominal ($\alpha=0.05$) significant miRNAs obtained through our meta-analysis with the miRNAs "featured" in the abstracts of the included studies, for each specimen type analysed (i.e. brain, CSF and blood).

2.2.6. Pathway enrichment analysis

Following the meta-analysis, I aimed at establishing which biological pathways are affected by the study wide significant dysregulated miRNAs in the brain by conducting a pathway enrichment analysis.

First, I retrieved a list of genes targeted by each of the 25 miRNAs using miRTarBase, a resource referencing experimentally validated miRNA-gene pairs [126]. Then, I constructed two distinct gene lists, one gene list containing all genes targeted by downregulated miRNAs and the other gene list containing all genes targeted by upregulated miRNAs. Then, for each gene list, I performed a pathway enrichment analysis using gene-sets obtained from Gene Ontology biological process (GO BP), Kyoto Encyclopaedia of Genes and Genomes (KEGG) and the Reactome databases [127-129]. Functional enrichment analysis was based on a Fisher's exact test and was undertaken with the g:Profiler package in R [130]. Only gene sets of a minimum of 5 and a maximum of 500 genes were considered. To control for multiple testing, I used the Benjamini-Hochberg False Discovery Rate method with a significance threshold set at a $\alpha \leq 0.05$.

Enriched biological pathways which passed the significance filter, were then uploaded into Enrichment Map, a plugin in Cytoscape v3 [131]. Enrichment Map offers a visualisation method of all the significant gene sets significant after functional enrichment, while considering possible overlapping genes between gene-sets. In this network, nodes represent gene-sets and edges represent overlap between gene sets. The thresholds of the Jaccard and overlap combined coefficients (two values representing the similarity between two sets) were set to 0.225 [131]. Due to the high numbers of enriched pathways, clusters of biological function were manually identified and labelled. Labels were created according to which "parent" category the pathways belonged to in the database. For example, pathways such as *Toll Like*

Receptor TLR6:TLR2 Cascade, *Toll Like Receptor TLR1:TLR2 Cascade*, *Toll Like Receptor 10 (TLR10) Cascade*, *Toll Like Receptor 7/8 (TLR7/8) Cascade*, *Toll Like Receptor 5 (TLR5) Cascade*, *Toll Like Receptor 3 (TLR3) Cascade*, *Toll Like Receptor 2 (TLR2) Cascade* and *Toll Like Receptor 9 (TLR9) Cascade* were grouped into a cluster "TLR cascade". Nodes were coloured in red, blue or green if the pathway was significantly enriched by the upregulated, downregulated or both up- and downregulated miRNAs gene lists respectively.

For the functional enrichment analysis and the network analysis I applied a previously described analysis protocol [132].

Results are presented as median [IQR].

2.3. Results

2.3.1. Characteristics of included studies

We identified a total of 895 studies through our research in PubMed and excluded 770 records through title and abstract screening. We conducted a full text assessment on 125 studies and excluded 18 of them: nine studies did not include healthy controls, two studies were experimental studies and/or animal only based studies, three studies were reviews, one study did not report a clear number of controls, one study reported no quantitative data, one was a correction of published paper and one study contained missing data. In total, we included 107 studies, which consisted of 147 datasets, among which 60 datasets were brain samples, 53 datasets were blood samples, 32 datasets were CSF samples and two datasets were analysed from anterior nasal mucosa (*Supplementary Table 1*) [25-116, 133-147]. These 147 datasets regrouped 3799 entries. Due to overlap between samples within the same study (i.e. overlap in subtype of tissue analysed) and within different studies, 183 entries had to be excluded.

The total sample size consisted of 7964 individuals, 4135 AD patients and 3829 healthy controls. The median sample size per dataset was 34.00 [16.50-68.00] with 17.00 [8.00-35.50] AD patients and 18.00 [8.00-30.50] healthy controls. We extracted 1121 different miRNAs, among which 73 miRNAs were investigated in at least 10 different datasets. Two miRNAs hsa-miR-125b-5p and hsa-146a-5p were replicated in 28 and 26 datasets respectively. 295 miRNAs

were investigated in at least three independent datasets and were eligible for meta-analysis. Finally, the median number of analysed miRNAs per study was 4.00 [2.00-13.00] with a minimum of one miRNA and a maximum of 539 miRNAs.

2.3.2. Meta-analysis results

We conducted a total of 461 meta-analyses: 260 for brain samples, 66 for CSF samples and 135 for blood samples. The median number of datasets per meta-analysis was 4.00 [3.00-5.00] in the brain, 3.00 [3.00-4.00] in the CSF and 4.00 [3.00-5.00] in the blood. The maximum number of datasets analysed was 19.00, 11.00 and 10.00 in the brain, CSF and blood respectively.

In brain samples, the median total sample size was 42.50 [23.00-85.00], with a median of 20.00 [11.00-46.25] cases and 22.00 [12.00-34.25] controls. A total of 25 miRNAs were significantly dysregulated in AD patients versus controls: 13 were downregulated and 12 were upregulated. 97 miRNAs showed a statistical significance of $P < 0.05$, however they did not pass the multiple correction testing. The most significantly dysregulated miRNA was hsa-miR-125b-5p with a $P=4.13x10^{-13}$; it was reported as upregulated in all 11 meta-analysed studies (*Table 1*).

In CSF samples, the median total sample size was 164.00 [97.75-204.50]. The median number of cases and controls was 79.00 [46.75- 103.00] and 85.00 [52.50- 106.25] respectively. The number of miRNAs statistically significantly dysregulated a study wide significance ($\alpha = 1.08x10^{-4}$) was five, all of which were downregulated. miR-598-3p was the most significantly dysregulated with a $P=3.48x10^{-7}$, and a downregulation across all 4 meta-analysed studies. In addition, 23 miRNAs were dysregulated at a statistical significance of $\alpha < 0.05$ but did not pass the multiple comparison corrected P value significance (*Table 1*).

Finally, the median total sample size was 259.00 [195.00-318.00] in blood samples, 144.00 [108.00-172.00] cases and 117.00 [87.00-144.50] controls. Thirty-two miRNAs were significantly dysregulated ($\alpha=1.08x10^{-4}$): 19 were downregulated and 13 upregulated. The three most dysregulated miRNAs were miR-342-3p ($P=9.16x10^{-24}$), miR-191-5p ($P=4.23x10^{-16}$) and let-7d-5p ($P=9.82x10^{-15}$) (*Table 1*).

We found that five miRNAs were dysregulated at study wide significance level ($\alpha=1.08x10^{-4}$) in both brain and blood samples; hsa-miR-181c-5p and hsa-miR-29c-3p were downregulated in both brain and blood, hsa-miR-363-3p is upregulated in both brain and blood, whereas hsa-miR-125b-5p, and hsa-miR-146a-5p were upregulated in brain and downregulated in blood (*Table 1*).

Table 1. Significant meta-analysis results of differentially expressed miRNAs in brain, CSF and blood in Alzheimer's Disease patients and controls

BRAIN	miRNA	# Total (AD/HC)	# datasets	Differential expression (PMID)		Overall expression	P value
				up	down		
	hsa-miR-125b-5p	122 (64/58)	11	17314675 18434550 18525125 19406203 20347935 22509485 23403535 23462268 24304186 25001178 28947385		up	4.13E-13
	hsa-miR-501-3p	68 (38/30)	4	23403535 24014289 24304186 28137310		up	2.03E-11
	hsa-miR-885-3p	23 (11/12)	3	24304186	23403535 24014289	down	2.86E-11
	hsa-miR-132-5p	57 (27/30)	5	24304186	23403535 24014289 26594146 29523845	down	3.01E-10
	hsa-miR-7-1-3p	23 (11/12)	3	24014289 24304186	23403535	up	5.71E-09
	hsa-miR-138-5p	161 (96/65)	6		27816213 24304186 24014289 24014289 23403535 18434550	down	5.50E-08
	hsa-miR-340-5p	40 (21/19)	4	23403535 24304186	24014289 18525125	down	1.41E-07
	hsa-miR-34a-5p	122 (65/57)	7	22160687 22509485 23462268 23962497 27235866	24304186 18434550	up	1.89E-07
	hsa-miR-195-5p	177 (104/73)	7	18434550 20660113 23403535 24014289 24014289 27816213	24304186	up	3.74E-07
	hsa-miR-129-5p	166 (100/66)	6	18434550	18525125 23403535 24014289 24304186 27816213	down	3.84E-07
	hsa-miR-146a-5p	235 (124/111)	12	18434550 18801740 19406203 20937840 22509485 23462268 24304186 27235866 27929395	23962497 23403535 18525125	up	4.88E-07
	hsa-miR-181c-5p	65 (31/34)	6		26594146 24304186 23403535 21994399 20126538 18434550	down	9.49E-07
	hsa-miR-129-2-3p	161 (95/66)	5	24304186	27816213 26594146 24014289 23403535	down	1.16E-06
	hsa-miR-223-3p	97 (57/40)	5	23403535 24014289 24014289 24304186	18434550	up	1.65E-06
	hsa-miR-454-3p	33 (16/17)	4	22509485 23403535 24014289 24304186		up	4.86E-06
	hsa-miR-363-3p	97 (57/40)	5	23403535 24014289 24014289 24304186	18434550	up	6.57E-06
	hsa-miR-487b-3p	97 (57/40)	5	18434550 24304186	24014289 24014289 23403535	down	7.14E-06
	hsa-miR-323a-3p	97 (55/42)	5	18434550 24304186	27816213 24014289 23403535	down	1.05E-05
	hsa-miR-769-5p	109(62/47)	5	24304186	26594146 24014289 24014289 23403535	down	1.33E-05
	hsa-miR-152-3p	97 (55/42)	5	23403535 24014289 24304186 27816213	18434550	up	1.54E-05
	hsa-miR-455-5p	85 (51/34)	4	18434550 23403535 24014289 24304186		up	1.58E-05
	hsa-miR-488-3p	23 (11/12)	3	24014289 24304186	23403535	up	2.53E-05

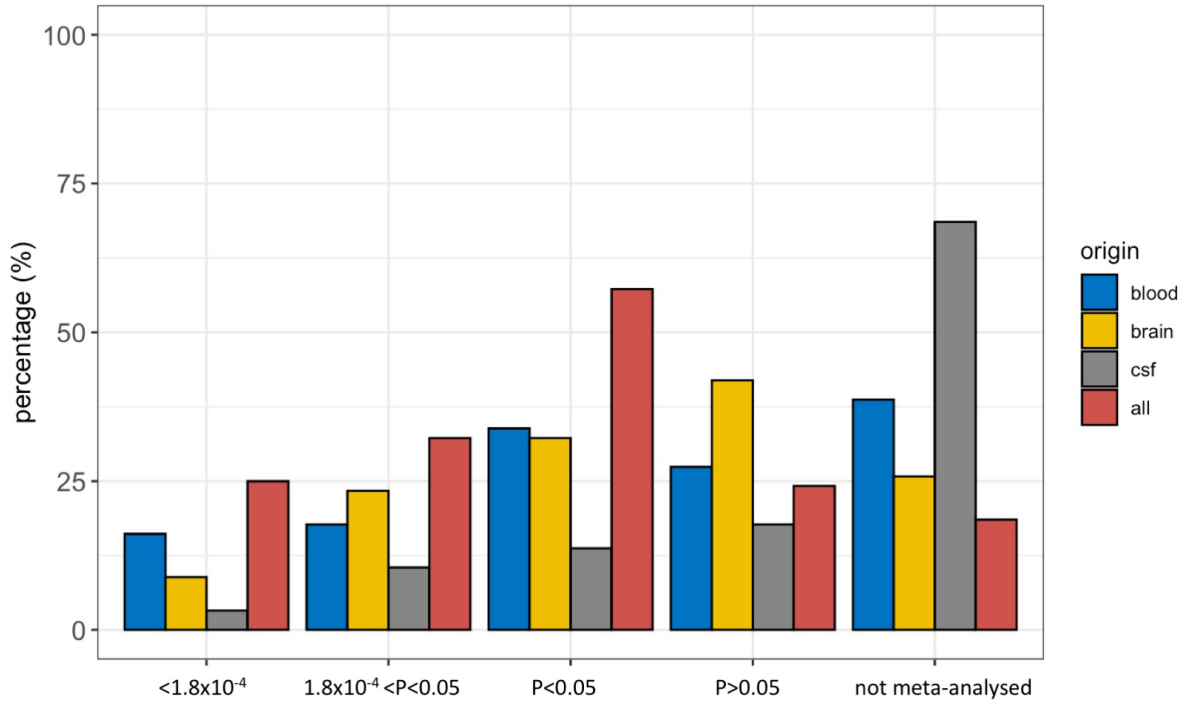
	hsa-miR-29c-3p	**89 (45/44)**	5		18434550 20126538 23403535 24304186 25973041	down	2.65E-05
	hsa-miR-370-3p	**97 (57/40)**	5	18434550 24304186	24014289 24014289 23403535	down	6.23E-05
	hsa-miR-485-5p	**113 (56/57)**	6	18434550 24304186	24014289 23403535 20507594 20507594	down	9.10E-05
CSF	hsa-miR-598-3p	**233 (112,121)**	4		24797360 25992776 28269782 28269782	down	3.48E-07
	hsa-miR-451a	**106 (49,57)**	4		18525125 24212398 25992776 29603092	down	4.86E-07
	hsa-miR-9-5p	**226 (111,115)**	6	22660168	24157723 24212398 24797360 28269782 28269782	down	1.22E-05
	hsa-miR-127-3p	**248 (119,129)**	4		18525125 24797360 25992776 26497684	down	2.79E-05
	hsa-miR-139-5p	**215 (103,112)**	3		24797360 25992776 26402772	down	3.76E-05
BLOOD	hsa-miR-342-3p	**703 (363,340)**	6		23895045 24577456 24577456 25349172 26426747 26806387	down	9.16E-24
	hsa-miR-191-5p	**674 (349,325)**	8	23895045	26078483 25024331 24577456 24577456 23922807 23922807 22155483	down	4.23E-16
	hsa-let-7d-5p	**703 (359,344)**	8	26497032	23895045 23922807 23922807 24577456 24577456 26806387 27631879	down	9.82E-15
	hsa-miR-107	**684 (394,290)**	6		23895045 25024331 25742200 26806387 27501295 29036829	down	4.26E-11
	hsa-miR-425-5p	**164 (97,67)**	3	23895045 26497032 26497032		up	1.73E-10
	hsa-miR-361-5p	**220 (120,100)**	3	23895045 25349172 26806387		up	3.01E-10
	hsa-miR-98-5p	**587 (305,282)**	4		23895045 24577456 24577456 26806387	down	4.19E-10
	hsa-miR-671-3p	**289 (150,139)**	3	23895045 24797360 26806387		up	3.10E-08
	hsa-miR-31-5p	**263 (134,129)**	3		25024331 26078483 26078483	down	3.78E-08
	hsa-miR-5001-3p	**244 (132,112)**	3	23895045 26426747 26806387		up	3.87E-08
	hsa-let-7d-3p	**182 (101,81)**	3	23895045 26497032 26806387		up	7.87E-08
	hsa-miR-93-5p	**568 (299,269)**	7	25349172	23895045 25024331 26078483 26078483 26806387 28626163	down	9.96E-08
	hsa-miR-146a-5p	**662 (349,313)**	9	28626163	23895045 24157723 25024331 26078483 26078483 26806387 27631879 29746584	down	1.21E-07
	hsa-miR-125b-5p	**986 (525,461)**	9	23895045 26806387	27501295 27027823 26426747 25024331 25024331 24157723 24139697	down	3.48E-07
	hsa-miR-26a-5p	**272 (151,121)**	4	23895045 26806387 29746584	25024331	up	5.17E-07
	hsa-miR-181c-5p	**443 (209,234)**	4	23895045	22155483 24139697 26806387	down	7.99E-07

	hsa-miR-144-5p	**212 (118,94)**	3		23895045 26806387 29036829	down	8.95E-07
	hsa-miR-30d-5p	**187 (104,83)**	3	23895045 26806387	25024331	up	1.04E-06
	hsa-miR-128-3p	**296 (159,137)**	5	23895045 24064186 26806387	29036829 25024331	up	1.53E-06
	hsa-miR-210-3p	**255 (130,125)**	4		23895045 25024331 25667669 26806387	down	2.22E-06
	hsa-miR-17-3p	**187 (104,83)**	3		23895045 25024331 26806387	down	2.40E-06
	hsa-let-7a-5p	**195 (108,87)**	4	26497032	23895045 25024331 26806387	down	5.00E-06
	hsa-miR-29c-3p	**327 (176,151)**	5	26497032	23895045 25955795 26806387 28626163	down	6.55E-06
	hsa-miR-363-3p	**212 (118,94)**	3	23895045 26806387	29036829	up	1.08E-05
	hsa-let-7c-5p	**187 (104,83)**	3		23895045 25024331 26806387	down	1.16E-05
	hsa-miR-30a-5p	**116 (73,43)**	3	23895045 26497032	29036829	up	1.39E-05
	hsa-miR-885-5p	**426 (215,211)**	3		24577456 24577456 25024331	down	1.84E-05
	hsa-miR-550a-3p	**182 (101,81)**	3	23895045 26497032 26806387		up	2.49E-05
	hsa-miR-340-3p	**182 (101,81)**	3	23895045 26806387	26497032	up	2.50E-05
	hsa-miR-483-3p	**517 (257,260)**	3		24577456 24577456 26806387	down	3.16E-05
	hsa-miR-26b-3p	**274 (147,127)**	3	23895045 24577456 26806387		up	3.90E-05
	hsa-miR-143-3p	**576 (305,271)**	8	25349172 26497032 29746584	26806387 26078483 26078483 25024331 23895045	down	4.64E-05
Legend: AD = Alzheimer's disease; CSF = Cerebrospinal Fluid; HC = healthy controls; PMID = Pubmed ID							

2.3.3. Comparison of featured miRNAs vs meta-analysis results

One hundred and twenty-four different miRNAs featured in the abstract of articles included in our study, 31 (25.0%) of which were found to be differentially expressed with study-wide significance ($\alpha=1.08x10^{-4}$), and another 40 (32.3%) with only nominal significance ($\alpha=0.05$), while 30 (24.2%) did not have significant differential expression in our meta-analyses. In addition, 23 (18.5%) featured miRNAs were not included in the meta-analysis as they were not investigated in at least three independent datasets. Studies using blood-derived and brain derived specimen included most of the featured miRNAs with 42 (33.9%) and 40 (32.3%) at nominal significance respectively. Noteworthy, we identified 26 miRNAs, which were dysregulated at study wide significance, but were not mentioned in any of the included studies' abstracts (*Figure 2*).

Figure 2: Percentage of featured miRNAs per meta-analysis significance



Each bar represents the percentage of featured miRNAs for each significance level (study wide, nominal, not significant, not meta-analysed) per tissue type analysed.

2.3.4. Pathway enrichment analysis results

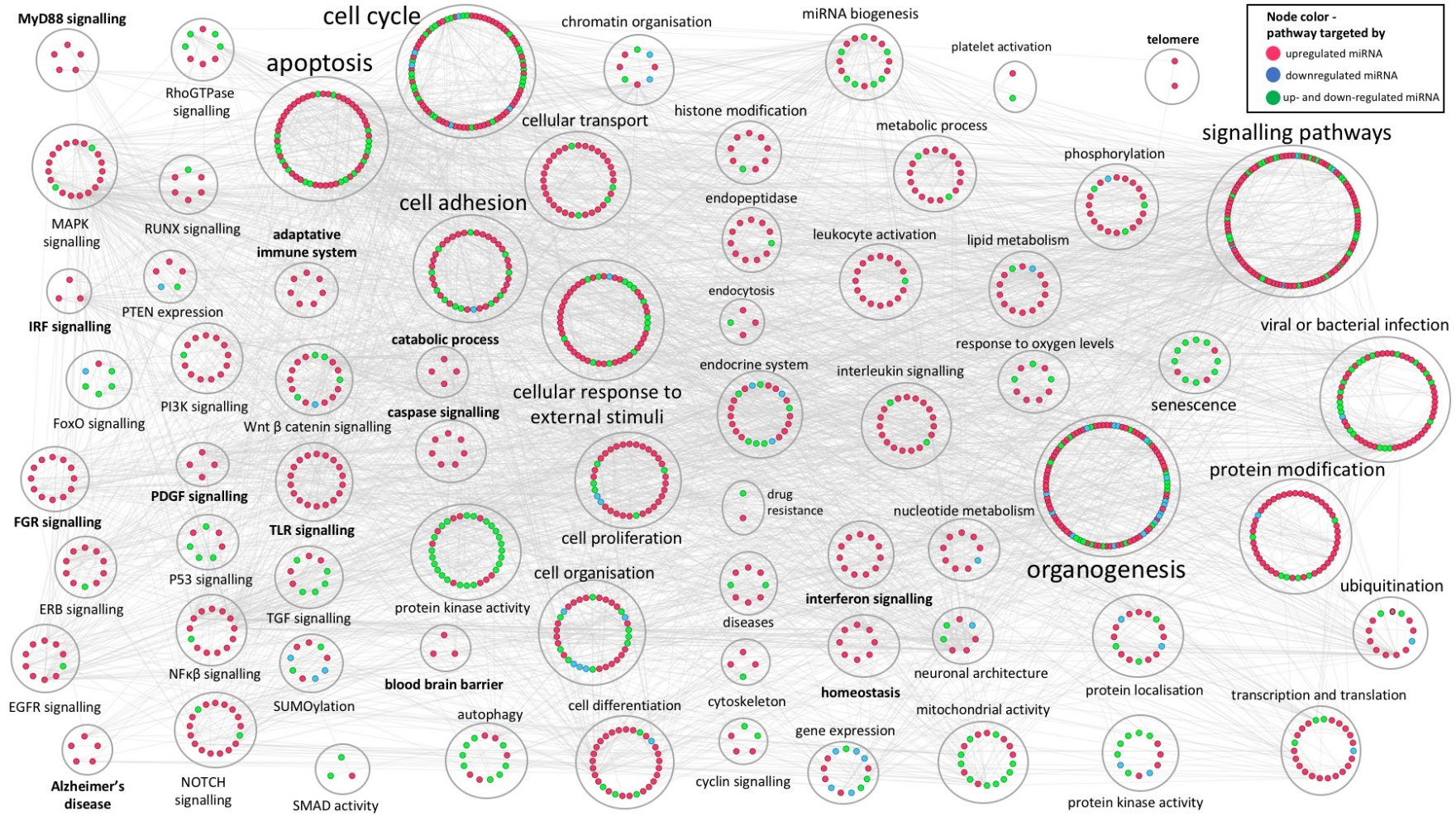
For the 25 significantly dysregulated miRNAs in brain which passed nominal significance (α=1.08 x 10^{-4}), miRTarBase identified 2859 and 2419 experimentally validated targeted genes for the up and downregulated miRNAs, respectively. The median number of target genes was 278.50 [166.20 - 593.50] and 178.00 [101.00 - 367.00] for the up- and downregulated miRNAs, respectively.

In total, 1264 unique pathways were enriched, 907 pathways were enriched by the upregulated miRNAs gene list and 62 pathways for the downregulated miRNAs gene list. In addition, 295 pathways were enriched by both gene lists. The most significantly enriched pathway for the upregulated miRNAs gene list was "protein-DNA complex disassembly"(GO:0032986) (P=1.02x10^{-4}) which involved 12 genes, *SMARCD2, HMGA1, SET, SUPT16H, SMARCD1, MYC, SMARCC2, SMARCA4, SMARCC1, RPL23, ARID1A, GRWD1*. Interestingly, the KEGG gene set "herpes simplex virus 1 infection" (KEGG:05168) was most significantly enriched (P=1.39x10^{-4}) for the downregulated miRNAs gene list and consisted of 100 genes (Table 2 for top enriched pathways and Supplementary Table 2 for all pathways).

Table 2: Top dysregulated pathways by genes targeted by the 25 significant miRNAs in the brain				
Database code	Pathway name	Cluster	P value	direction
GO:0032986	protein-DNA complex disassembly	cell cycle	1.02E-04	up
GO:0002009	morphogenesis of an epithelium	organogenesis	1.08E-04	up
GO:1902275	regulation of chromatin organization	chromatin organisation	1.09E-04	up
GO:0070997	neuron death	apoptosis	1.10E-04	up
REAC:R-HSA-1227986	signaling by ERBB2	ERB signalling	1.11E-04	up
REAC:R-HSA-426486	small interfering RNA (siRNA) biogenesis	miRNA/siRNA biogenesis	1.11E-04	up
REAC:R-HSA-8943723	regulation of PTEN mRNA translation	PTEN expression	1.11E-04	up
REAC:R-HSA-2173788	downregulation of TGF-β receptor signaling	TGF signalling	1.15E-04	up
GO:0030316	osteoclast differentiation	cell differentiation	1.20E-04	up
KEGG:04380	osteoclast differentiation	cell differentiation	1.21E-04	up
KEGG:05168	herpes simplex virus 1 infection	viral of bacterial infection	1.39E-04	down
GO:0022604	regulation of cell morphogenesis	organogenesis	4.85E-04	down
GO:0060284	regulation of cell development	organogenesis	4.85E-04	down
GO:1904886	β-catenin destruction complex disassembly	Wnt β-catenin signaling	5.89E-04	down
GO:0007098	centrosome cycle	cell cycle	1.46E-03	down
REAC:R-HSA-8943724	regulation of PTEN gene transcription	PTEN expression	2.69E-03	down
GO:0048701	embryonic cranial skeleton morphogenesis	organogenesis	3.13E-03	down
GO:0071901	negative regulation of protein serine/threonine kinase activity	protein kinase activity	5.69E-03	down
GO:0043687	post-translational protein modification	protein metabolism	8.00E-03	down
GO:0010464	regulation of mesenchymal cell proliferation	cell proliferation	8.15E-03	Down
Legend: **ERBB2**: Erb-B2 Receptor Tyrosine Kinase 2, **PTEN**: Phosphatase And Tensin Homolog, **TGF**: Transforming Growth Factor				

Enriched pathways were grouped into 69 different clusters of biological function. The clusters related to signalling pathways and organogenesis regrouped the highest numbers of pathways with 111 and 96 respectively. Strikingly, 11 clusters contained pathways enriched only by the upregulated miRNAs gene list suggesting that these biological functions are particularly repressed in AD. Of these clusters some were related to inflammatory response, such as TLR and interferon signalling or adaptive immune system activation, others to caspase signalling. No biological cluster was only enriched by the downregulated miRNAs gene list. (*Figure 3*).

Figure 3: Enrichment map of the pathways enriched by genes targeted by up- and downregulated miRNAs



Legend: ERK: extracellular signal regulated kinase, IL: interleukin, MAPK: mitogen-activated protein kinases, MyD88: MYD88 Innate Immune Signal Transduction Adaptor, PTEN: Phosphatase and tensin homolog, SMAD: fusion of Sma genes of *Caenorhabditis elegans and Mad genes*, Mothers against decapentaplegic from Drosophilia, SUMO: small ubiquitin modifier, TGF: transforming growth factor.

2.4. Discussion

After a systematic review, a P-value based meta-analysis of 107 studies identified 25, 32 and 5 dysregulated miRNAs in AD at study wide significance in the brain, the blood and the CSF respectively. Also, we identified 26 miRNAs which were not reported as significant in the abstracts of the included papers. Finally, I conducted a pathway enrichment analysis for the list of genes targeted by miRNAs dysregulated at study wide significance in the brain of AD patients. This showed that these miRNAs target experimentally validated genes, which regulate among others biological pathways related to intracellular signalling and inflammatory response.

The meta-analysis revealed that miR-125b-5p was the most significant dysregulated miRNA in AD patients compared to healthy controls. Most importantly, all of the 11 meta-analysed studies including miR-125b-5p reported an upregulation in AD patients hereby confirming numerous reports from experimental studies linking miR-125b to AD pathogenesis. miR-125b is largely expressed in the brain and is pivotal during brain development [148, 149]. However, in the postnatal period, miR-125b was reported to stimulate apoptosis by targeting genes of the cyclin dependent kinase 5 and p35/25 pathways [144]. Moreover, in rat neurons injected with Aβ, miR-125b inhibited neurite outgrowth and increased the levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL6) by decreasing the expression of the transcription factor FOXQ1 [150]. In the line with these results, upregulation of miR-125b in AD likely stimulates neuronal apoptosis and induces the release of pro-inflammatory markers. miR-125b was also reported to stimulate tau hyperphosphorylation by upregulating Cdk5/p35 and repressing two phosphatases, DUSP6 and PPP1CA, in hippocampal rat neurons [151]. These findings highlight the critical role of miR-125b in the pathogenesis of AD and opens the discussion on miR-125b as a novel target for AD therapy. This is suggested by a recent study revealing how overexpression of a long non-coding RNA MALAT1, by repressing miR-125b expression, reduced the levels of IL-6 and TNF α and increased neurite outgrowth [152].

Interestingly, I found that 11 clusters of biological function grouped pathways targeted only by upregulated miRNAs. Three clusters were related to inflammatory response, with interferon

and TLR signalling. Despite results from GWAS linking inflammatory genes variants such as TREM2 to increased risk for AD, the complex interplay between inflammatory response and neurodegeneration is yet to be fully understood [153]. TLR4, a member of the TLR family perfectly exemplifies the difficulty in disentangling the effects of inflammatory mediators in AD. Numerous reports show that stimulation of TLR4 by Aβ leads to microglia activation, release of pro-inflammatory markers and neuronal loss (reviewed here: [154]). However, TLR4 signalling may change over the course of the disease resulting in decreased microglial Aβ clearance over time [155]. Moreover, a regulatory feedback between TLR4 and TREM2 expression was described in BV2 cells and AD mouse models where overexpression of TREM2 led to downregulation of TLR4 [156, 157]. Therefore, it is possible that upregulated miRNAs may have decreased TLR4 signalling hereby increasing the expression of TREM2. The consequences of altered TREM2 expression on microglial cell although intensively investigated in the last decades remains yet to be fully understood. Indeed, latest evidence postulates that TREM2 function may vary over the course of the disease, with a neuroprotective role at early stages and neurotoxic role at later stages of the disease [158].

A signalling cascade can be regulated through a feedback mechanism, it is therefore possible that upregulation of a downstream component may exert a negative feedback on the upstream component. This may explain why signalling pathways such as the mitogen-activated protein kinase (MAPK), Forkhead Box (FOXO), RUNX, phosphoinositide 3-kinase (PI3K) pathways are enriched for both up- and downregulated miRNAs targeted gene lists. The MAPK signalling cascade provides a good example of possible interplay between upregulated and downregulated miRNAs. Overactivation of *MAPK* is reported in AD brains where it increases tau phosphorylation, reduces neurite outgrowth, stimulates Aβ formation and induces apoptosis [159]. Most importantly, Aβ deposition can further activate the MAPK signalling pathway, thereby fuelling a vicious circle (reviewed here: [160]). Consequently, downregulated miRNAs may lead to an overactivation of components of the MAPK signalling cascade. Conversely, upregulated miRNAs may increase the repression of downstream mediators, such as MKP-1, which would normally exert a negative feedback within the cascade. MKP-1 is a phosphatase that dephosphorylates tyrosine and threonine residues; it has been associated with increased Aβ formation, impaired long-term potentiation and altered cognitive function in AD mice models [160]. MKP-1 inhibits ERK, another component of the MAPK cascade, which

is positively correlated with Aβ deposition in AD brains (reviewed here: [161]). As such, it is possible that upregulated miRNAs reduce the expression of MKP-1, which leads to an increase in ERK levels while in parallel, downregulated miRNAs lead to a further increased expression of ERK thereby contributing to a vicious circle leading to neurodegeneration.

My functional pathway enrichment analysis shows that the gene set related to herpes simplex virus 1 (HSV-1) infection was highly enriched by the downregulated miRNAs targeted genes list. This finding is interesting as the link between HSV-1 and AD has been the source of intense debate. The first hypothesis of an association between HSV-1 reactivation and AD pathology was put forward by Ball in 1982 and was based on anatomopathological reports noting an overlap between CNS regions affected by HSV-1 reactivation and AD [162]. Since then, numerous reports describing increasing HSV-1 load in AD brains have corroborated this hypothesis [163, 164]. Also, experimental findings in mice models found increased amyloid deposits, tau hypersphosphorylation and neuronal loss in regions with HSV reactivation [165, 166]. Therefore, it is possible that downregulation of miRNAs normally repressing herpes replication may stimulate HSV replication and catalyse or at least accentuate further amyloid deposition or tau hyperphosphorylation. Undoubtedly, experimental findings are needed to further explore the association between downregulated miRNAs in AD brains with HSV reactivation in the brain.

Five miRNAs were dysregulated in the brain and the blood with miR-363-3p, miR-29c-3p and hsa-miR-181c-5p showing the same overall direction of dysregulation, while hsa-miR-125b-5p and hsa-miR-146a-5p showed opposite direction. These results suggest that dysregulation in the blood and the brain may not be in the same direction. Similar situation is observed for Aβ, which is increased in AD brains but decreased in the CSF, due to reduced clearance in AD brains. Future work will need to explore the importance of the clearance of miRNAs in brain tissues and the role of the blood brain barrier.

When comparing our results with miRNAs featured in the abstracts of the included papers, we identified 26 miRNAs which passed study wide significance in the meta-analysis but were not mentioned in the abstracts. However, many of these miRNAs are involved in biological pathways altered in AD pathogenesis. For instance, hsa-miR-132-5p, which shows an overall

downregulation, is involved in neurite growth and synaptic function [167-169]. Moreover, inhibition of miR-132 expression reduces the expression VE-cadherin, which is essential in maintaining blood brain barrier (BBB) integrity [170]. Notably, disruption of this BBB is described in AD pathogenesis [171]. Another interesting miRNA is hsa-miR-488-3p as it represses the expression of POMC, a mediator of the hypothalamic-pituitary-adrenal axis [172]. POMC is cleaved into α-melanocyte stimulating hormone, which activates the melanocortin 4 receptor (MC4R); the latter was reported to increase synaptic plasticity and long term potentiation [173]. Interestingly, we found that hsa-miR-488-3p is upregulated in AD brains suggesting that repression of POMC is increased and results in reduced activation of the MC4R. Interestingly, a search in HMDD v3, shows that 33 (58%) of the study wide significant miRNAs from the meta-analysis are not listed under the significant miRNAs in AD. All in all, our approach confirms the need for a systematic review and meta-analytical approaches when considering prioritising miRNA for particular diseases. Moreover, it highlights limitations of the growing number of studies that use machine learning approaches to predict miRNA-disease associations by training their model on databases such as HMDD and it advocates for further experimental validations of these *in silico* findings [174-176].

Finally, it is important to consider that miRNA dysregulation measured in AD brains could also represent the consequences of neurodegeneration and neuroinflammation. For instance, miR-181c, which showed an overall downregulation in the meta-analysis, is downregulated by the presence of Aβ [177]. Furthermore, it is now well established that transcription factors (TF) and miRNAs can regulate each other in a so called feed forward loop. In recent years, a wealth of data highlights the importance of feed forward loops in the development of diseases, such as schizophrenia or cancer [178-180]. At the same time, numerous studies report that Aβ and tau may affect the expression of TF, some of which may potentially alter the expression of miRNA genes [181-183]. For instance, injection of Aβ42 inhibited the activation of CREB, a TF critical for neuronal functioning [184]. Noteworthy, this TF was shown to increase miR-132 expression the brain [185]. In this respect, we found an overall downregulation of miR-132 in AD brains suggesting that accumulating Aβ42 deposits in AD brains may have resulted in decreased CREB expression which in turn downregulated miR-132 expression. Overall, these findings suggest that dysregulated miRNAs in AD may not only be the driver of the pathogenetic changes but also the consequences of it.

Results presented in this chapter are associated with some limitations. The included studies differed in terms of analytical method and platform used to measure the miRNA, which could have led to heterogeneity in our results. In addition, the sample population was highly heterogeneous. While we tried to always include the most advanced stages of the disease, some studies did not specify the stages of the AD disease. Moreover, we did not exclude individuals which were under AD treatment. However, it was shown that some miRNAs such as miR-132 can interact with acetylcholinesterase in the brain [186]. Therefore, it is possible that the use of AChEi may have altered the expression of miR-132. Finally, effect sizes were summarised as up-regulated or downregulated; due to the inconsistencies in reporting and the heterogeneity of analytical methods used, we did not have more detailed information on the magnitude of dysregulation and the standard error of that effect. Furthermore, the pathway enrichment analysis is associated with several limitations. First, although miRNA-gene pairs have been experimentally validated, the findings may have been obtained from non-neuronal cells. Second, it is possible that genes not involved in brain function may have been included in the pathway enrichment analysis resulting in the identification of pathways which are not related to AD pathogenesis. Third, gene sets referenced in KEGG, GO and REACTOME are either manually curated or obtained through data mining. Although I used the most updated version of each database, it is possible that latest evidence in the literature linking a miRNA to a particular gene is pending consideration. Finally, clustering of the 1264 enriched pathways was done manually following a systematic approach which consisted in grouping the pathways into the first parent category. Nevertheless, considering that some pathways may participate in different biological functions, it is possible that some pathways could as well have been classified in another cluster.

2.5. Conclusion

This section identifies a set of dysregulated miRNAs in the brain, blood and CSF of patients with AD. Moreover, it highlights potential pathways which may be altered by genes targeted by these miRNAs. Results obtained in this section further raise interest towards miRNA dysregulation in AD. Investigating the expression of these miRNAs in the blood of individuals

with early cognitive decline would offer a valuable insight and a promising asset to identify and characterise individuals at risk of progression towards more advanced stages of the disease, using a minimally invasive method. It would also unveil underlying molecular mechanisms involved in the transition towards neurodegeneration and the onset of clinical symptoms.

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Chapter 3: miRNAs as biomarker for cognitive decline in the CHARIOT-PRO cohort

3.1. Introduction

In the previous chapter, a meta-analysis of 107 studies investigating dysregulated miRNAs in AD patients prioritised 32 miRNAs in the blood of AD patients. Interestingly, numerous reports from experimental studies show that these miRNAs, albeit reported as dysregulated in the blood, target genes involved in early stages of AD pathogenesis. For instance, miR-191, which shows an overall downregulation across the meta-analysed studies, was reported to stimulate long term depression (LTD) in synapses [1]. LTD is critical in maintaining visual recognition memory, a cognitive domain impaired early in AD [2]. The meta-analysis also revealed overall downregulation of miR-146a in the blood of AD patients. This miRNA represses the expression of neurofilament light chain (NfL), a marker of neurodegeneration elevated in *APP*, *PSEN1* or *PSEN2* mutation carriers several years before the onset of the first symptoms [3, 4]. Another downregulated miRNA, miR-125b, was shown to reduce the expression of Sphingosine kinase 1 (SphK1), an enzyme linking lipid metabolism to inflammation in AD [5]. Notably, reduced levels of SphK1 are already noted at early stages of AD and recent findings suggest that SphK1 is a key mediator between amyloid deposition and inflammatory response [6]. Indeed, in *APP/PS1* mice, Aβ injection reduced expression levels of SphK1, which resulted in a change in microglial phenotype and in the release of anti-inflammatory markers such as IL-4, TGF-β and Arg1 [7]. Several *in vivo* studies report that inflammatory proteins and markers of microglial activation are already expressed at early stages of AD. Increased CSF levels of soluble triggering receptor expressed on myeloid cells (sTREM2), a marker of microglial activation, were already measured in individuals with subjective cognitive decline compared to healthy controls [8]. Most importantly, longitudinally studies showed that increased pro-inflammatory cytokines levels in the CSF and plasma at preclinical to prodromal stages are associated with an increased risk for cognitive decline. In 169 individuals with preclinical AD, consistent increase in YKL-40, another marker of microglial activation, was associated with significant cognitive decline longitudinally [9]. Similarly, in the BIOCARD study, which included 191 cognitive healthy participants, increased baseline plasma levels of TNFR1, a pro-inflammatory cytokine, were significantly associated with an increased risk for progression from normal cognition to MCI within 7 years [10]. These results confirm early findings reporting that MCI patients, who had increased TNFR1 and TNFR2 levels in the plasma and CSF, had increased risk for developing AD

after 6 years [11]. Consequently, it is likely that some of the previously prioritised miRNAs in the blood of AD patients are already dysregulated in early stages of the disease, where they initiate the first pathological changes leading to neuronal loss.

Measuring these miRNAs in individuals at prodromal stages would offer new insights into the early pathogenic changes of AD. Recently, six differentially expressed miRNAs were identified in the CSF of 30 individuals with prodromal Huntington disease (HD). Noteworthy, these miRNAs were different from those identified in post-mortem samples, hereby suggesting that dysregulated miRNA expression at prodromal stages may reflect different ongoing pathogenic changes [12]. While these findings opened a new therapeutic avenue for HD, they also corroborate the hypothesis that changes in miRNA expression profile during the course of the disease, may reflect different stages in the disease severity. This was particularly suggested in cancer studies reporting that some miRNAs regulate the transition from local tumour development to lymph nodes' or other organs' metastases. For instance, in an animal model of breast cancer, upregulated expression of miR-31 was associated with ability to metastasise in the lung, while in another experimental mouse model of breast cancer, experimental downregulation of miR-10b through the administration of a miR-10b antagomir inhibited metastasis [13, 14]. Some miRNAs may also show the same dysregulation during the entire disease. In Parkinson's disease (PD), downregulation of miR-19b was reported as early as 5 years before the conversion to PD or Lewy Body disease in the blood of patients with idiopathic rapid eye movement sleep behaviour disorder [15]. Considering that this same miRNA was reported to be downregulated in another cohort of PD patients, miR-19b is suggested as a potential blood based biomarker for prodromal α-synucleinopathies [16].

While more than 100 studies to date have compared expression levels of miRNAs in AD patients versus healthy controls, rare studies have investigated whether miRNAs can predict progression from MCI to AD. In a small 2-year long longitudinal study of 30 participants, increased expression of miR-206 was reported in the plasma of individuals with MCI converting to AD compared to the cognitively stable participants [17]. In another recent study, MCI participants converting to AD within 2 years showed increased baseline expression levels of miR-146a and miR-181a compared to patients who remained cognitively stable [18].

So far, to our knowledge, no study has investigated our previously prioritised dysregulated blood miRNAs in individuals showing subtle cognitive changes. Yet, this would undoubtedly highlight possible novel non-invasive biomarkers for the detection of individuals with early

cognitive changes. In this chapter, I took advantage of the CHARIOT PRO study, a cohort of cognitively healthy older individuals, to investigate the expression profile of the 32 miRNAs prioritised from blood of AD patients using RT-qPCR analysis. In addition, I added 6 of the top dysregulated miRNAs in AD brains.

3.2. Material and methods

3.2.1. Subjects

Subjects were part of the CHARIOT PRO (Cognitive Health in Ageing Register: Investigational, Observational, and Trial studies in dementia research: Prospective Readiness cOhort study). The main study recruited cognitive healthy participants over the age of 60, at different levels of risk of progression towards MCI due to AD. These participants volunteered to participate and were referred by surgeries of General Practitioners in Primary Care in West London. Data and blood sample collection were obtained at baseline and every 6 months thereafter until study termination. Informed consent was obtained from each participant during the baseline clinic visit. Further details of the study can be found elsewhere [19].

3.2.2. Neuropsychological measurements

Cognitive function was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [20]. This test consists of 12 tests which are grouped into five cognitive domains: immediate memory (list learning, story memory), visuospatial/constructional (figure copy, line orientation), language (picture naming, semantic fluency), attention (digit span, coding), and delayed memory (list recall, list recognition, story memory, figure recall). A total scale is defined by the sum of the individual indices. Raw scores were converted to age based index and total scores based on normative information available in the test manual. The RBANS score has been validated in community dwelling individuals and is used as a screening tool for dementia in clinical practice but also in trials investigating novel therapies [21].

Using the RBANS score, two performance groups were defined based on previous evidence from the literature suggesting a cut-off of 1.5 standard deviation (SD) below the mean to define

mild-cognitive impairment [22]. As I was targeting individuals at preclinical stages, i.e. before the onset of overt clinical symptoms, I chose a cut-off of 1 SD: lower performance was defined as < - 1 SD on the total RBANS scale and normal performance as ≥ - 1 SD on the total RBANS scale.

3.2.3. qPCR analysis

Blood specimens were collected in PAXgene Blood RNA Tubes. Following steps were performed by QIAGEN, a company specialising in PCR diagnostics. First, total RNA (including miRNA) was extracted using the QIAsymphony PAXgene Blood RNA Kit on the QIAsymphony SP, an automated sample preparation platform, which performs all steps of the RNA extraction procedure; 72 samples, in 3 batches of 24, were processed per run. Then, RNA samples were quantified by spectrophotometry (Nanodrop) and quality assessed by gel densitometry (Agilent TapeStation). Then, reverse transcription of 10 ng RNA in 10 µl reactions was performed using the miRCURY LNA RT Kit (QIAGEN). cDNA was diluted 100 x and assayed in 10 µl PCR reactions according to the protocol for miRCURY LNA miRNA PCR. Each miRNA was assayed once by qPCR on the miRNA Ready-to-Use PCR Custom panel using miRCURY LNA SYBR Green master mix. Finally, the amplification was performed in a LightCycler 480 Real-Time PCR System (Roche) in 384 well plates. The amplification curves were analysed using the Roche LC software, both for determination of Ct (by the 2nd derivative method) and for melting curve analysis.

The panel consisted of 32 miRNAs which were reported to be significantly dysregulated in the blood of patients with AD compared to healthy controls and 6 of the top dysregulated miRNAs in AD brains [23]. I added 8 miRNAs reported to be stable in qPCR analysis of blood samples as endogenous controls: hsa-miR-150-3p, hsa-miR-16-5p, hsa-miR-92a-3p, hsa-miR-15a-3, hsa-miR-27b-3p, hsa-miR-21-3p, hsa-miR-19a-5p and hsa-miR-19a-3p [24]. UniSp3 and UniSp6 were used as spike-in to control for the reverse transcription efficiency.

3.2.4. Quality control and normalisation procedure

According to the manufacturer recommendations, I replaced Ct values > 35 or Ct values reported as N/A by 35 in order to minimise the effect of high quantification cycle values. For each miRNA the percentage of samples with Ct values > 35 was calculated. Any miRNA with Ct values ≥ 35 in over 50% of the samples was removed as recommended in the literature [25].

Then I used the geNorm algorithm to identify the most stable miRNAs. In a study investigating the best normalisation method to apply for miRNA profiling with qPCR, the geNorm algorithm performed better than other normalisation methods such as NormFinder or the global mean calculation [25]. Briefly, geNorm calculates a M value for each miRNA; this represents the stability in miRNA expression across the samples with a high M value corresponding to a least stable miRNA. At each step of the process, the miRNA with the highest M value is excluded. At the end, a ranking of the most stable miRNAs is provided. A pairwise variation allows identifying how many housekeeping genes are necessary for normalisation. In a last step, a pseudo-housekeeping gene, defined as the geometric mean between the most stable housekeeping genes, is subtracted from each remaining miRNA for each sample [26]. Finally, Ct expression values were converted in fold change using equation 1. The package NormqPCR in R was used for the quality control and normalisation [27].

Equation 1

Fold change = $2^{-\Delta\Delta Ct}$.

3.2.5. Statistical analysis

Statistical analysis was performed using R. Distribution of continuous variables was examined for normality using Shapiro-Wilk test and transformed when appropriate. Baseline characteristics were described as mean ± standard deviation (range) for normally distributed variables, and median [IQR] (range) for non-normally distributed variables.

For continuous variables, differences between performance groups were assessed by using Student's t-test for parametric testing and Mann-Whitney for non-parametric testing. Chi-square test was used for categorical variables.

Partial correlation adjusted for age and gender was used to measure the relationship between the miRNAs concentration and RBANS scores. Pearson correlation was used for normally distributed variables and Spearman correlation for non-normally distributed variables. I further applied a linear multiple regression analysis to ascertain the independent effects of

miRNA concentration on RBANS index scores and total scores while adjusting for age, sex, education years, ethnicity and *APOE* ε4 carrier status.

Differences in miRNA concentrations between the two performance groups at baseline were analysed using an analysis of covariance (ANCOVA) while adjusting for age, sex, education years and *APOE* ε4 carrier status. For the significant miRNAs, a receiver operating characteristics (ROC) curve was constructed and area under the curve (AUC) calculated to identify the performance of each miRNA in discriminating between the different groups.

In order to account for the analyses of multiple miRNAs, P values were adjusted for multiple comparisons using the false discovery rate (FDR). Significance level was set at $\alpha < 0.05$.

For the statistical analysis, ethnicity and *APOE* genotype were converted into binary variables (white=0, other ethnicities=1; *APOE* genotypes ε3/ε4 or ε4/ε4 = 1, other *APOE* genotypes = 0)

3.2.6. Pathway enrichment analysis

I conducted a functional enrichment for the miRNAs showing a significant differential expression in the blood of lower versus normal RBANS performers.

I applied the same strategy for the identification of miRNA gene pairs as in Chapter 2. Briefly, miRNA targeted genes pairs were retrieved in the latest version of miRTarBase (8.0) [28]. Then, using the Human Protein Atlas, which provides RNA and protein expression data by tissue and cell type, I extracted sets of genes expressed in the brain [29].

In a second step, I conducted a functional enrichment in Gene Ontology, KEGG and REACTOME, three databases referencing list of genes involved in a particular biological pathway (so called gene sets) [30-32]. I decided to focus on genes reported to be highly expressed in the brain according to the Human Protein Atlas as this would help me gaining a further understanding of the biological pathways in which the targeted genes are involved in the brain. Only gene sets of a minimum of 5 and a maximum of 500 genes were considered. I controlled for multiple testing by using the Benjamini-Hochberg-False-Discovery-Rate method. Significance threshold was set at a $\alpha \leq 0.05$.

Grasping the biological meaning behind the myriad of enriched pathways can be challenging. In this regard, network graphs provide a valuable tool to visualise complex relationship between pathways and to identify clusters of biological function. Additionally, these graphs can be used to highlight pathways targeted by several miRNAs, or biological clusters unique to a single miRNA. Like in my previous chapter, I used the plugin Enrichment Map in Cytoscape to visualise an overlap between the statistically significant enriched gene sets for each miRNA [33]. Briefly, in this network, nodes represent gene-sets and edges represent overlap between gene sets. The Jaccard and overlap combined coefficient threshold was set to 0.225. Nodes were coloured based on whether the pathway was enriched by genes targeted by one or several differentially expressed miRNAs. Pathways with similar biological function were grouped into manually identified and labelled clusters.

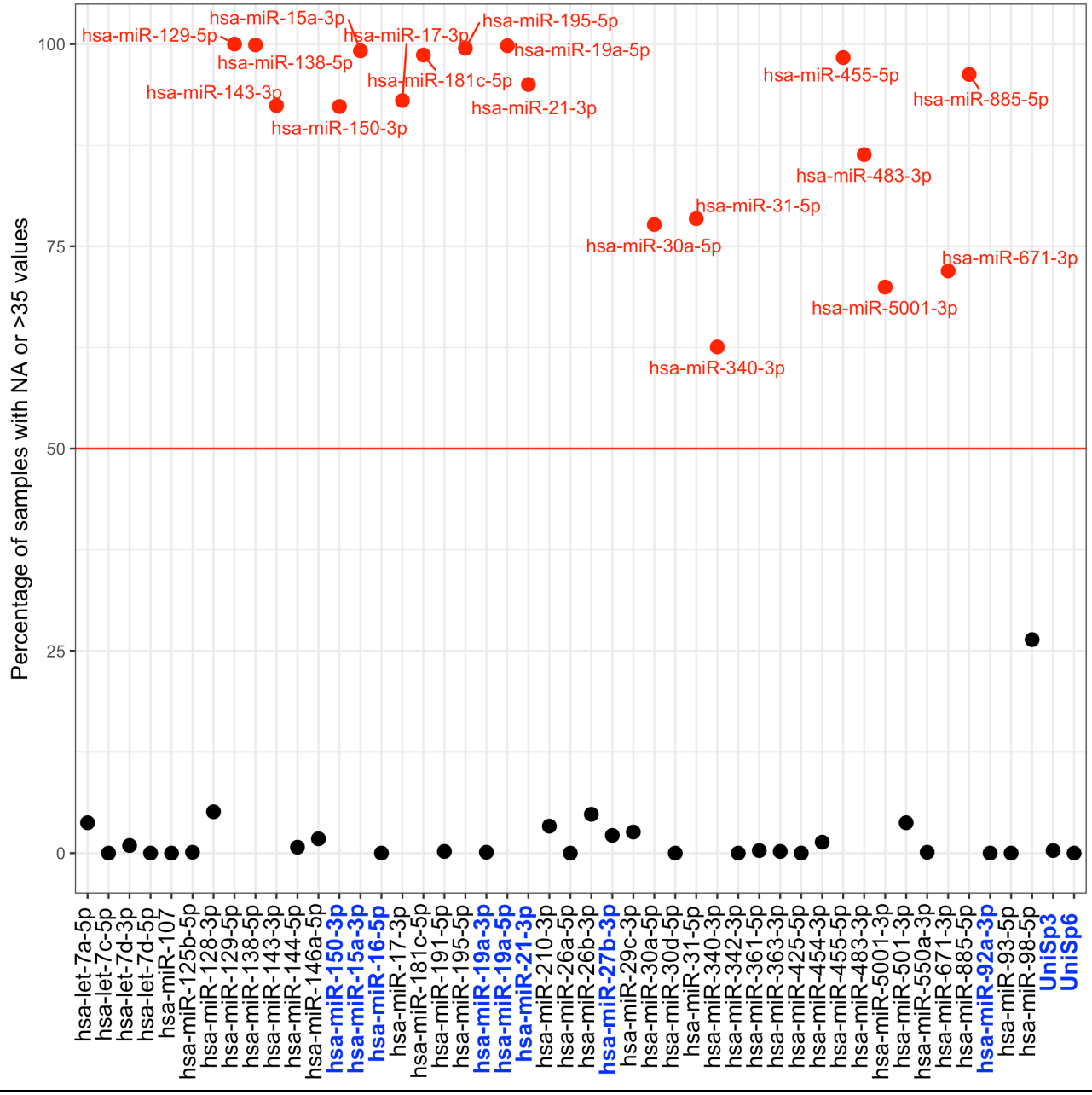
Analysis were undertaken in R using the packages g:Profiler for enrichment analysis and ggplot2 for graphical representation [34].

3.3. Results

3.3.1. Quality control

I analysed a total of 862 samples among which 96 were replicated. The median number of undetected probes per marker and per sample was 6.00 [0-306.80] (percentage: 0.63% [0.00-31.99]) and 8.00 [7.00-10.00] (percentage 16.67% [14.58-20.83]) respectively. I removed a total of 18 (39.13%) miRNAs which contained more than 50% of samples with values above Ct > 35 or NA among which four were endogenous controls: hsa-miR-129-5p, hsa-miR-138-5p, hsa-miR-143-3, hsa-miR-150-3p, hsa-miR-15a-3p, hsa-miR-181c-5p, hsa-miR-195-5p, hsa-miR-19a-5p, hsa-miR-21-3p, hsa-miR-30a-5p, hsa-miR-31-5p, hsa-miR-340-3p, hsa-miR-455-5p, hsa-miR-483-3p, hsa-miR-5001-3p, hsa-miR-671-3p and hsa-miR-885-5p (*Figure 1*).

Figure 1: Percentage of samples with NA or Ct > 35 values and distribution of NA by 384-well plate



Legend: miRNAs in blue represent the endogeneous and spike-in controls.

3.3.2. Demographics

The sample size consisted of 830 individuals with a median of 68.00 years [66.00-71.00]. The number of female participants was 475 (57.23%) and the median education years was 16 years [12.00-17.00]. *APOE* ε4 heterozygotes (ε3/ε4) and homozygotes (ε4/ε4) represented 159 (20.28%) and 9 (1.15%) respectively. Family history of dementia (any type) was reported in 258 (31.08%) of the participants (*Table 1*). At baseline, the low performance group (defined as a RBANS total scale < -1SD) represented 132 participants (15.9%) while 697 participants (84.1%) were in the normal performance group. A significant difference in gender (P = 0.007), ethnicity (P <0.0001), *APOE* ε4 carrier status (P = 0.042), BMI (P = 0.019) and education years (P < 0.0001) was observed between the two performance groups. As expected, significant differences in RBANS index scores and total scales (P <0.0001) were detected between the two groups.

3.3.3. Relationship between miRNAs and RBANS

In total, 17 miRNAs correlated with RBANS index scores or with total scales when unadjusted P values were considered. After adjusting for multiple comparisons, only two miRNAs remained statistically significant: hsa-miR-363-3p significantly correlated with the RBANS attention index (r(808)=-0.11, P_{adj} = 0.032) and hsa-miR-144-5p significantly correlated with the RBANS total scale (r(795) = -0.12, P_{adj} = 0.018). After adjusting for multiple comparisons and independent of age, gender, education years, ethnicity and *APOE* ε4 carrier status, multiple linear regression analysis showed a significant effect of five miRNAs expression values (hsa-let-7a-5p, hsa-let-7c-5p, hsa-let-7d-5p, hsa-miR-144-5p, hsa-miR-93-5p and hsa-miR-98-5p) on the RBANS language index, one miRNA expression value (hsa-miR-363-3p) on the RBANS attention index and one miRNA expression value (hsa-miR-144-5p) on the RBANS total scale (*Table 2*).

Table 1: Demographics of the study cohort				
	All participants N=830	RBANS total scale <-1SD (N=132)	RBANS total scale > - 1SD (N=698)	P value
Age (years)	68.00 [66.00-71.00] (60.00-85.00)	68.00 [66.00-71.00] (62.00-85.00)	68.00 [66.00-71.00] (60.00-85.00)	0.6782
Gender				**0.0067**
female	475 (57.23)	61 (46.21)	414 (59.40)	
male	355 (42.77)	71 (53.79)	283 (40.60)	
Ethnicity				**0.0000**
white	737 (92.01)	96 (73.85)	640 (95.52)	
black	6 (0.75)	5 (3.85)	1 (0.15)	
asian	36 (4.49)	20 (15.38)	16 (2.39)	
chinese	10 (1.25)	5 (3.85)	5 (0.75)	
multiple	12 (1.50)	4 (3.08)	8 (1.19)	
***APOE* genotyping**				
ε2/ε2	5 (0.64)	1 (0.79)	4 (0.61)	
ε2/ε3	83 (10.59)	12 (9.52)	71 (10.81)	
ε2/ε4	27 (3.44)	8 (6.35)	19 (2.89)	
ε3/ε3	501 (63.90)	71 (56.35)	429 (65.30)	
ε3/ε4	159 (20.28)	30 (23.81)	129 (19.63)	
ε4/ε4	9 (1.15)	4 (3.17)	5 (0.76)	0.0427
FX of dementia				0.1277
NO	572 (68.92)	99 (75.00)	473 (67.86)	
YES	258 (31.08)	33 (25.00)	224 (32.14)	
Education (years)	16.00 [12.00-17.00] (7.00-20.00)	13.00 [11.00-17.00] (7.00-20.00)	16.00 [13.00-17.00] (7.00-20.00)	**0.0000**
BMI	25.00 [23.00-29.00] (15.00-43.00)	26.76 ± 4.53 (17.00-39.00)	25.00 [23.00-28.00] (15.00-43.00)	**0.0188**
CVD risk factors				**0.3087**
NO	254 (30.60)	35 (26.52)	219 (31.42)	
YES	576 (69.40)	97 (73.48)	478 (68.58)	
RBANS				
Immediate Memory	106.00 [94.00-112.00] (49.00-144.00)	83.41 ± 12.89 (9.00-123.00)	106.00 [100.00-114.00] (69.00-144.00)	**0.0000**
Constructional Index	100.00 [87.00-109.00] (50.00-131.00)	82.11 ± 14.19 (50.00-121.00)	100.00 [92.00-112.00] (58.00-131.00)	**0.0000**
Language Index	104.00 [96.00-112.00] (51.00-134.00)	92.00 [83.00-98.00] (51.00-116.00)	105.00 [99.00-116.00] (79.00-134.00)	**0.0000**
Attention Index	103.00 [94.00-115.00] (49.00-146.00)	87.26 ± 12.30 (49.00-132.00)	106.00 [97.00-118.00] (68.00-146.00)	**0.0000**
Delayed Memory Index	102.00 [95.00-107.00] (40.00-134.00)	88.00 [80.25-95.00] (40.00-113.00)	102.00 [98.00-110.00] (56.00-134.00)	**0.0000**
Total Scale	102.72 ± 13.83 (55.00-143.00)	82.00 [78.00-86.00] (55.00-88.00)	106.00 [99.00-114.00] (89.00-143.00)	**0.0000**

Legend: Values are expressed as mean ± standard deviation (range), or median [interquartile range] (range) for data that is not normally distributed, or for prevalence data as n (%). Variables were compared using $\chi 2$ and Mann-Whitney U-tests. Abbreviation: *APOE*= Apolipoprotein E, *BMI* = Body Mass Index, CVD = Cardiovascular diseases, FX= Family history, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status

3.3.4. Differences in miRNA expression between the low performer and normal performer groups based on RBANS total scale at baseline.

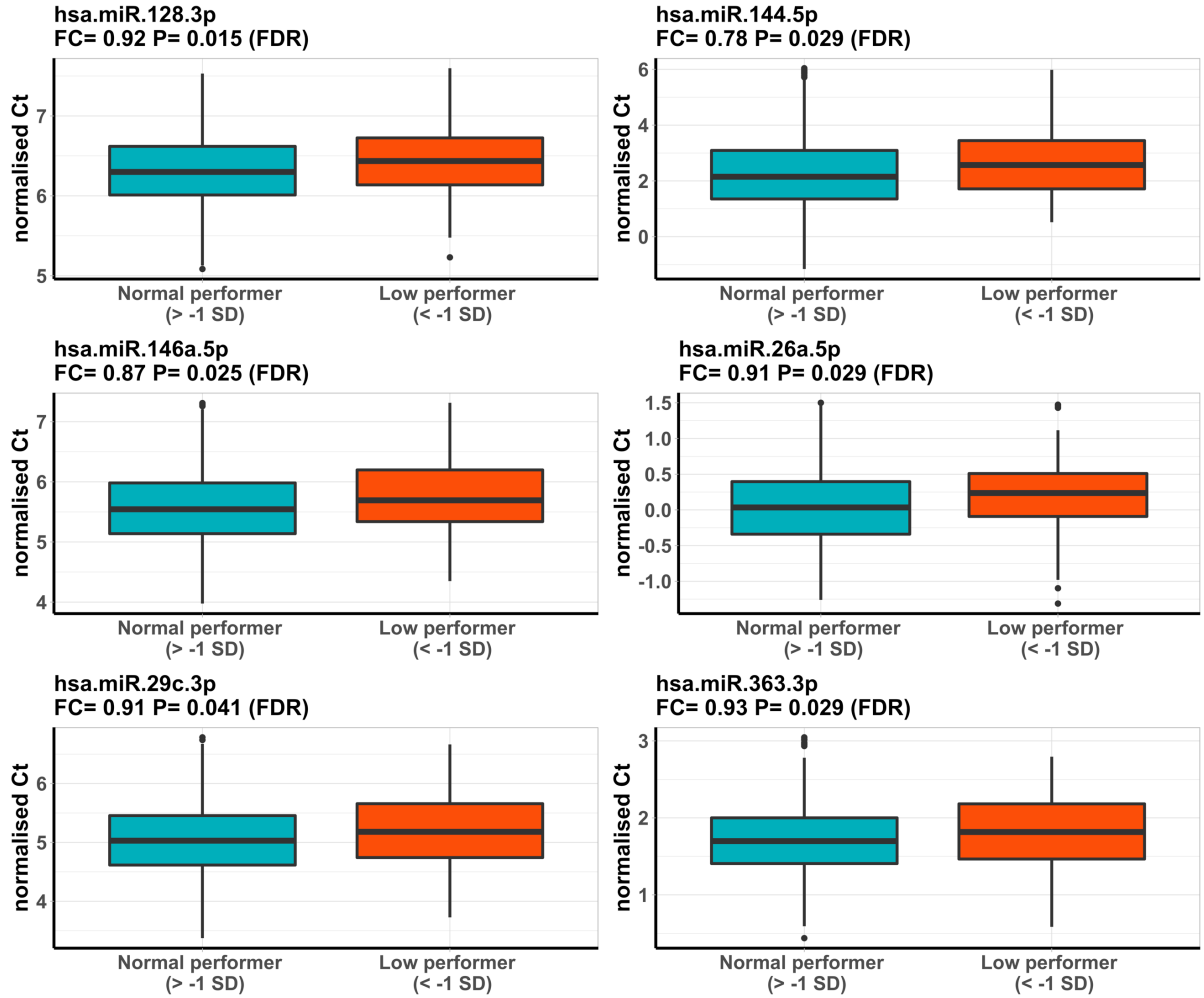
Independent of age, sex, education years, ethnicity and *APOE* ε4 carrier status, subjects who performed lowest on the RBANS total scale showed significantly higher Ct values for hsa-miR-128-3p (Mean difference ± SEM = 0.2 ± 0.04, F(1,764) = 10.11, P_{FDR}=0.031, ω^2=0.014), hsa-miR-144-5p (Mean difference ± SEM = 1.78 ± 0.13, F(1,746) = 7.407, P_{FDR} =0.031), hsa-miR-146a-5p (Mean difference ± SEM = 0.42 ± 0.06, F(1,762) = 8.27, P_{FDR} =0.031), hsa-miR-26a-5p (Mean difference ± SEM = 0.28 ± 0.05, F(1,763) = 7.782, P_{FDR} =0.031), hsa-miR-29c-3p (Mean difference ± SEM = 0.36 ± 0.06, F(1,755) = 6.959, P_{FDR} =0.033) and hsa-miR-363-3p (Mean difference ± SEM = 0.20 ± 0.04, F(1,758) = 8.717, P_{FDR} =0.031) (*Figure 2*). These results correspond to a downregulation of these miRNAs in patients showing the lowest performance on the RBANS total scale. The same direction of expression between these miRNAs is explained by a significant positive correlation in the expression of most of the miRNA pairs (except for hsa-miR-128-3p and hsa-miR-144-5p), with hsa-miR-363-3p and hsa-miR-29c-3p showing the strongest correlation (r(607)= 0.53, p<0.0001) (*Figure 3*). The effect sizes of the cognitive performance on the miRNAs Ct levels after controlling for the covariates were small (η^2=0.015 for hsa-miR-128-3p, η^2=0.011 for hsa-miR-144-5p, η^2=0.012 for hsa-miR-146a-5p, η^2=0.010 for hsa-miR-26a-5p, η^2=0.008 for hsa-miR-29c-3p and η^2=0.010 for hsa-miR-363-3p) (*Table 3*).

Table 2: Regression coefficient with RBANS as outcome variable and miRNA normalised Ct value as predictor, model adjusted for age, gender, education years, ethnicity, *APOE* ε4 carrier status

domain	miRNA	β	[95% CI]	Std. Error	t value	Pr(>|t|)	FDR adj. P value
Language Index	hsa.let.7a.5p	-2.39	[-4.10, -0.69]	0.868	-2.752	0.006	0.048
	hsa.let.7c.5p	-2.26	[-3.97, -0.56]	0.871	-2.601	0.009	0.049
	hsa.let.7d.5p	-3.06	[-1.67, 1.75]	1.023	-2.992	0.003	0.048
	hsa.miR.144.5p	-0.89	[-1.53, -0.25]	0.327	-2.723	0.007	0.048
	hsa.miR.93.5p	-1.88	[-3.31, -0.45]	0.728	-2.577	0.010	0.049
	hsa.miR.98.5p	-1.95	[-3.34, -0.55]	0.712	-2.735	0.006	0.048
Attention Index	hsa.miR.363.3p	-4.27	[-6.70, -1.85]	1.236	-3.457	0.001	0.017
Total Scale	hsa.miR.144.5p	-1.17	[-1.84, -0.51]	0.339	-3.464	0.001	0.016

Ethnicity coded as white = 0, other = 1; *APOE* genotype coded as ε3/ε4 or ε4/ε4 = 1, other = 0

Figure 2: Differences in Ct values between low performance and normal performance group for the significant miRNAs



Legend: **FC:** Fold change, **FDR**: False Discovery Rate, **SD**: Standard Deviation

Table 3: Comparison of Ct values in the two performance groups for the significant miRNAs

miRNA	Mean ± SD *normal performer (> -1 SD)*	Mean ± SD *low performer (<-1SD)*	Mean difference ± SEM	F statistic	P_{FDR}	η^2
hsa.miR.128.3p	6.31 ± 0.45	6.44 ± 0.45	0.2 ± 0.04	F(1,766) = 11.687	p=0.015	0.015
hsa.miR.144.5p	2.32 ± 1.34	2.68 ± 1.32	1.78 ± 0.13	F(1,757) = 8.413	p=0.029	0.011
hsa.miR.146a.5p	5.58 ± 0.64	5.78 ± 0.65	0.42 ± 0.06	F(1,763) = 9.461	p=0.025	0.012
hsa.miR.26a.5p	0.03 ± 0.54	0.17 ± 0.52	0.28 ± 0.05	F(1,763) = 7.782	p=0.029	0.010
hsa.miR.29c.3p	5.03 ± 0.6	5.17 ± 0.61	0.36 ± 0.06	F(1,758) = 6.541	p=0.041	0.008
hsa.miR.363.3p	1.71 ± 0.44	1.81 ± 0.49	0.2 ± 0.04	F(1,763) = 7.51	p=0.029	0.010

Legend: **FDR**: False Discovery Rate, **SD**: Standard Deviation, **SEM**: Standard Error of Mean, **η^2:** effect size

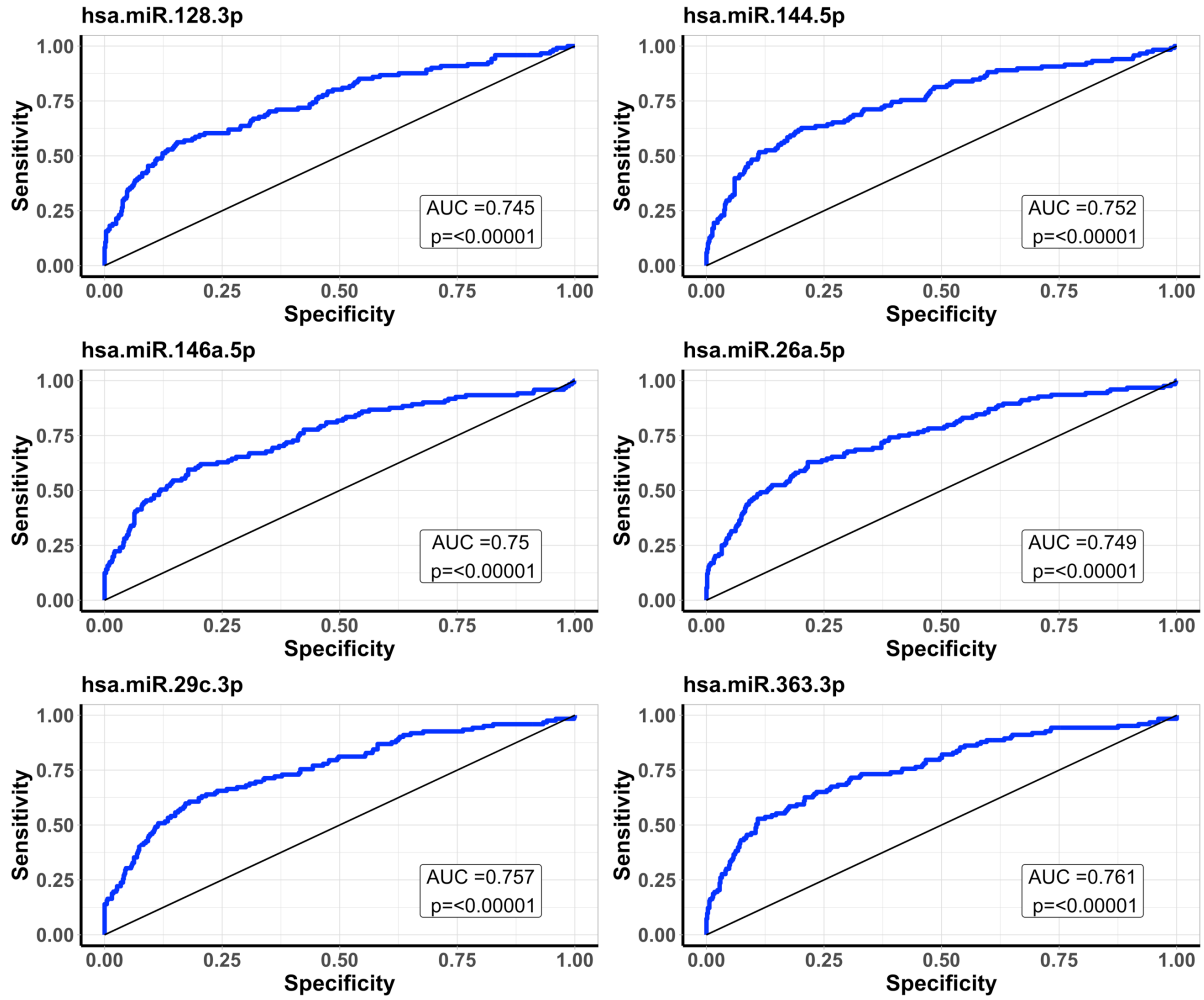
Figure 3: Correlation matrix between miRNAs

Values are Spearman correlations. The color of the cell represents the direction of the correlation coefficient (scale on the right of the correlation table)

3.3.5. Diagnostic performance of the significant miRNAs

ROC curves were calculated for all significant miRNAs using a logistic regression adjusting for age, sex, education years, *APOE* genotyping status and ethnicity. The five miRNAs showed similar performance, with hsa-miR-363-3p showing the highest performance AUC 0.761 [0.711-0.812] (*Figure 4*).

Figure 4: ROC curves for the significant miRNAs



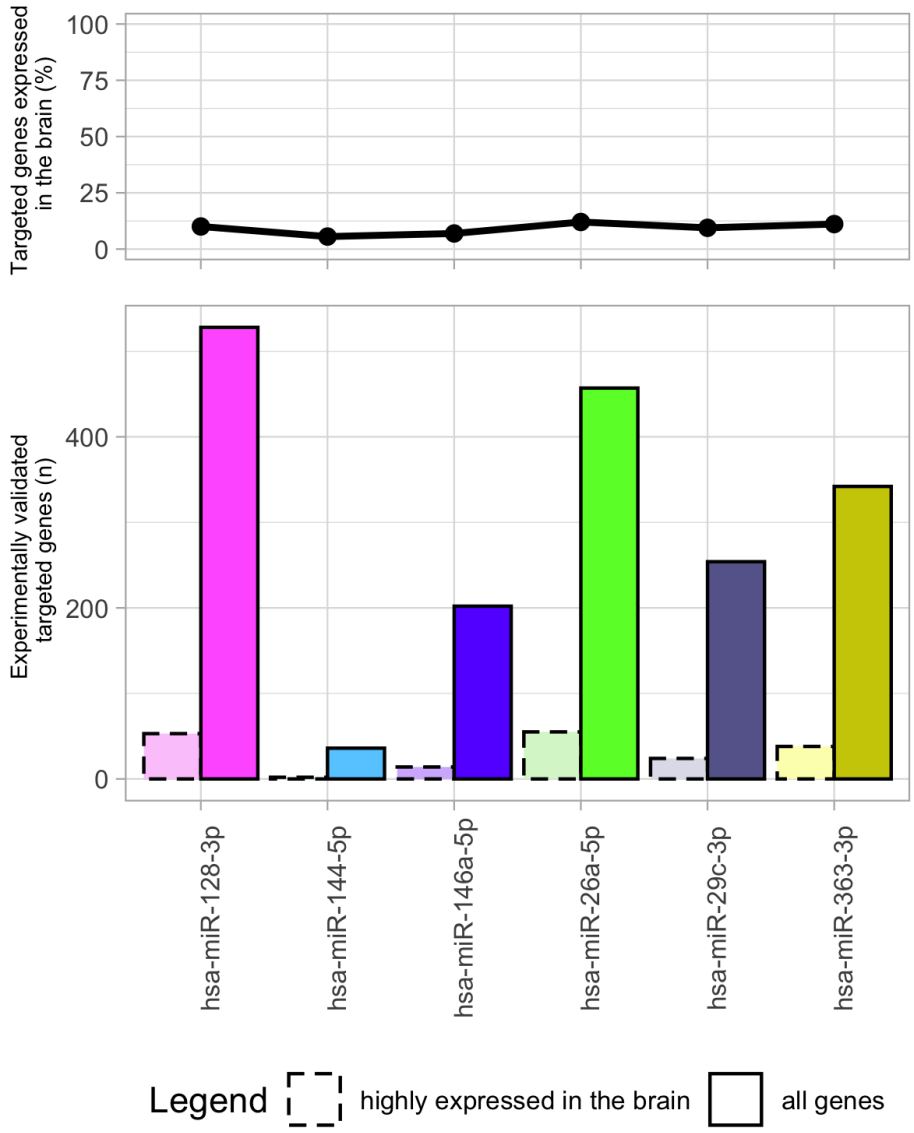
3.3.6. Pathway enrichment analysis results

miRNA-gene pair prediction was conducted for the six significantly dysregulated miRNAs, hsa-miR-128-3p, hsa-miR-144-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-29c-3p and hsa-miR-363-3p. I identified a total of 1432 experimentally validated targeted genes, with a mean of 303.2 ± 178.7 per miRNA; hsa-miR-128-3p targets the highest number of genes with 528 genes while hsa-miR-144-5p targets the lowest number with 36 genes. Noteworthy, there was no overlap in targeted genes between all six miRNAs. However, a total of 11 genes (*LBR, PTGS2, IFTM1, PTEN, TMTC3, PLAG1, NUFIP2, CPEB4, SMAD4, CCND2, MDM2*) are targeted by at least three of the dysregulated miRNAs (*Table 4*). Finally, from the targeted genes, I identified 186

(10.23%) genes which are highly expressed in the brain according to the HPA, with hsa-miR-26a-5p containing the highest percentage (12.04%) (*Figure 5*).

Table 4: Intersection between targeted genes and miRNAs		
Intersection	N	genes
miR-128, miR-144, miR-146	1	*LBR*
miR128, miR146, miR26	1	*PTGS2*
miR128, miR146, miR363	1	*IFITM1*
miR128, miR26, miR29	3	*PTEN TMTC3 PLAG1*
miR128, miR26, miR363	2	*NUFIP2 CPEB4*
miR144, miR146, miR26	1	*SMAD4*
miR146, miR26, miR29	1	*CCND2*
miR26, miR29, miR363	1	*MDM2*

Figure 5: Experimentally validated targeted genes by miRNA and percentage of targeted genes with high expression in the brain



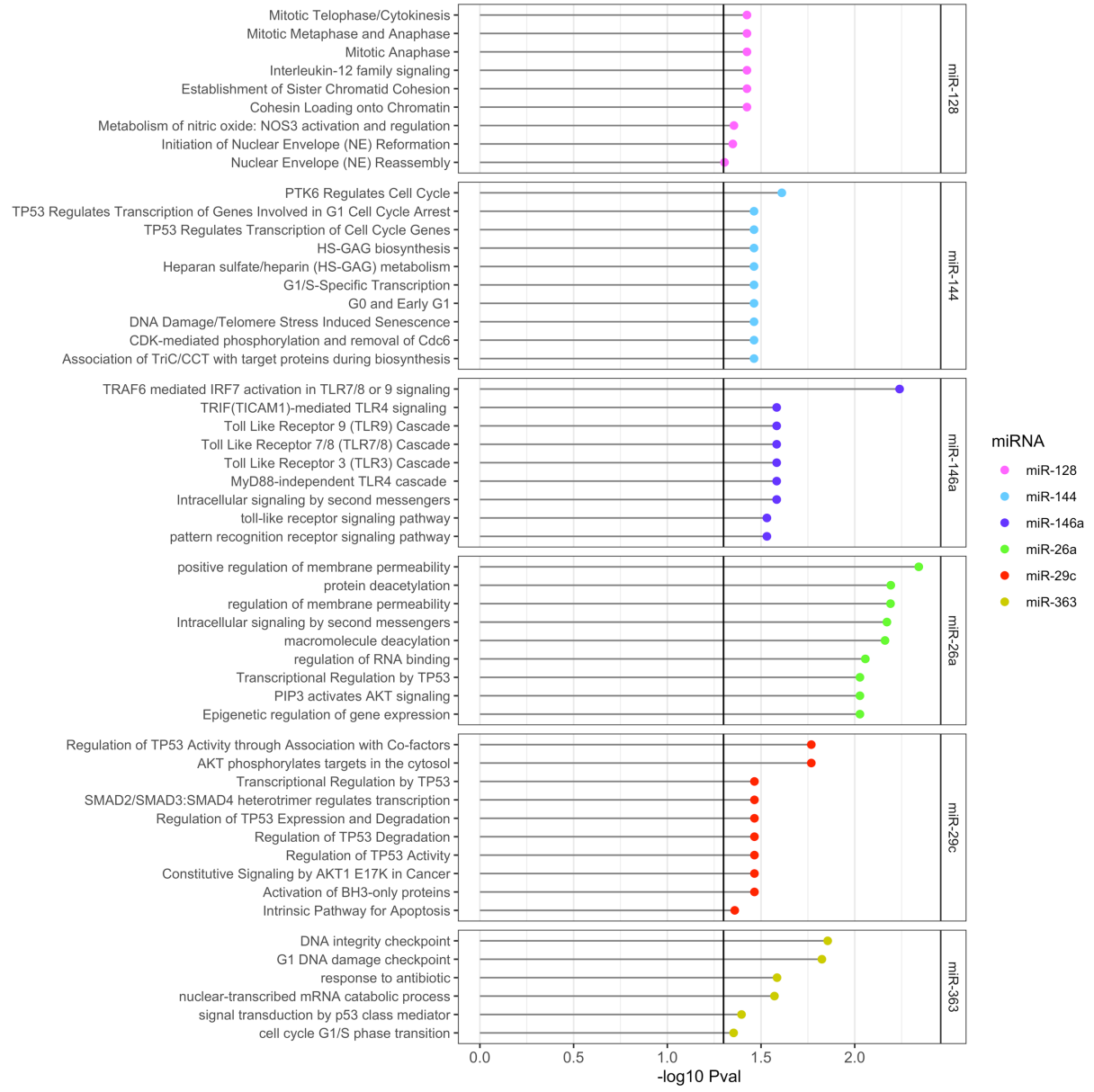
Finally, for each miRNA, only targeted genes highly expressed in the brain were selected and a pathway enrichment analysis conducted in KEGG, GO and REACTOME. Here, 152 unique pathways were enriched with a mean of 25.33 ± 22.75 per miRNA; hsa-miR-26a-5p targets 66 pathways while hsa-miR-363-3p targets only 6 pathways (*Supplementary Table 3*). I did not find any overlap in enriched pathways between the five miRNAs. I identified 9 pathways which are targeted by more than 1 miRNA; these belonged to biological function related to cell cycle regulation, transcription and splicing, cellular signalling, senescence, and tyrosine kinase signalling (Table 5). Pathways related to TLR signalling were part of the top enriched pathways

of miR-146a (*Figure 6*). When grouped into clusters of biological function, signalling pathways related to cell cycle regulation regrouped the most pathways. Interestingly, some clusters contained pathways enriched by genes targeted by a single miRNA. The "Wnt ß catenin signalling" cluster contained pathways enriched by genes targeted by hsa-miR-26a-5p only. Similarly, the clusters related to inflammation, such as "NF-κß signalling", "cytokine production" and "toll like receptor signalling" pathways contained pathways enriched only for genes targeted by hsa-miR-146a-5p. These findings reveal potential specificity in the role of each miRNA in regulating a particular pathway. The enrichment map also shows that genes regulating pathways in the "Wnt ß catenin signalling" are also involved in pathways related to cellular, toll like receptor and cytokine signalling (*Figure 7*).

Table 5: Intersection between targeted genes and miRNAs

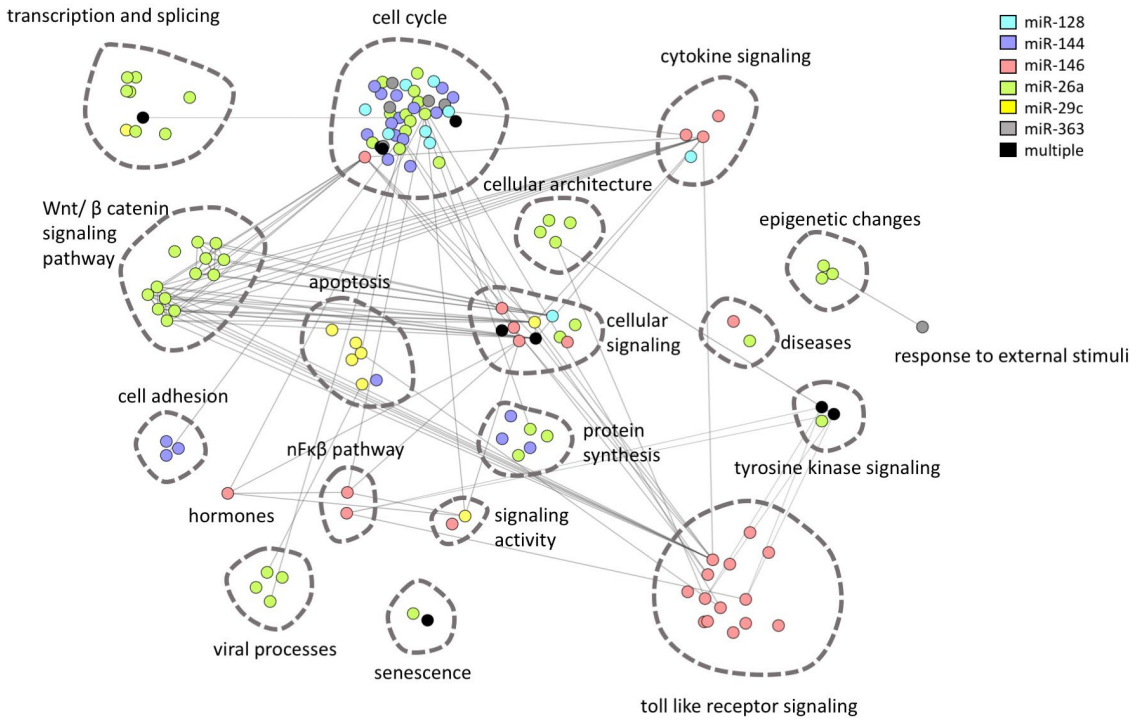
Intersection	N	Pathways
miR144, miR26a	6	Signalling by Non-Receptor Tyrosine Kinases (REAC:R-HSA-9006927) G1/S DNA Damage Checkpoints (REAC:R-HSA-69615) p53-Dependent G1/S DNA damage checkpoint (REAC:R-HSA-69580) p53-Dependent G1 DNA Damage Response (REAC:R-HSA-69563) Cellular Senescence (REAC:R-HSA-2559583) Signalling by PTK6 (REAC:R-HSA-8848021)
miR146, miR26a	1	Intracellular signalling by second messengers (REAC:R-HSA-9006925)
miR26a, miR29c	2	AKT phosphorylates targets in the cytosol (REAC:R-HSA-198323) Transcriptional Regulation by TP53 (REAC:R-HSA-3700989)

Figure 6: Top enriched pathways by miRNA



This graph shows the top 10 enriched pathways in KEGG, GO and REACTOME for the six significantly dysregulated miRNAs at $P_{FDR}<0.05$. In some cases, less than 10 pathways are displayed as less than 10 pathways were enriched at $P_{FDR}<0.05$.

Figure 7: Enrichment pathways for the targeted genes, highly expressed in the brain, that are targeted by the six downregulated miRNAs in the RBANS low performer group



Each node represents an enriched pathway from KEGG, GO and REACTOME. The color of the node represents whether a pathway is enriched by genes targeted by one or several miRNAs. The edges represent the overlap in genes between two pathways. The edge's width is proportional to the size of the overlap. Enriched pathways have been manually grouped into clusters of biological function.

3.4. Discussion

In this chapter I aimed at investigating whether miRNAs, known to be dysregulated in the blood of AD patients, are already differentially expressed in individuals showing early signs of cognitive impairment. In order to answer this question, I selected cognitively healthy individuals from the CHARIOT-PRO cohort and defined a cut-off of < - 1 SD on the total RBANS scale as low cognitive performance. Using RT-qPCR analysis, I identified 6 miRNAs, hsa-miR-128-3p, hsa-miR-144-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-29c-3p and hsa-miR-363-3p to be significantly downregulated in individuals with lower cognitive performance. A pathway enrichment analysis in KEGG, GO and REACTOME revealed that these miRNAs target brain specific genes involved in inflammatory and apoptotic processes hereby suggesting an involvement of these pathways in early stages of the disease.

In my analysis, miR-146a-5p was downregulated in individuals with lower cognitive performance on the RBANS score. Similar direction of regulation was found in the previous meta-analysis, where eight of the nine included studies reported downregulation of miR-146a-5p in AD patients. This miRNA is widely expressed in the brain where it stimulates and regulates axonal development [35]. Several lines of evidence in the literature corroborate the idea that miR-145a-5p could be involved early in the pathogenesis of the disease. First, *MIR146A* knockout mice had reduced hippocampal volume, a finding which can be detected several years before the onset of the first symptoms [36, 37]. Second, miR-146a-5p targets members of the NF-κB signalling pathway such as CARD10, COPS8, IRAK1 and TRAF6 [38]. Increased levels of NF-κB are reported in AD brains, with activated NF-κB localised close to the amyloid plaques [39]. Nevertheless, intense debate surrounds the role of NF-κB in AD. Zhao et al reported that NF-κB downregulates TREM2 expression in microglia by upregulating the expression of miR-34a [40]. This is an interesting finding as *TREM2* deletion is associated with reduced Aβ deposition in the early stages of the disease in AD mice models hence suggesting a protective effect of NF-κB [41]. Conversely, NF-κB is also known to stimulate the expression of IL-1β and TNF-α, two pro-inflammatory markers reported to be expressed early in the pathogenesis of AD, preceding amyloid plaque deposition and cognitive impairment [42]. My findings suggest that downregulation of miR-146a may lead to an increase in NF-κB in

individuals at early stages of the disease and initiate an inflammatory response that eventually leads to amyloid deposition. Further studies are needed to clarify the role of NF-κB in preclinical stages of AD.

Individuals with lower cognitive performance showed downregulation of miR-26a. Interestingly, the pathway enrichment analysis identified miR-26a as the only dysregulated miRNA targeting genes from the Wnt ß catenin signalling pathway. The interaction of miR-26a with Wnt and ß catenin was reported in several diseases such as non-small cell lung cancer and cholangiocarcinoma, where a downregulation of miR-26a was associated with reduced levels of ß catenin [43, 44]. Unfortunately, so far, no study has investigated the relationship between miR-26a and components of the Wnt ß catenin cascade in AD. Yet, decreased expression of Wnt and ß catenin proteins was associated with impaired amyloid clearance and increased cognitive impairment in AD mice models [45, 46]. We may therefore postulate that individuals with lower cognitive performance in our CHARIOT PRO cohort may have reduced levels of Wnt and ß catenin. Additionally, we may postulate that lower cognitive performance may be due to early accumulation of amyloid that failed to be cleared due to miR-26a induced reduced levels of ß catenin. This hypothesis is suggested by a study showing that ß catenin inhibits Aβ formation by repressing BACE1 expression [47]. Unfortunately, for this cohort, I did not have data on amyloid biomarkers, either through imaging or measured in the CSF. Nevertheless, dysregulation of miR-26a in individuals at early stages of cognitive impairment and its role in the Wnt ß catenin signalling pathways, are particularly interesting when considering novel drug targets. Indeed, several drugs, such as statins are known to activate the Wnt ß catenin signalling pathway. In an AD mice model, simvastatin was able to increase expression of substrates from the Wnt ß catenin pathway and increase neuronal growth in the hippocampus [48]. Yet, in humans, the role of statins in AD has been the source of intense debates and controversies, with some studies failing to show a benefit in preventing AD, and other reporting reduced risk for cognitive decline [49, 50]. Considering that miR-26a is also influencing the Wnt ß catenin signalling pathway, this miRNA may represent a novel therapeutic opportunity to explore.

In individuals with lower cognitive performance on the RBANS, miR-29c was downregulated. Similarly, downregulation of miR-29c was reported in the blood of AD patients. Interestingly,

my pathway enrichment analysis reveals that this miRNA targets brain specific genes that are involved in regulating apoptosis. This was reported in several cell lines. In glioma cell lines, upregulation of miR-29c resulted in cell cycle arrest via downregulation of cyclin D1 and cyclin E. It also downregulated VEGF and led to impaired angiogenesis in the same cells [51]. In cell models of PD, overexpression of miR-29c led to reduced accumulation of α-synuclein in neurons, reduced production of pro-inflammatory cytokines, and inhibited apoptosis by decreasing expression of caspase-3 and caspase-9 [52]. These results suggest that downregulation of miR-29c in our individuals might have increased pro-inflammatory cytokines production and apoptosis, supporting the hypothesis for a link between inflammation and neurodegeneration at early stages of the disease.

Three miRNAs, hsa-miR-128-3p, hsa-miR-26a-5p and hsa-miR-363-3p were downregulated in our study, whereas they were reported to be upregulated in blood of AD patients in our previous meta-analysis. A possible explanation is that the overall direction of effect in the meta-analysis was based on the most frequently reported dysregulation for a particular miRNA. However, for these three miRNAs, at least one study reported also downregulation in blood. Another explanation could be that our meta-analysis included patients with dementia, whereas individuals from the CHARIOT-PRO cohort were at early stages of the disease. A dynamic temporal expression of miRNAs during lifetime was reported recently with diseases, such as schizophrenia [53]. We might therefore postulate, that the direction of dysregulation might change along the different stages of the disease. One recent finding indirectly corroborates this hypothesis. It is now well established that miRNAs regulate different function in microglia ranging from cytokine production, response to external stimuli and cellular homeostasis [54]. Interestingly, a recent study using single cell RNA sequencing of microglia from an AD mouse model revealed a change of microglial phenotype over time: at early stages of neurodegeneration, microglia upregulated genes coding for inflammatory, immune response and protease proteins, while at later stages, genes coding for components of the complement cascade, MHC and interferon response were upregulated [55]. It is therefore possible that this change in gene expression is mediated by a change in miRNA expression profile over time.

The AUC for the six dysregulated miRNAs to distinguish low performers from normal performers was approximately 0.75. One study investigating the performance of miR-128 in differentiating MCI from AD patients revealed an AUC of 0.97. These findings were however obtained from a smaller sample size (100 individuals) and weren't validated in a larger cohort [56]. Furthermore, the population of this study included patients with overt clinical symptoms whereas individuals from the CPRO cohort were still at a preclinical stage. Other studies investigating miR-107, miR29b or miR-181c reported similar levels of performance as our dysregulated miRNAs (reviewed here: [57]). Further studies are needed to investigate the diagnostic performance of our identified miRNAs in a larger cohort of individuals showing early cognitive changes.

The statistical analyses reveal a statistically significant but small effect size of the cognitive performance on the miRNA expression values in the blood. Following these analyses, I conducted a pathway enrichment analysis which showed how these blood derived miRNAs are involved in biological pathways specific to neuronal cells and AD pathogenesis. These findings suggest that these blood miRNAs may therefore represent non-invasive biomarkers, which would reflect the ongoing pathogenesis in the brain. Moreover, as revealed in previous chapter, one of the significantly downregulated miRNAs in low cognitive performers, miR-363-3p, is upregulated in both the brain and blood of AD patients. Nevertheless, the relationship between miRNA blood expression with miRNA brain expression in AD is yet to be fully unveiled. So far, due to methodological barriers, no study has been able to explore miRNA expression in the brain and the blood of a same individual, let alone in AD individuals. Indeed, exploring miRNA expression in vivo in the brain of AD patients would entail a brain biopsy; this diagnostic procedure is very rarely undertaken in dementia work-up, which relies primarily on clinical, CSF and neuroimaging biomarkers [58]. Interestingly, studies investigating the relationship between miRNAs in the blood and the brain are also scarce in other pathologies. One study conducted in rat models of brain injuries following surgery, stroke, brain haemorrhage and seizure revealed that three miRNAs, miR-298, miR-155 and miR-363-3p were dysregulated in both brain and blood in the same rat [59]. Similarly, miR-290 was upregulated and let-7i was downregulated simultaneously in the brain and blood of rats following transient focal ischemia [60]. Recently, novel in vivo tracking techniques of miRNAs in cell culture have been developed. In the future, these methods could be extended to neuroimaging; this would provide a novel

non-invasive opportunity to explore the association between miRNA expression in the blood and the brain of AD patients in vivo [61]. Lately, the role of miRNA to miRNA interactions has attracted increasing attention [62]. Therefore, we could hypothesise that a blood miRNA may regulate the expression of a brain miRNA via a specific transcription factor. Indeed, transcription factors are able to cross the blood-brain barrier and regulate gene expression in the brain [63].

Several limitations need to be mentioned in this study. First, individuals were categorised as low performers based on the RBANS score. Information on biomarkers such as amyloid, tau CSF levels or imaging findings, which could have helped us better characterise cognitive impairment in those individuals, was not available. Also, it is not to be excluded that individuals with poorer cognitive function might be affected by another type of neurodegenerative diseases, or even early stages of vascular dementia. Second, during the quality control of the RT-qPCR data, several miRNAs not passing the required quality standards, had to be removed and could not be investigated. Third, further experimental studies are needed to explore the relationship between these miRNAs and known actors of AD pathogenesis in brain models. I tried to explore these miRNAs function in the brain, by conducting a pathway enrichment analysis only on experimentally validated brain specific genes; however, only experimental models conducted in brain will help further confirm these miRNAs influence on the brain. Recently, a thorough investigation of the effect of miR-298 on amyloid, tau and BACE1 activity in mice model, human CSF and brain tissues, offered a novel understanding of this miRNA's role in the AD pathogenesis. Additionally, this study revealed the association between polymorphism surrounding *MIR298* and AD-related CSF biomarkers [64]. Finally, these analyses were undertaken in a single cohort using qPCR, a commonly used technique. Previous studies show how data obtained from qPCR need to be reproduced in another cohort [65]. As such, although the analysed miRNAs were already prioritised based on a systematic review and meta-analysis of 107 studies, the presented findings need to be replicated in a larger cohort. In particular, the same quantification method as well as neurocognitive assessment battery should be applied. Here I believe that the strength of my study was to follow the MIQE (minimum information for the publication of quantitative PCR experiments) guidelines when reporting the qPCR analysis; this facilitates the reproducibility of the analysis pipeline [66, 67].

Also, this study is a cross-sectional analysis. Longitudinal data analysis in the same cohort would help explore the potential of these miRNAs in predicting cognitive decline in the long-term.

3.5. Conclusion

To summarise, this is the first work measuring blood miRNAs prioritised from a previous meta-analysis on blood miRNAs in AD patients, in individuals at early stages of cognitive impairment. My results confirm that some of these miRNAs are already dysregulated in individuals presenting first signs of cognitive decline and suggest that inflammation may play a central role in early stages of AD. In the future, the investigation of the association between these dysregulated miRNAs and biomarkers of neurodegeneration will provide further understanding of these miRNAs' roles in AD pathogenesis.

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Chapter 4: Association of miRNA gene polymorphisms with CSF biomarkers of neurodegeneration in the Alzheimer's Disease Neuroimaging Initiative cohort.

4.1. Introduction

Single nucleotide polymorphism (SNP) is the most frequent genetic variation; it consists of the substitution of one single nucleotide in an individual's DNA. Large GWAS have shown that SNPs can alter gene expression and result in the development of diseases such as AD [1]. SNPs can either be located within coding or non-coding sequences.

The discovery of SNPs has catalysed the understanding of the pathogenesis underlying diseases; it has also highlighted the role of miRNAs in some diseases. miRNAs are small noncoding RNA molecules which regulate gene expression at post-transcriptional level. Briefly, miRNA biogenesis begins with the transcription of a miRNA gene into a primary-miRNA (pri-miRNA) which is then cleaved into a precursor miRNA (pre-miRNA) in the nucleus. Next, pre-miRNA is exported into the cytoplasm where it undergoes further transformation to become a mature miRNA [2]. In 2005, the first role of variants within binding sites of a miRNA were reported in 174 patients with Tourette's syndrome. It was shown that the presence of variant var321 within *SLITRK1* affects the binding site of miR-189 and results in dendritic loss in brain regions involved in the disease's pathogenesis [3]. Later, experimental and *in silico* studies described variants directly located within miRNA genes that affected the transcription process, the pri-miRNA and pre-miRNA processing stages and maturation as well as the miRNA-mRNA interaction [4]. For example, the presence of SNP rs895819 within *MIR27A*, a pro-oncogene, was associated with a reduced risk for breast cancer. This SNP is located in the centre of the gene's terminal loop and is likely affecting the binding of Drosha, a protein complex essential in the miRNA maturation process [4]. Some miRNAs such as hsa-miR-146a are expressed in different cell lines and target several oncogenic genes. Consequently, the presence of a SNP rs2910164 within *MIR146A* was associated with increased risk for papillary thyroid tumour, prostate cancer and hepatocellular cancer [5-7]. Moreover, it is believed that rs2910164 could also influence the development of other non-cancer diseases by influencing NF-κB, a TF regulating inflammatory genes [8]. While a large body of evidence comes from cancer studies where both protective and deleterious effects of these miRNA gene polymorphisms on cancer risk were reported, evidence for non-cancer diseases has also been described. In a study conducted in 557 patients with non-syndromic oral cleft, SNP rs7205289 located within *MIR140* affected the processing of the pre-miRNA-140; this resulted in the downregulation of

miR-140-5p, which is a miRNA critical for palatal development [9]. In another study on 221 patients with dilated cardiomyopathy, the presence of two SNPs rs11614913 and rs3746444 in *MIR196A2* and *MIR499* were associated with increased risk for the disease [10].

Several studies have linked variants in miRNA genes with phenotypic traits of AD, characterised by Aβ deposition and NFT accumulation in the brain. In the recent ATN classification, Aβ (A) and phosphorylated-tau (T) and total-tau (N) are CSF biomarkers used to differentiate individuals across the AD spectrum [11]. Those markers are clinically useful predictors of the progression from normal cognitive status to MCI and dementia [12]. Recently, SNP rs6070628 within *MIR298* was associated with higher CSF tau phosphorylated at threonine 181 (p-tau$_{181p}$) levels in a dose dependent fashion [13]. Early accumulation of Aß42, the isoform predominantly found in senile plaques, and tau stimulates microglia mediated immune response. In 103 patients with AD, rs2910164 within *MIR146A* led to reduced expression of mature hsa-miR-146a-5p which in turn resulted in increased levels of TLR-2 [14]. Importantly, TLR-2 is a receptor expressed on microglia; its binding with Aß42 results in neuroinflammation [15]. In another sample of 292 AD cases, homozygotes for allele A of rs57095329 had increased levels of microglial induced pro-inflammatory cytokines (IL-6 and IL-1ß) and increased risk for cognitive decline [16]. So far, no studies have explored the association of miRNA gene polymorphisms with other key players in the AD pathogenic cascade, such as the microglial receptor TREM2, the key Aβ producing enzyme BACE1 or the neuroaxonal protein NfL. TREM2 is expressed on microglial cells and regulates microglial response to Aß deposition; rare variants causing a loss of function of TREM2 have been linked to increased risk for AD [17]. A dynamic pattern in soluble TREM2 (sTREM2) levels in the CSF has been reported along the AD spectrum, with a peak of sTREM2 CSF levels described in early stages of MCI [18]. BACE1 is an enzyme catalysing the production of Aß42 from the APP [19]. Elevated levels of BACE1 activity are reported in both the brains and CSF of patients with MCI and AD [20-22]. Moreover, in 31 patients with AD, BACE1 activity in the CSF was associated with Aβ plaques measured using Pittsburgh Compound B PET (PiB-PET) [23]. In AD mouse models, BACE1 accumulation colocalised with neurofilaments [24]. These are intracellular structures involved in the cell structure and morphology; neuronal injury or death lead to release of neurofilaments in the extracellular space [25]. Increased CSF concentrations of NfL in AD cases compared to healthy controls were reported in a total of 29 studies [26].

To date, studies have focused on investigating the association of SNPs located in the proximity of a single miRNA gene. However, investigating the association of SNPs in close proximity of several miRNA genes known to be dysregulated in AD with biomarkers of the disease would provide new mechanistic insights into the pathogenesis of AD; it would also help to identify potential novel biomarkers and therapeutic targets. In the previous chapter, I have reported six miRNAs dysregulated in the blood of individuals with poorer cognitive performance in the CHARIOT-PRO dataset. To understand the relationship between miRNA gene polymorphism and biomarkers of neurodegeneration, I investigate the association between polymorphisms within these six dysregulated miRNA genes with AD related biomarkers levels in the CSF of participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

4.2. Methods

4.2.1. ADNI cohort

Data were obtained from the ADNI after project approval by the principal investigators [27]. ADNI was created in 2003 in joint collaboration with different partners of the private and public sector such as the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), pharmaceutical companies and non-profit organisations. The initiative's founding aim is to investigate the clinical, neuropsychological and neuroimaging changes associated with the development of AD and facilitate the development of novel therapeutics. Participants were recruited in 50 sites in the United States and Canada; Michael Weiner, MD from VA Medical Centre and University of California, San Francisco is the principal investigator. At the initial stages of ADNI, the goal was to recruit a total of 800 individuals – 200 healthy controls, 400 with mild cognitive impairment and 200 with AD dementia. Later, these stages were followed by ADNI2, ADNI3 and ADNI-GO. As of 2021, a total of 2585 participants are recruited. The present cohort used for this analysis consisted of 812 individuals for whom genotyping was undertaken. For each study site, ethical approval was obtained by the principal investigators and all participants provided written and informed consent. The study is registered at www.ClinicalTrials.gov (identifier NCT00106899). Subjects were classified as AD dementia if they met the criteria of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). AD dementia subjects had MMSE scores between 20-26 (inclusive) and had a Clinical Dementia Rating between 0.5-1 (inclusive). Participants with a MMSE 24-30, CDR 0.5 (with a memory box score of 0.5 or greater), memory complaints, no functional complaints and who did not meet the NINCDS-ADRDA were classified as MCI [28]. Furthermore, individuals with MCI were categorised as early MCI (eMCI) or late MCI (lMCI) based on their performance on the Wechsler Memory Scale Revised Logical Memory II Story A [29].

4.2.2. Whole genome sequencing

Whole genome sequencing data were downloaded in PLINK format from https://ida.loni.usc.edu/. Whole genome sequencing was performed in ADNI on 812

individuals using the Illumina Omni 2.5 M Bead Chips by the ADNI genetics core. The analyses were undertaken following the Genome Analysis Toolkit (GATK) provided by the Broad Institute and are extensively described here [30]. Briefly, following steps were undertaken by the ADNI genetics core: at pre-processing stage, raw sequence reads were mapped to the genome reference and duplicates were marked and removed. Then, local realignment was performed to remove mismatching occurring in the initial mapping; base quality scores were recalibrated using a machine learning approach. For the variant discovery, variant calling was undertaken per sample using the GATK HaplotypeCaller and then combined into a single gvcf file using GATK CombineGVCFs. This step was followed by joint genotyping. Quality score recalibration was run to remove artefacts raw calls using a machine learning method provided by GATK (Variant Quality Score Recalibration). During this process, 10 individuals were removed either in the pre-processing stage or because of low quality genotyping content. A total of 2379855 variants were genotyped with a genotyping rate reaching 0.997187.

I then undertook following quality control procedures on the downloaded data using the PLINK software: check for discordant sex information, identification of individuals with high missing rates and outlying heterozygosity rate (cut-off call-rate 0.03, cut-off heterozygosity 3 SD), identification of duplicated individuals and related individuals (cut-off Pi-hat 0.2). Following these first procedures, a total of 41 individuals were removed. Then, I undertook a population stratification using 1000 Genome Project data for reference to select only individuals with European ancestry. During this step, a further 21 individuals were removed leading to a final total sample of 750 individuals. At last, I removed a total of 826321 markers with call rates < 0.1, MAF <0.05 and those which deviated from the Hardy Weinberg Equilibrium at a P value > 10^{-6}. Quality control procedures followed a previously described protocol [31].

4.2.3. Biomarker measurements in the CSF

At baseline, lumbar puncture with a 20- or 24-gauche spinal needle was undertaken in the morning after an overnight fast to minimise measurement bias due to circadian peptide fluctuations. CSF samples of individuals were transferred into polypropylene tubes which were then stored on dry ice 1 hour after the collection. The samples collected from 56 participating centres were then shipped to the ADNI Biomarker Core Laboratory at the University of Pennsylvania Medical Centre which was in charge of the analysis following ADNI standardised

operating procedures. Aliquots of 0.5 mL were obtained from each sample after thawing and gentle mixing and stored into freezer at -80° [32].

4.2.3.1. Amyloid-β 1-42 peptide ($A\beta_{1-42}$), total tau (t-tau), and tau phosphorylated at the threonine 181 ($p\text{-}tau_{181p}$)

Measurement were undertaken in the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use-only reagents) immunoassay kit–based reagents. These consisted of monoclonal antibodies specific for $A\beta_{1-42}$(4D7A3), t-tau(AT120), and $p\text{-}tau_{181p}$ (AT270). Full details can be found elsewhere [32].

4.2.3.2. Neurofilament light chain

NfL levels in the CSF were assessed using a sandwich enzyme-linked immunosorbent assay ELISA (NF-light ELISA kit, UmanDiagnostics AB, Umeå, Sweden) following the manufacturer's protocol. CSF samples were analysed in duplicate and a control CSF sample was used to control for interplate variation. Duplicates showed < 8% of coefficient of variation. Interbatch CV was < 12%. The lower limit of quantification was 50 ng/L.

4.2.3.3. Soluble TREM2 (sTREM2)

Measurements of sTREM2 in the CSF of ADNI participants were conducted following two different validated protocols. The first method was undertaken by the German Centre for Neurodegenerative Disorders Munich using the MSD electrochemiluminescence platform. The second method relied on an ELISA and was undertaken in the Department of Neurology, University of Washington. Previous reports have highlighted high correlation between the two methods ($\rho = 0.83$, $p < 0.001$) but higher sensitivity of the MSD platform [33]. I have therefore considered only measurement undertaken on MSD platform. Briefly, the capture antibody was a goat polyclonal anti amino-acid 19-175 of human TREM2 IgG. The detection antibody consisted of a mouse anti amino-acid 1-160 of human TREM2 IgG. Finally, a SULFOTAG-labelled goat polyclonal IgG anti-mouse antibody was used. Standard curves were generated using a recombinant human TREM2 protein. CSF samples were measured in duplicate and were randomly distributed across the plates. CSF samples obtained from routine leftovers from the Ludwig-Maximilian's Universität Munich Department of Neurology were used as internal control and were run on each ELISA plate to check for interplate variability. Finally, a correction

factor for each plate was calculated based on the concentration of each internal control (in an individual plate and across all plates) and multiplied with the raw values for each CSF samples.

4.2.3.4. BACE 1 activity in the CSF

BACE1 activity was measured using a two-step assay. First, a cleavage product of a biotinylated peptide substrate by the CSF BACE1 was obtained. Second, the product was measured on a streptavidin-coated plate via ELISA. Standard curves were obtained for recombinant BACE1 and used to calculate absolute values for the samples. Internal control for each plate was achieved via non-human primate rhesus CSF obtained from cisterna magna ported rhesus monkey model [34].

4.2.4. Definition of region of interest within the miRNA gene

Based on previous reports from the literature, I chose a 200 kb (kilo base) window size to identify SNPs located around the miRNA gene [35, 36]. The genetic environment for each miRNA gene was explored using the University of California Santa Cruz (UCSC) genome browser [37, 38].

4.2.5. Linkage disequilibrium and haplotype blocks

Linkage disequilibrium (LD) is defined as the non-random association between two alleles at different sites [39]. A haplotype is a combination of genetic variants that occurs on the same chromosome and are inherited together. LD within a haplotype reflects few recombination events. Haplotype blocks correspond to a small number of common haplotypes (2-4) separated by region with high recombination events [40]. To identify haplotype blocks, I used the default algorithm implemented in Haploview [41]. Briefly, the method calculates D prime, a parameter of linkage disequilibrium, between two SNPs and categorises them as in strong LD, inconclusive or strong recombination. A block is defined by the presence of 95% SNPs in strong LD [42].

4.2.6. Statistical analysis

Demographics are presented as mean ± SD. Each biomarker's distribution was checked for normality using the Kolmogorov Smirnov test and log transformed when necessary to fit a normal distribution.

Association between the miRNA genotype and the biomarker was conducted in PLINK v1.07 using the linear regression function for continuous phenotype. The first 5 principal components of the population stratification were included as covariates. In addition, age, sex, *APOE* ε4 allele carrier status and diagnosis at baseline were included in all analyses as covariates. This is based on previous studies reporting the association between *APOE* ε4 status and the CSF levels for these biomarkers [43-49]. Benjamini Hochberg FDR was applied in order to take into account for multiple comparisons and statistical significance was set at $\alpha < 0.05$. This method for multiple comparisons adjustment was preferred over the Bonferroni method which is considered too conservative as SNPs may be in LD and may therefore not be independent from each other.

A Pearson correlation was conducted between biomarkers significantly associated with SNPs within the same miRNA gene region. The link between these biomarkers was further assessed using a multivariate regression analysis including age, sex, diagnosis at baseline and *APOE* ε4 carrier status as covariates.

4.2.7. Functional annotation of significant variants

In order to further explore the biological effect of SNPs within +/- 200 kb of each miRNA gene significantly associated with CSF biomarkers of AD, I applied following methods:

First, I conducted LD analysis in LDlink 5.0 using the function LDmatrix tool [50]. LD threshold was set to default 0.8 and populations of European ancestry were selected. Data were downloaded and imported in R. Visualisation of LD data within the genomic environment was undertaken using the Gviz package in R and Bioconductor [51]. After delimiting the region of interest, genes within that region were downloaded from the Ensembl repository using the BioMart package [52, 53]. A heatmap of LD data imported from LDlink was created. Finally, data were plotted using the plotTrack function in Gviz.

Second, I customised a recently developed R package eQTpLot to analyse co-localisation between association signals and eQTLs signals [54]. Briefly, expression quantitative trait loci (eQTL) signals from fresh frozen hippocampal tissue (from the Miami Brain Bank) were downloaded from GTEx Portal. This publicly available repository provides eQTL analysis from

449 individuals across 44 tissues [55]. The following information was retrieved for each eQTL signals for genes within the locus of interest (LOI): Ensembl gene ID, variants ID (dbSNP), normalized effect size (NES), nominal P value. The NES corresponds to the ß regression coefficient of the association between the minor allele and the transcript expression level. The plot produced (eQTL colocalization GWAS plot) highlights SNPs passing the P_{FDR} threshold of 0.05. Each SNP passing the eQTL threshold of $1x10^{-4}$ is represented by a triangle. The direction of the triangle shows the direction of the variant's effect on the biomarker in the association analysis. The colour of the triangle shows whether the association effect with the biomarker and the eQTL normalised effect size for the variant is congruent (going in the same direction) or incongruent (going in the opposite direction). The more intense the colour, the more significant the statistical association is.

Third, regulatory information was retrieved from Haploreg v4.1 [56]. Histone modification marks based on CHiP (Chromatin Immunoprecipitation) were obtained from the Roadmap Epigenomics project [57]. Available information for genomic regions enriched in histone H3 lysine 4 monomethylation (H3K4me1) and H3K27 acetylation (H3K27ac), which are known to be associated with enhancers and enhancer activation, as well as regions enriched in H3K4 trimethylation (H3K4me3) and H3K9ac (histone H3 lysine 9 acetylation marks), which are associated with promoters and increased promoter activation, respectively, was utilised. I obtained data on chromatin states from Roadmap Epigenomics which used ChromHMM. Briefly this algorithm based on a multivariate Hidden Markov Model classifies regions of the genome into 15 states based on the absence or presence of typical chromatin marks [58]. Additionally, I obtained information on DNase hypersensitivity, which denotes chromatin regions often associated with the binding of transcription regulators. Finally, the effects on regulatory motifs (also called TF binding sites), which are short sequences of 6-15 bp located upstream of a gene and control transcription, were collected from CHiP sequencing data from the ENCODE Project [59]. For all above mentioned steps, I selected only information related to cell lines from the hippocampus (E071).

Fourth, risk SNPs for diseases were obtained from VARAdb v1.0, a recent functional annotation database which implements a data mining approach from following open-access repositories: NHGRI GWAS catalog, GWASdb v2.0, GAD, Johnson and O'Donnell and GRASP [60].

4.3. Results

4.3.1. Demographics

The total sample size with whole genome sequencing data consists of 750 individuals. The mean age is 73.42 ± 7.03 years and female participants represent 42.93% (322) of the total cohort. Mean years of education was 16.13 ± 2.79 years. A total of 306 (40.80%) individuals carried at least one *APOE* ε4 allele. The number of genotyped individuals for whom biomarker measurements was available varied according to the biomarker: 580 for $A\beta_{1\text{-}42}$ and p-tau_{181p}, 573 for t-tau, 187 for sTREM2, 114 for BACE1 activity in the CSF and 123 individuals with NfL measurements in the CSF (*Table 1*)

4.3.2. Description of the miRNA gene environment

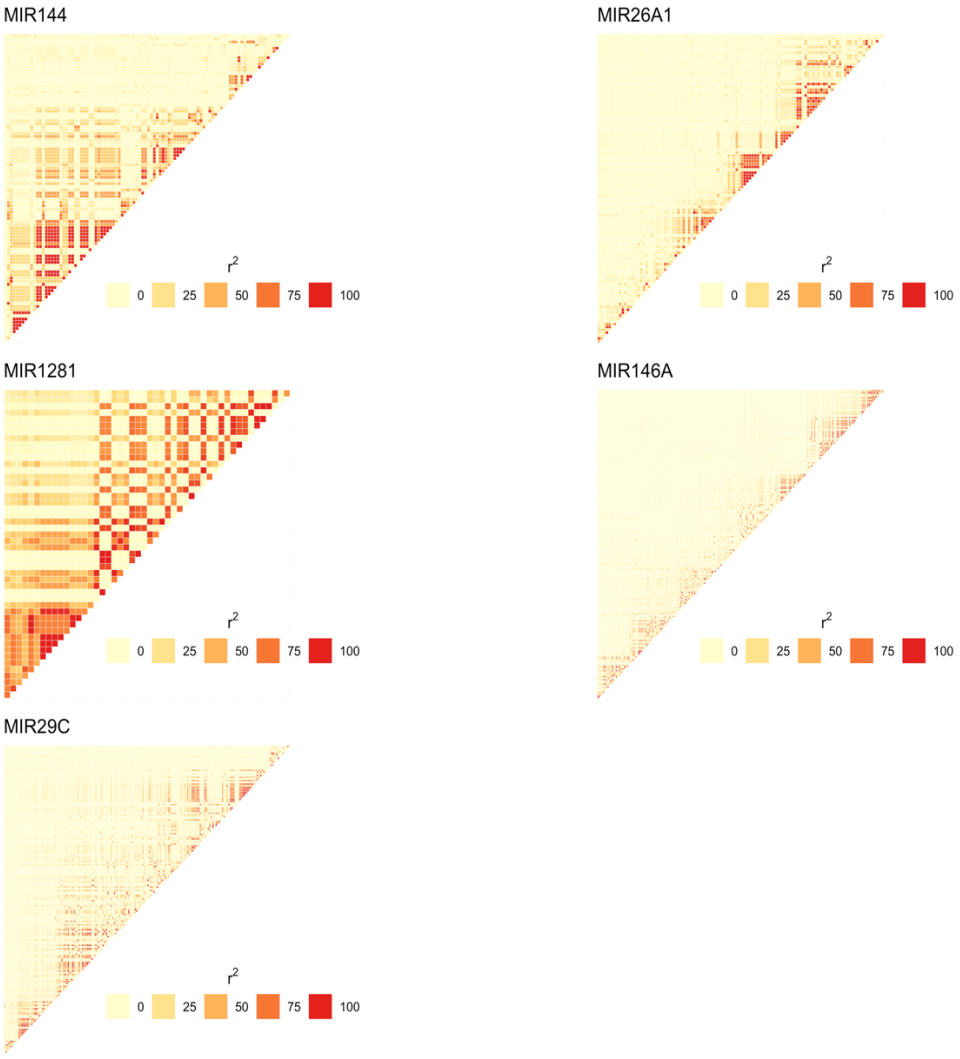
All miRNA genes were located on separate chromosomes (*Table 2*). The median miRNA gene length was 84.00 [78.25-87.50] with *MIR146A* being the longest gene. None of the 99 SNPs located within the six miRNA genes had a MAF > 0.05. The number of SNPs with MAF > 0.05 located within 200kb varied between the miRNA genes, with a minimum of 25 for *MIR363* to a maximum of 206 for *MIR146A*. Using the latest UCSC genome browser, 40 genes within 200 kb of the six miRNA genes were identified, with a maximum of 25 genes for *MIR144*. The length of haplotype blocks varied from no haplotype block to 34 haplotype blocks (*Figure 1*).

Table 1: Demographics of the whole genome sequencing cohort and the individual biomarker cohort							
	ALL	BIOMARKER COHORT					
		$A\beta_{1-42}$	t-tau	p-tau_{181p}	sTREM2	BACE1 activity	NfL
N	750	580	573	580	187	114	123
Age (years)	73.42 ± 7.03	73.03 ± 7.12	73.04 ± 7.14	73.03 ± 7.12	72.85 ± 6.82	74.45 ± 6.23	74.36 ± 6.15
Sex (F:M)	322:428	250:330	248:325	250:330	71:116	41:73	46:77
Education (years)	16.13 ± 2.79	16.18 ± 2.75	16.18 ± 2.75	16.18 ± 2.75	15.87 ± 2.94	16.05 ± 3.03	15.88 ± 3.14
APOE ε4 status (≥ 1 risk allele : < 1 risk allele)	306:444	231:349	227:346	231:349	75:112	43:71	47:76
DIAGNOSIS							
CN	255	188	187	188	47	55	57
eMCI	218	197	195	197	91	0	0
lMCI	232	153	152	153	49	59	66
AD	45	42	39	42	0	0	0
BIOMARKERS							
$A\beta_{42}$ (pg/mL)		179.75 ± 54.01					
ttau (pg/mL)			83.15 ± 45.82				
ptau181 (pg/mL)				38.69 ± 23.02			
sTREM2 (pg/mL)					4599.19 ± 2576.53		
BACE1 activity (pM)						49.08 ± 20.04	
NF-L (pg(mL)							1211.86 ± 444.27

Legend: AD (Alzheimer's Disease), CN (Cognitive Normal), eMCI (early Mild Cognitive Impairment), lMCI (late Mild Cognitive Impairment), NF-L (Neurofilament Light Chains). Results are presented as mean ± standard deviation.

Table 2: miRNA gene environment							
RefSeq MIRNA	chr	strand	length	start	end	N SNPs*	RefSeq of genes within ± 200 kb of the gene
MIR128-1	2	+	82	136422967	136423048	60	*R3HDM1, MIR128-1*
MIR144	17	-	86	27188551	27188636	99	*SDF2, SUPT6H, PROCA1, RAB34, RPL23A, SNORD42B, SNORD4A, SNORD42B, SNORD4B, SNORD42A, TLCD1, NEK8, TRAF4, FAM222B, ERAL1, MIR451A, MIR451B, MIR144, MIR4732, FLOT2, DHRS13, PHF12, LOC101927018, SEZ6, PIPOX*
MIR146A	5	+	99	159912359	159912457	206	*MIR3142HG, MIR146A*
MIR26A1	3	+	77	38010895	38010971	109	*CTDSPL, MIR26A1*
MIR29C	1	-	88	207975197	207975284	181	*CR1, CR1L, CD46, MIR29B2CHG, MIR29C, MIR29B2, LOC148696, CD34*
MIR363	X	-	75	133303408	133303482	25	*MIR363*
*number of SNPS Minor Allele Frequency ≥ 0.05 **Legend:** chr: chromosome, RefSeq National Center for Biotechnology Information Reference Sequence, SNP: Single Nucleotide Polymorphism							

Figure 1: Haplotype block for each miRNA gene



* no haplotypes were identified for the region of interest *MIR363*

4.3.3. Association analysis with $A\beta_{1-42}$ levels in the CSF

After adjusting for age, sex, education years, *APOE* ε4 status and diagnosis at baseline, I identified eight SNPs within *MIR29C* to be significantly associated with Aß42 levels after multiple testing correction. The top associated SNPs are rs2724384 and rs2761437, two SNPs in high LD (r^2 0.99). Individuals with the minor allele "G" for rs2724384 and "A" for rs2761337 had lower $A\beta_{1-42}$ levels in the CSF in a dose dependent fashion. (rs2724384: ß: -0.03023, 95% CI: -0.04728 ; -0.01319, P = 5.464 x 10^{-04}, P_{FDR}= 1.648 x 10^{-02}; rs2761437: ß: -0.03023, 95% CI: -0.04728 ; -0.01319, P = 5.464 x 10^{-04}, P_{FDR}= = 1.648 x 10^{-02}) (*Table 3*).

4.3.4. Association analysis with t-tau and p-tau_{181p} levels in the CSF

I did not find any SNPs significantly associated with t-tau and p-tau_{181p} CSF levels at FDR significance levels.

4.3.5. Association analysis for neurofilament levels in the CSF

I did not find any SNPs significantly associated with NfL levels in the CSF

4.3.6. Association analysis with sTREM2 levels in the CSF

After multiple testing correction, three SNPs rs17041871 (T: ß: -0.17030, 95% CI: -0.26010 ; -0.08055, P = 2.705 x 10^{-04}, P_{FDR}= 1.632 x 10^{-02}), rs606714 (G: ß: -0.15980, 95% CI: -0.24230 ; -0.07732, P = 2.024 x 10^{-04}, P_{FDR}= 1.632 x 10^{-02}) and rs671273 (A: ß: -0.15980, 95% CI: -0.24230 ;-0.07732, P = 2.024 x 10^{-04}, P_{FDR}= 1.632 x 10^{-02}) within ± 200 kb of *MIR29C* were associated with sTREM2 levels in the CSF after adjusting for age, sex, education years, *APOE* ε4 status and diagnosis at baseline. SNP rs606714 and rs671273 are in high LD. For each SNP, carrier of the respective minor allele had lower sTREM2 levels in the CSF (*Table 3*).

4.3.7. Association analysis with BACE1 activity in the CSF

I found a total of 20 SNPs within ± 200 kb of *MIR29C* to be associated with BACE1 activity after multiple testing correction. The top SNP is rs1204682 and carrier of the minor allele A had lower BACE1 activity levels in the CSF (ß= -0.08436, 95% CI: -0.12450 ; -0.04425, P= 7.624 x 10^{-05}, P_{FDR}= 8.473 x 10^{-03}) (*Table 3*).

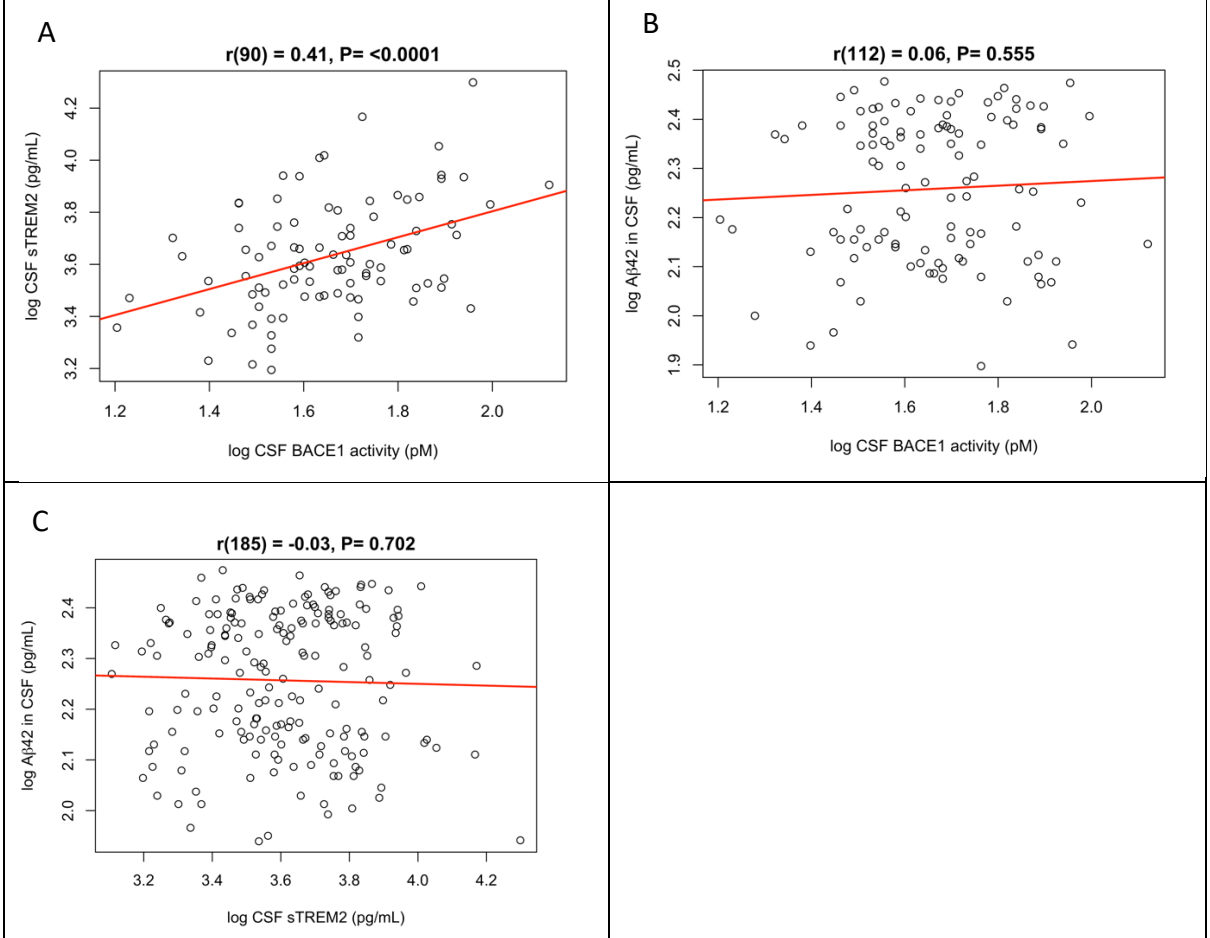
4.3.8. Overlapping SNPs within the *MIR29C* are associated with multiple AD biomarkers

In the previous analysis I have identified that SNPs within ± 200kb of *MIR29C* were significantly associated with CSF biomarkers of microglial activation sTREM2 and CSF biomarkers of the amyloid cascade: BACE1 activity levels and Aß42 levels. I identified a total of 7 SNPs (rs2724384, rs2761437, rs4844390, rs4844623, rs7532674, rs7550821 and rs882198) which were significantly associated with both BACE1 activity levels and Aß42 levels in the CSF. A correlation between *MIR29C* associated biomarkers revealed a positive correlation between log BACE1 activity and log sTREM2 levels (r(90)=0.41, P value < 0.0001) (*Figure 2*). In a multivariate regression analysis adjusting for age, sex, diagnosis at baseline, APOE ε4 status, log sTREM2 levels were significantly associated with log BACE1 activity levels in the CSF ($F(5,86)=5.38$, $p<0.0001$, $R^2=0.24$, R^2adjusted=0.19). The regression coefficient (ß=0.34, 95% CI [0.18,0.49]) shows that for a 10% increase in BACE1 activity in the CSF, the sTREM2 levels in the CSF increase by 3.3%. Multivariate regression analysis did not show significant association between sTREM2 and Aß42 as well as BACE1 activity and Aß42.

Table 3: Significant association analysis results							
Chr	SNP	bp	Minor allele	N	ß [L95;U95]	P_{UNADJ}	P_{FDR}
$A\beta_{42}$ (pg/mL)							
1	rs2724384	207930203	G	572	-0.03 [-0.05;-0.01]	5.46E-04	0.01648
1	rs2761437	207923081	A	572	-0.03 [-0.05;-0.01]	5.46E-04	0.01648
1	rs4844390	207934849	G	571	-0.03 [-0.05;-0.01]	5.26E-04	0.01648
1	rs4844623	208035434	A	571	-0.03 [-0.05;-0.01]	3.05E-04	0.01648
1	rs7532674	208026739	T	572	-0.03 [-0.04;-0.01]	1.41E-03	0.03638
1	rs7541230	207957555	C	572	-0.02 [-0.04;-0.01]	2.20E-03	0.04967
1	rs7550821	208029947	T	571	-0.03 [-0.05;-0.01]	2.68E-04	0.01648
1	rs882198	208036509	T	572	-0.03 [-0.05;-0.01]	3.39E-04	0.01648
BACE1 activity (pM)							
1	rs1009897	208063505	A	114	-0.07 [-0.11;-0.02]	4.07E-03	0.04095
1	rs1204682	208077006	A	114	-0.08 [-0.12;-0.04]	7.62E-05	0.008473
1	rs12409962	208044601	C	114	-0.08 [-0.13;-0.03]	2.34E-03	0.03046
1	rs1555138	208086100	C	114	0.11 [0.05;0.16]	1.60E-04	0.008473
1	rs2250321	208065610	A	114	-0.08 [-0.12;-0.04]	2.34E-04	0.008473
1	rs2724373	207999200	T	112	0.07 [0.02;0.11]	2.52E-03	0.03046
1	rs2724384	207930203	G	114	-0.09 [-0.14;-0.03]	2.38E-03	0.03046
1	rs2761437	207923081	A	114	-0.09 [-0.14;-0.03]	2.38E-03	0.03046
1	rs2785627	208154852	T	114	-0.10 [-0.15;-0.05]	2.11E-04	0.008473
1	rs2796247	208036976	C	114	-0.06 [-0.11;-0.02]	3.28E-03	0.03626
1	rs3738460	208071105	C	114	0.12 [0.05;0.18]	4.88E-04	0.0126
1	rs4844390	207934849	G	114	-0.09 [-0.14;-0.03]	2.38E-03	0.03046
1	rs4844623	208035434	A	113	-0.09 [-0.15;-0.04]	9.49E-04	0.01717
1	rs656801	208077643	C	114	0.11 [0.05;0.17]	3.41E-04	0.0103
1	rs7532674	208026739	T	114	-0.08 [-0.14;-0.03]	4.89E-03	0.04428
1	rs7550821	208029947	T	114	-0.09 [-0.15;-0.04]	7.84E-04	0.01576
1	rs761277	207993011	G	113	0.06 [0.02;0.11]	4.89E-03	0.04428
1	rs882198	208036509	T	114	-0.09 [-0.15;-0.04]	7.84E-04	0.01576
1	rs926628	208040165	C	114	0.09 [0.04;0.13]	2.09E-04	0.008473
1	rs984984	208035088	G	113	-0.06 [-0.11;-0.02]	3.41E-03	0.03626
sTREM2 (pg/mL)							
1	rs17041871	208156967	T	184	-0.17 [-0.26;-0.08]	2.71E-04	0.01632
1	rs606714	208151575	G	184	-0.16 [-0.24;-0.08]	2.02E-04	0.01632
1	rs671273	208145061	A	184	-0.16[-0.24;-0.08]	2.02E-04	0.01632

Legend: ß: regression coefficient, L95: lower limit of 95% confidence interval, N: Number of individuals, P_{FDR}: FDR adjusted P value , P_{UNADJ}: unadjusted P value, U95: upper limit of 95% confidence interval

Figure 2 : Correlation plots between biomarkers associated with SNPs located in close proximity to *MIR29C*



A. Correlation between log CSF BACE1 activity and log CSF sTREM2. **B.** Correlation between log CSF BACE1 activity and log CSF Aβ42. **C.** Correlation between log CSF sTREM2 and log CSF Aβ42. **Legend**: CSF: cerebrospinal fluid, r: Spearman correlation

4.3.9. Functional relevance of SNPs associated with CSF biomarkers

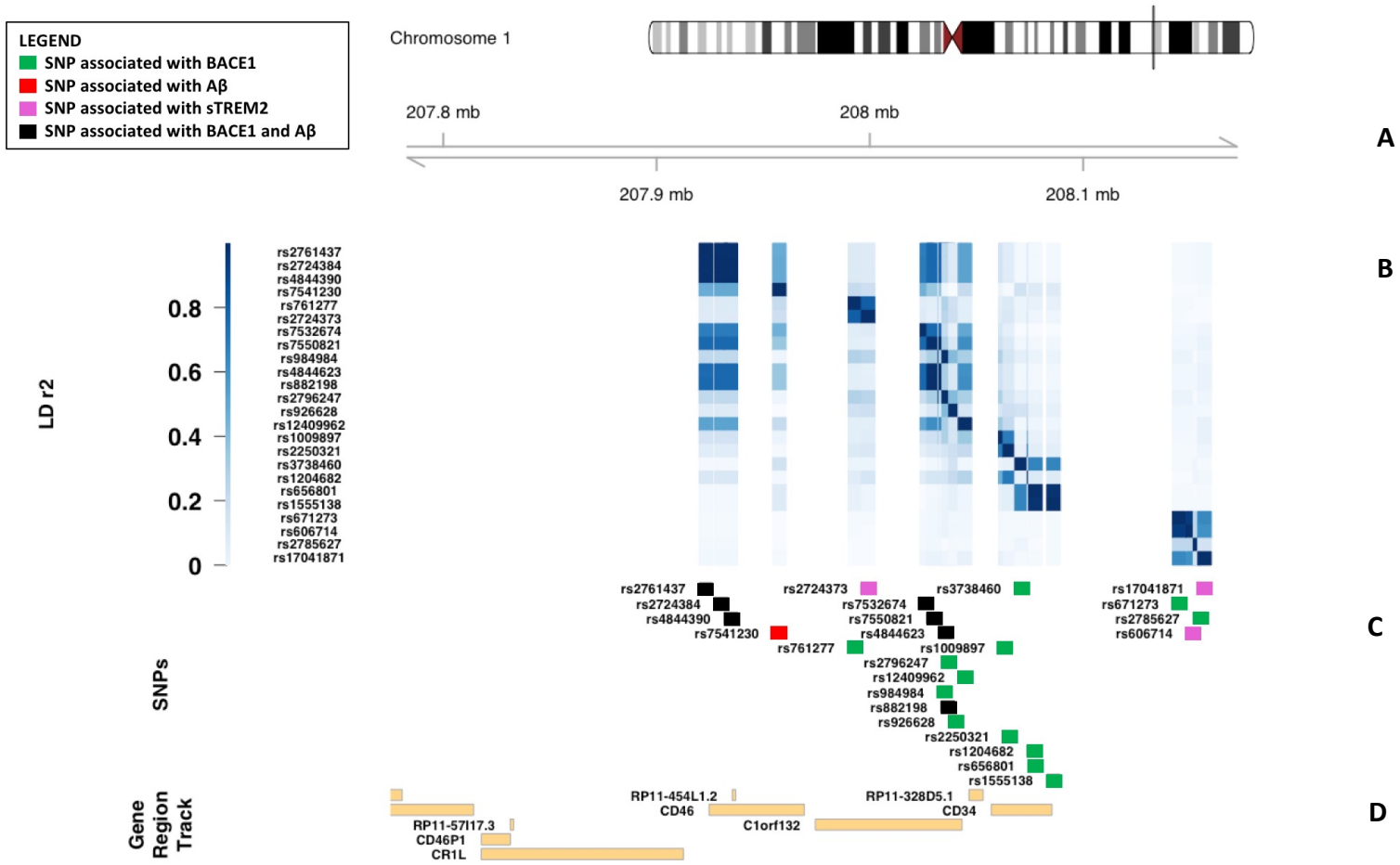
Within ± 200 kb of *MIR29C*, the association analysis in the CSF revealed 8 significant SNPs associated with Aß42 levels, 20 significant SNPs associated with BACE1 activity and 3 significant SNPs associated with sTREM2 levels. Seven SNPs (rs2724384, rs2761437, rs4844390, rs4844623, rs7532674, rrs7550821, s882198) were associated both with Aß42 levels and BACE1 activity. Two of these SNPs (rs2724384, rs4844390) are intronic variants of *CD46*. Among the 24 SNPs identified, 9 SNPs (37.5%) occurred within an intronic region of a gene (*CD34, CD46, LOC148696*) (*Figure 3*). A search in VARAdb revealed GWAS associations with glioma, gene expression of *CD46, CD34* and *MIR29C* as well as PD (*Table 4*).

Investigation of chromatin marks revealed that in hippocampal cells, significant SNPs associated with Aß42 and BACE1 activity are located within regulatory regions predominantly with enhancer activity. Chromatin states analysis using ChromHMM showed that three SNPs (rs4844623, rs7532674 and rs7550821) associated with Aß42 and BACE1 activity and three SNPs (rs12409962, rs2796247and rs2250321) associated with BACE1 activity alone, were in enhancer regions. Two SNPs associated with BACE1 activity (rs2724373 and rs926628) were in TssAFlnk promoter like states and one SNP (rs761277) was located in TxFlnk, both a promoter and enhancer signature (*Figure 4*). The latter is an intronic SNP for *LOC148696* which was reported to regulate the expression of *CD34* in dendritic cells. No SNPs locate in a DNase I hypersensitivity region.

Chromatin Immunoprecipitation sequencing data from ENCODE reveals that SNPs associated with BACE1 activity, Aß42 and sTREM2 are affecting the binding of several brain specific transcription factors (TF) among which the REST (repressor element-1 silencing) TF (alias Neural-Restrictive Silencer Factor) (*Table 5*). SNPs rs1555138 and rs2250321, which are associated with BACE1 activity, are affecting binding sites of Sin3 and TCF12, which are TF regulating neurogenesis and neuronal differentiation. SNP rs2250321, an intronic variant of *CD34*, which is also associated with BACE1 activity, affects the binding of AP-1, a TF reported to increase brain derived neurotrophic factor (BDNF) production in cortical neurons. Interestingly, SNP rs7532674 which is associated with Aß42 interferes with the binding of the zinc-finger TF specificity protein 1 (Sp1) which is reported to regulate the expression of *BACE1*, *APP*, *TAU* and *PSEN2*. Other SNPs associated with Aß42 levels were in regions affecting the

binding of TF involved in regulating neuronal differentiation. One SNP rs2761437 also associated with BACE1 activity was located within binding region for Mef2, a TF involved in regulating microglial phenotype in the presence of amyloid plaques. SNP rs7541230, which is an intronic variant of *CD46* altered the binding of PLZF, which interacts with CEBPD (CCAAT/enhancer binding protein delta), a TF involved in apoptosis in astrocytes of AD mice models. Finally, one SNP rs606714 associated with sTREM2 affected the binding of TF belonging to the Forkhead box transcription family, which is involved in regulating apoptosis, neuronal mitochondrial dysfunction in response to Aß exposure as well as microglial production of pro-inflammatory cytokines in response to amyloid ß.

Figure 3: Integrated genomic plot showing genomic region for *MIR29C*



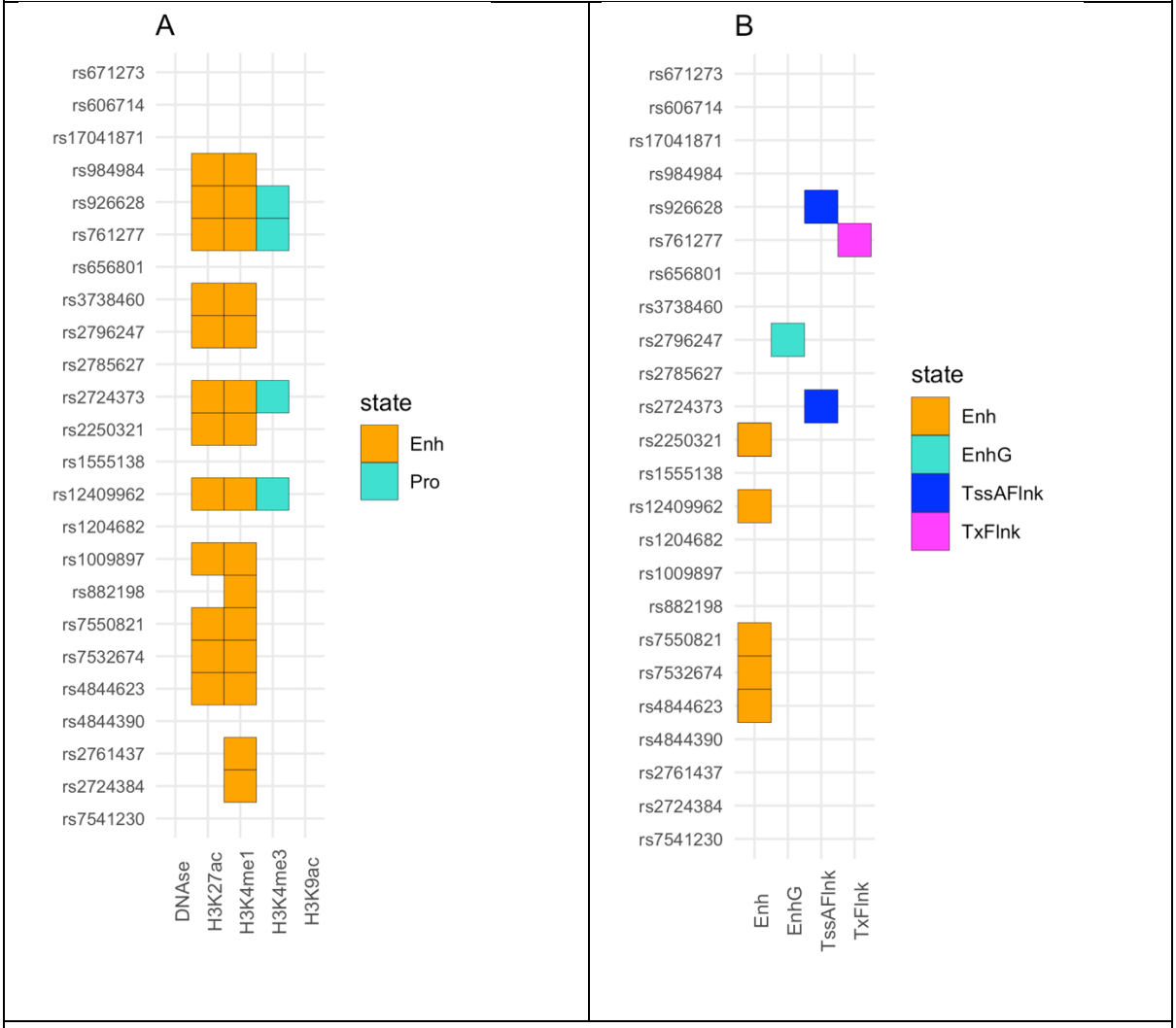
Panel A shows the genomic location of *MIR29C*. **Panel B** shows the LD (r^2) for the SNPs significantly associated with the CSF biomarkers. **Panel C** shows the genomic location for each significant SNP. The color of each SNP represents the biomarker with which the SNP is associated. **Panel D** shows the genes in close proximity of the significant SNPs.

Table 4: Significant SNPs overview										
Chr	Start	End	Name	Strand	Ref NCBI	Function	Nearest gene	Distance	Motifs	Diseases
Aß										
1	207957554	207957555	rs7541230	+	T	intron	CD46	0	Foxj2_2;PLZF; Sox_18;Sox_19	refractive error, glioma
Aß BACE1										
1	207930202	207930203	rs2724384	+	G	intron	CD46	0	Hoxa5_1; Zfp691	gene expression of *MIR29C* in normal prepouch ileum, febrile seizures, immune response to measles vaccine, glioma
1	207923080	207923081	rs2761437	+	A	unknown	CD46	2300	Hbp1; Mef2_known3	paternal transmission distortion, glioma
1	207934848	207934849	rs4844390	+	A	intron	CD46	0	CTCF_disc1; TCF12_disc2	glioma
1	208035433	208035434	rs4844623	+	T	unknown	CD34	24447	Myf_1;PEBP; SEF-1	glioma
1	208026738	208026739	rs7532674	+	G	unknown	LOC 148696	30797	CCNT2_disc2; NRSF_known3; SP1_disc3; SP2_disc3	none
1	208026738	208026739	rs7532674	+	G	unknown	LOC 148696	30797	CCNT2_disc2;NRSF_known3;SP1_disc3;SP2_disc3	none
1	208036508	208036509	rs882198	-	C	unknown	CD34	23372	Myf_1; SMC3_disc2	glioma
1	208029946	208029947	rs7550821	+	C	unknown	CD34	29934	Foxa_known4; Foxo_2; HNF1_5; Nanog_disc2; Pou5f1_disc1; Pou5f1_known2; Sox_13;Sox_4	glioma
BACE1										
1	208063504	208063505	rs1009897	+	G	intron, untrsl 5'	CD34	0	NA	hypertension (early onset hypertension), primary rhegmatogenous retinal detachment, glioma
1	208077005	208077006	rs1204682	+	G	intron	CD34	0	Bbx	primary rhegmatogenous retinal detachment, transmission distortion, infant head circumference
1	208044600	208044601	rs12409962	+	T	unknown	CD35	15280	YY1_disc2	glioma

Continued										
1	208086099	208086100	rs1555138	+	C	near-gene-5	CD36	1416	HDAC2_disc3; NRSF_known1; NRSF_known2; NRSF_known3; Sin3Ak-20_disc7; Znf143_known1	mitral annular calcium, Parkinson's disease
1	208065609	208065610	rs2250321	-	G	intron, near-gene-5	CD34	0	AP-1_known1; BRCA1_known2; Mxi1_disc1; SREBP_disc1; TCF12_disc2	gene expression of CD34 in dendritic cells, gene expression of CD34 in dendritic cells treated with Mycobacterium tuberculosis
1	207999199	207999200	rs2724373	+	C	unknown	LOC 148696	3258	NA	refractive error, obesity with early age of onset (age >2), general cognitive ability
1	208154851	208154852	rs2785627	-	T	unknown	PLXNA2	40734	NA	none
1	208036975	208036976	rs2796247	+	C	unknown	CD34	22905	RXRA_known4	primary rhegmatogenous retinal detachment, obesity with early age of onset (age >2), glioma
1	208071104	208071105	rs3738460	-	A	intron	CD34	0	GATA_known1; TAL1_disc1	Parkinson's disease, years of education
1	208077642	208077643	rs656801	+	C	intron	CD34	0	Ets_known1	mitral annular calcium, Parkinson's disease
1	207993010	207993011	rs761277	+	A	intron, ncRNA	LOC 148696	0	Pax-4_4	gene expression of CD34 in dendritic cells, gene expression of CD34 in dendritic cells treated with Mycobacterium tuberculosis, automobile speeding propensity, glioma
1	208040164	208040165	rs926628	+	T	unknown	CD34	19716	NA	none
1	208035087	208035088	rs984984	+	G	unknown	CD34	24793	NA	obesity with early age of onset (age >2), glioma
sTREM2										
1	208156966	208156967	rs17041871	+	C	unknown	PLXNA2	38619	Sox_10;Sox_14;Sox_16;Sox_18;Sox_19; Sox_2;YY1_known6	none
1	208151574	208151575	rs606714	+	G	unknown	PLXNA2	44011	CEBPA_2; Foxa_known4; Foxf1;Foxf2; Foxl1_1;Foxo_1; Foxo_2;Foxq1; Hsf_disc1;TEF	none
1	208145060	208145061	rs671273	+	A	unknown	PLXNA2	50525	CTCF_known1; Pax-_4; Rad21_disc1	None
Legend: intron variant occuring within an intron, near-gene-5: variant located 5' of a gene, untsl-5: a UTR variant of the 5' UTR										

A large number of SNPs significantly associated with BACE1 and or Aß42 levels are in LD with the two intronic variants of *CD46* (rs2724384, rs4844390). To examine whether the association with BACE1 activity could be mediated by the effect on *CD46* expression, I extracted eQTL information from GTEx for the hippocampus. Among the SNPs significantly associated with BACE1, 8 (40%) were eQTLs for *CD46*. All 6 SNPs were in LD with the two intronic SNPs; all showed the same direction of effect in the association analysis – with carrier of at least one minor allele having lower BACE1 activity in the CSF. The eQTL effect size was however different between the SNPs: two SNPs, rs2761437 and rs2724384 increase the expression of *CD46* in the hippocampus, while the other five SNPs decrease its expression (*Figure 5*). For SNPs associated with Aß42 levels, all were eQTLs for *CD46* suggesting that the association might be mediated through the effect of these SNPs on *CD46* (*Figure 6*). None of the SNPs associated with sTREM2 were eQTLs for *CD46* (*Figure 7*). Finally, for all SNPs significantly associated with BACE1 activity, Aß42 levels in the CSF and sTREM2, I did not identify any eQTLs for *CD34*, *MIR29C* or *CR1* in the eQTL GTEx database for the hippocampus.

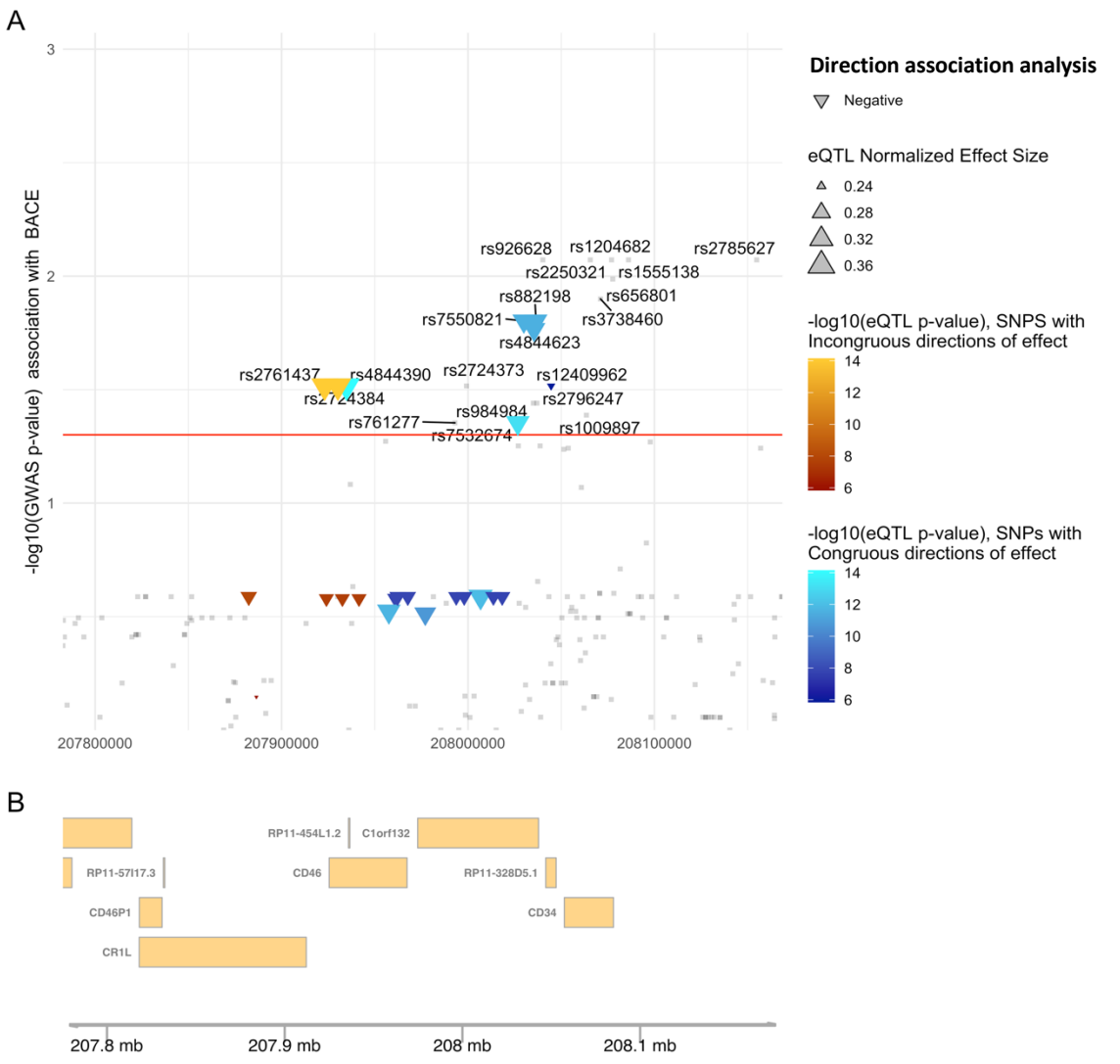
Figure 4: Chromatin marks (A) and states (B) for the significant SNPs from the Roadmap Epigenomics project



A. Histone modification marks and DNAse sensitivity for the significant SNPs with corresponding activity state (enhancer or promoter). **B** Chromatin states based on ChromHMM. **Legend:** Enh: enhancer, EnhG: genic enhancer, TssAFlnk: Flanking Active TSS, TxFlnk: Transcr. at gene 5' and 3'

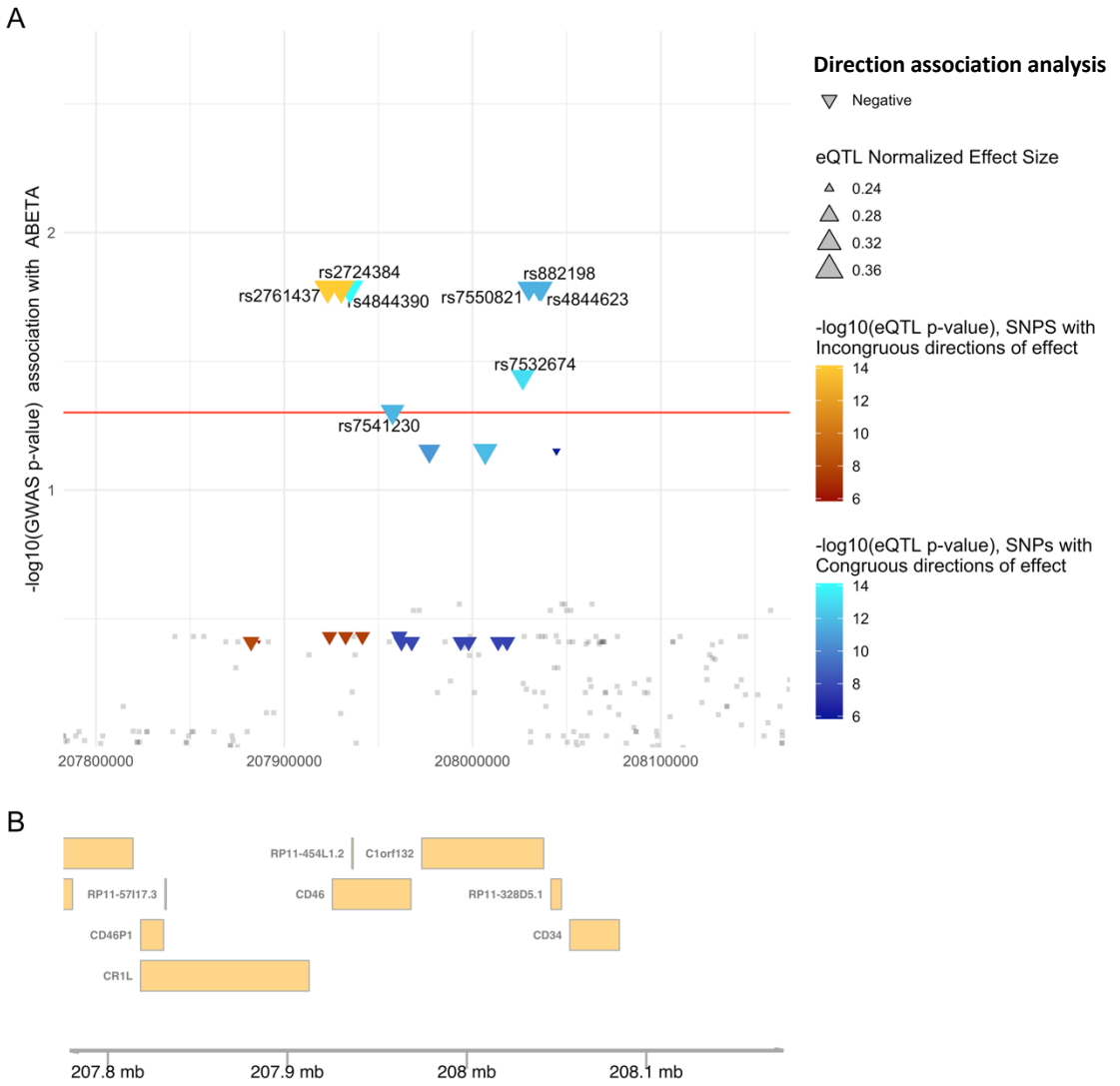
Table 5: Role of selected brain specific transcription factors for which binding is affected by significant SNPs associated with Aβ42, BACE1 and sTREM2 levels in the CSF	
Transcription factor	Clinical significance
AP-1_known1	upregulation of BDNF in cortical neurons of rats [61]; regulation of dendrite growth in the drosophilia [62]; involved in the regulation of APP in human glial cells [63]
CTCF_disc1, CTCF_known1	increased APP expression in hippocampus of rat model [64]; in mice downregulation of CTCF transcription factor increased in the number of microglia in the anterior cingulate cortex leading to gliosis and eventually neuronal death [65]
Ets_known1	regulates axon guidance and dendritic morphology during development [66]
Foxa_known4, Foxf1, Foxf2, Foxj2_2, Foxl1_1, Foxo_1, Foxo_2, Foxq1	Forkhead transcription factors family are involved in neuronal death, neuronal response to amyloid ß exposure leading to mitochondrial dysfunction, pro-inflammatory cytokines production, apoptosis [67, 68]
GATA_known1	regulates SCNA transcription in dopaminergic neurons leading to increased levels of α-synuclein [69]
Hbp1	neuronal differentiation in neurogenesis in mice models [70]
HDAC2_disc3	reduced expression of HDAC2-Sp3 in AD patients and AD mouse models, inhibition of HDAC2-Sp3 increased synaptic activity and plasticity in an AD mouse model [71]
Hoxa5_1	motor neuron differentiation in mice models [72]
Hsf_disc1	involved in proteostasis in neuronal cells through the regulation of HSP (heat shock protein) expression [73]; increases APP expression through binding of heat shock elements [74]
Mef2_known3	involved in microglial homeostasis; suppression of Mef2 associated with microglial phenotype associated with amyloid plaques in AD cortex [75]
Mxi1_disc1	involved in neuronal differentiation in xenopus [76]
NRSF_known1, NRSF_known2, NRSF_known3	NRSF (also known as repression element 1 silencing transcription factor) bind to neuron-restrictive silencer elements of the choline acetyltransferase gene in non-neuronal cells of animal models [77, 78]; protective effect on neuronal cells [79]; missense variation in REST associated with hippocampal volume loss [80];
PLZF	involved in cortical neurogenesis in mouse brains [81]; interacts with CEBPD to inhibit apoptosis in astrocytes of AD mice models [82]
Pou5f1_disc1, Pou5f1_known2	involved in cortical neurogenesis in mice [83]
RXRA_known4	variation in RXRa gene increases risk of AD through the regulation of genes involved in cholesterol metabolism [84]
Sin3Ak-20_disc7	regulated the expression of neuronal genes and neuronal differentiation [85]
Sox_2	stimulates the non-amyloidogenic processing of ßAPP by stimulating ADAM10 activity [86]
SP1_disc3	regulates expression of APP, tau, PSEN2 promoter transcription and BACE1 [87-92]; in AD mouse model, inhibition of Sp1 increased memory deficits [93]
SP2_disc3	involved in neurogenesis [94]
SREBP_disc1	regulates cholesterol metabolism for the synthesis of the myelin membrane [95]
TAL1_disc1	involved in neurogenesis of GABAergic neurons [96]
TCF12_disc2,	involved in neurogenesis in mice models [97]
YY1_disc2, YY1_known6	involved in neurogenesis in mice models [98]

Figure 5: eQTL results for SNPs associated with BACE1 activity and effect on *CD46* expression



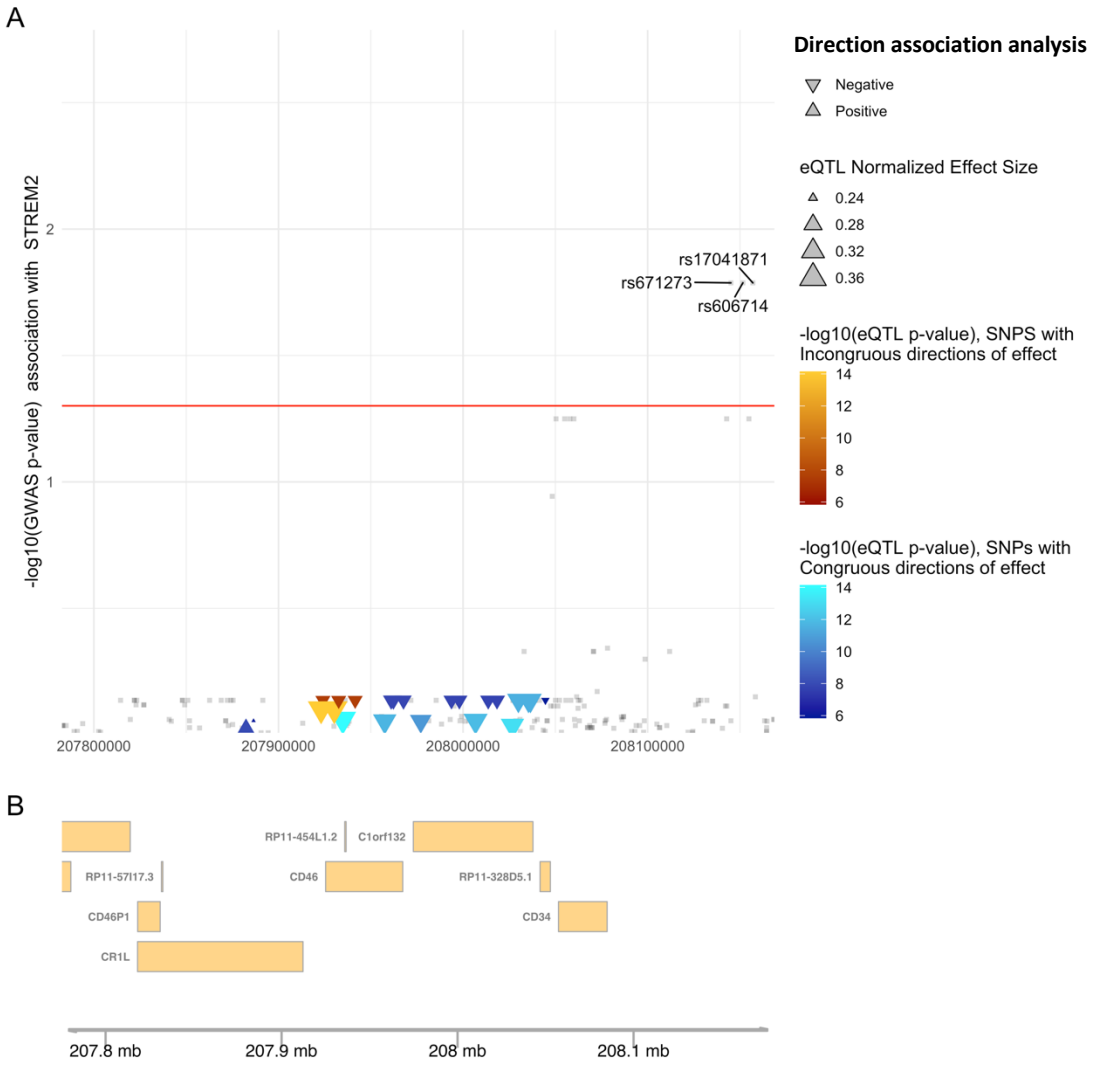
Part A: colocalization between eQTL signals and SNPs significantly associated with BACE1 activity levels in the CSF. The size of the triangle is proportional to the normalised effect size. The direction of the triangle shows the direction in the association analysis. The colour shows whether the direction of association is congruous or incongruous to the eQTL effect size.
Part B: genomic environment

Figure 6: eQTL results for SNPs associated with Aß42 levels and effect on *CD46* expression



Part A: colocalization between eQTL signals and SNPs significantly associated with Aß42 levels in the CSF. The size of the triangle is proportional to the normalised effect size. The direction of the triangle shows the direction in the association analysis. The colour shows whether the direction of association is congruous or incongruous to the eQTL effect size.
Part B: genomic environment

Figure 7: eQTL results for SNPs associated with sTREM2 levels and effect on *CD46* expression



Part A: colocalization between eQTL signals and SNPs significantly associated with sTREM2 activity levels in the CSF. The size of the triangle is proportional to the normalised effect size. The direction of the triangle shows the direction in the association analysis. The colour shows whether the direction of association is congruous or incongruous to the eQTL effect size.
Part B: genomic environment

4.4. Discussion

I identified significant associations for SNPs located within 200 kb of *MIR29C* with Aß42 and sTREM2 levels as well as BACE1 activity in the CSF. Functional annotations targeted on hippocampal cells show that these SNPs are located in regulatory regions and affect the binding of TF reported to be involved in regulating neuronal differentiation, microglial response to Aβ deposition as well as in the amyloidogenic pathway.

My results point towards a possible interplay between the amyloid cascade and microglial activation in early stages of cognitive impairment. In particular, I identified a positive correlation between BACE1 activity and sTREM2 levels in the CSF. Different indirect evidence in the literature offer some possible explanations for this positive correlation. First, increased BACE1 activity has been reported in MCI brains [99]; also in individuals with MCI, increased microglial activation on 11C-(R)PK11195 PET imaging has been described [100]. Microglial activation is mediated by TREM2 as suggested by a mouse model with the TREM2 p.T66M mutation [101]. Second, in an experimental AD mouse model, increased microglia activation with expression of pro-inflammatory cytokines IL-1ß and IL-6 were reported at the same time as increased total BACE1 activity in early stages of 3 months old APP transgenic mice [102]. However, some findings in the literature suggest a negative correlation between BACE1 activity and sTREM2. For example, administration of a BACE1 inhibitor in the ventricles of an AD mouse model resulted in an increase in microglial activation [103]. Furthermore, recent analyses from ADNI revealed decreased CSF sTREM2 levels in asymptomatic individuals with isolated decreased Aß CSF levels [101]. Further studies are needed to explore the relationship between these two biomarkers.

Our results highlight the role of *MIR29C* in regulating BACE1 gene expression which is in line with previous findings. For example, in 31 AD brains, downregulation of hsa-miR-29c-3p was positively correlated with increased BACE1 expression and increased Aß deposition [104]. In another study, downregulation of hsa-miR-29c-3p in the peripheral blood of AD patients correlated with reduced levels of BACE1. Authors then explored this association in

hippocampal neurons and confirmed that upregulation of hsa-miR-29c-3p decreased BACE1 expression levels [105].

Interestingly, ChiP data from the Roadmap Epigenomics project show that several SNPs alter the binding of TF linked to the pathogenesis of AD in hippocampal cells. For example, SNP rs2250321 which is significantly associated with BACE1 activity levels (minor allele carriers have reduced BACE1 activity levels in the CSF) affects the binding of AP-1, a TF shown to upregulate BDNF expression in cortical neurons. These results need further investigation as in an AD mouse model, BACE1 inhibition was associated with restoration of altered BDNF-TrkB signalling pathways which are involved in learning and long term potentiation [106]. I have also found that rs1555138 altered the binding of histone deacetylase 2 (HDAC2), an enzyme that deacetylates TF in promoter regions of genes involved in synaptic plasticity leading to synaptic loss [71]. Increased HDAC2 are noted in experimental models of AD [107, 108]. Interestingly, I found that carriers of the minor allele C for rs1555138 had increased BACE1 activity in the CSF. This result is in line with previous reports in the literature. Indeed, several years ago, the association between increased BACE1 activity and altered HDAC2 activity was described in relation to sphingosine-1-phosphate (S1P) activity. The latter was reported to both increase BACE1 activity and inhibit HDAC2 enzymatic activity in mouse neurons [109].

In total 7 significant SNPs were eQTLs for CD46 expression in hippocampal neurons. In particular two SNPs significantly associated with BACE1 were intronic variants of *CD46* suggesting that they may affect the splicing process or be located in an enhancer region. *CD46* codes for the CD46 type I transmembrane protein, which is involved in the complement cascade and regulates T cell phenotypes [110] [111]. In an experimental study conducted in 16HBE14o- cells, it was shown that CD46 is a substrate of Presenilin 1 and 2 [112]. Presenilins are γ-secretases which are involved in the cleavage of APP; mutations within *PSEN2* are associated with LOAD [113]. Interestingly, in microglial cells, CD46 is a receptor for the human herpesvirus HHV-6A, which induces Aß 42 production; it also activates microglial cells as measured by increased expression of TREM2 [114]. Therefore, my findings suggest that CD46 may participate in the amyloid cascade and mediate subsequent microglial activation. I did not detect any significant SNPs associated with sTREM2 to be eQTLs for CD46. However, one SNP

rs606714 affected the binding of TF of the Forkhead box family, which is involved in microglial inflammatory activation [115].

I can identify a number of limitations in this study. First, I cannot exclude that I was underpowered when running the association analyses for some biomarkers and might therefore have missed important SNPs. Additionally, I was not able to undertake subgroup analysis. Second, my results highlight association with biomarkers of AD. However, these findings will need to be correlated with clinical data or neuroimaging markers. When investigating the association between BACE1 activity and microglial activation, imaging studies with tracers targeting microglia such as [11C]PBR28 PET might offer additional insights. Third, I could not explore whether in this particular dataset, my six miRNAs were also dysregulated in the blood as no miRNA expression data are available so far in the ADNI dataset. Fourth, fine mapping as well as conditioning on the most important SNP could further unveil the lead SNP associated with the biomarker dysregulation. Fifth, while my data suggest that these SNPs are located in enhancer or promoter regions for gene transcription, it is possible that these SNPs may influence genes located several kb away. Indeed, it was reported that FTO variants, which are associated with obesity interacts with the promoter of *IRX3* which is located several megabases away [116]. Further explorations are needed.

4.5. Conclusion

In this study I found that SNPs in proximity of *MIR29C* coding for hsa-miR-29c-3p, which is downregulated in healthy older individuals with lower cognitive performance are associated with BACE1 activity, Aß42 and sTREM2 levels in the CSF. These results perpetuate the discussion on the role of the amyloid cascade and microglial activation in early stages of cognitive impairment. Further studies combining our results with clinical and imaging data will undoubtedly provide additional understanding. Finally, further work investigating the relationship between sTREM2 and BACE1 activity are needed as they may offer novel therapeutic options.

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Chapter 5 : Discussion

5.1. Summary of the main findings

My PhD aimed at investigating the role of miRNAs as blood-based biomarker in individuals showing early signs of cognitive impairment. The principal findings of my PhD are listed below:

- A systematic literature review combined with a P value based meta-analysis of 107 studies investigating miRNA dysregulation in AD patients prioritised 32, 25 and 5 dysregulated miRNAs in the blood, brain and CSF of AD patients
- Pathway enrichment analysis reveals clusters of biological function specific to genes targeted by upregulated miRNAs including inflammatory response pathways involving TLR and interferon signalling in addition to apoptosis related pathways.
- Cross-sectional RT-qPCR analysis of 38 miRNAs (32 and 6 top dysregulated miRNAs in the blood and brain of AD patients respectively) in the blood of 830 cognitively healthy individuals from the CHARIOT PRO cohort reveals 6 downregulated miRNAs at FDR significance level (hsa-miR-128-3p, hsa-miR-144-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-29c-3p and hsa-miR-363-3p) in individuals with lower cognitive performance on the Repeatable Battery for the Assessment of Neuropsychological Status.
- Pathway enrichment analysis of experimentally validated miRNA-gene pairs highly expressed in the brain, shows an enrichment for pathways involved in early stages of AD pathogenesis such as the NF-κB and Wnt ß catenin signalling hereby unveiling pathomechanisms underlying preclinical AD stages.
- Association analysis of whole genome sequencing data from 750 individuals from the Alzheimer's Disease Neuro-Imaging Initiative, revealed that 24 SNPs located in proximity of the *MIR29C* gene region are associated with CSF biomarkers of microglial activation and amyloid pathway at FDR significance level: 8 SNPs, 20 SNPs and 3 SNPs for CSF levels of Aß42, BACE1 activity and sTRME2, respectively. Seven SNPs were associated with both sTREM2 and Aß42 levels.

- These SNPs are located in enhancer regions and affect the binding of TF regulating neurogenesis, synaptic function, microglial response to Aβ deposition as well as *APP* expression.
- All SNPs associated with Aß42 levels as well as 8 SNPs associated with BACE1 activity were eQTLs for CD46 hereby suggesting a role for CD46 in the amyloid cascade.
- A positive correlation between sTREM2 levels and BACE1 activity in the CSF is found, independent of age, sex, diagnosis at baseline and APOE ε4 status.

In the next sections, I will discuss the clinical relevance of my work and will consider future development.

5.2. Clinical relevance of my findings

5.2.1. The need for novel biomarkers that will expedite development of disease modifying treatments

The interest in miRNA as a novel biomarker arises from the urgent need to improve our understanding of the disease, which would help us identify novel disease modifying treatments. Indeed, the current gold standard in AD treatment relies on anticholinergic therapies. These drugs' influence on memory and learning ability was first described in the 1970s [1-3]. Later on, accumulating evidence from AD brain and animal models reporting reduced cholinergic activity in AD, catalysed the development of acetylcholinesterase inhibitors such as tacrine, donepezil or rivastigmine for AD patients. In the 1990's, large randomised controlled trials of each of these compounds reported stabilisation to slight improvement in cognitive function, and lower risk of institutionalisation over follow-up periods ranging from 24 weeks to 2 years (reviewed in [4, 5]). These findings resulted in the approval of cholinesterase inhibitors as a gold standard treatment in the dementia stage of AD in the late 1990s. However, these drugs do not prevent the irreversible neuronal loss in the long term. Mounting evidence, since their approval, shows that their benefits rely mainly in delaying the progression of symptoms and decreasing the risk for developing behavioural and psychological symptoms of dementia (BPSD) [6, 7]. At the beginning of 2000s, the development of BACE1 inhibitors brought hope in the quest for a disease modifying treatment in AD. Indeed BACE1 inhibitors were investigated in several randomised controlled trials of Phase 2 and

Phase 3, following increasing evidence for the role of BACE1 in AD (reviewed in [8]). Unfortunately, all these trials had to be terminated prematurely, either due to toxicity (atabecestat), futility reasons (verubecestat, lanabecestat, LY3202626), an unfavorable risk/ benefit profile (elenbecestat) or due to worsening symptoms in the treatment group (umibecestat) [9]. As of 2020, more than 121 unique therapies are being evaluated as a treatment for AD (among which 80.2% as disease modifying treatment) [10]. However, the significant financial investment mandatory for AD drug development, combined with a high failure rate of past attempts, estimated at 99.6% in the period 2002-2012, was marked by an increased interest towards preclinical stages of AD, during which damages may still be contained and even reverted [11, 12].

5.2.2. Growing interest in preventive strategies at preclinical stages

Accumulating evidence has highlighted how events during an individual's lifetime, from childhood to later life, can influence an individual's risk of developing dementia. Indeed, large epidemiological studies have shown that nearly 40% of dementia cases could potentially be prevented or delayed by tackling 12 modifiable risk factors during lifetime: education, hearing impairment, cardiovascular risk factors such as hypertension, smoking, obesity and diabetes, traumatic brain injury, excessive alcohol consumption, social isolation, depression, physical inactivity and living in an environment with air pollution [13]. Numerous trials focusing on preventable risk factors have been launched in the last decade. Several studies have investigated the role of physical activity and its effect on dementia; a systematic review and meta-analysis revealed a reduced risk for dementia for individuals with weekly moderate physical activity. However the results were limited by a large heterogeneity of the included studies [13]. Other studies have focused on nutrition (MIND Diet, DASH, Nordic diet) and reported a reduced risk of developing dementia in the long term [14-16]. One study focusing on hypertension, the SPRINT MIND trial, which was conducted on 9361 adults aged 50 years or older showed that a more strict control of BP (systolic < 120 mmHg) was not associated with reduced risk for developing dementia at later stages [17]. Finally, multidomain trials such as the FINGER, MAPT and preDIVA trials have been conducted in order to tackle multiple risks at the same time. The FINGER trial which tested a multidomain intervention consisting of diet following the Finnish Nutrition Recommendations, physical exercise, cognitive training and vascular risk monitoring, showed a reduction in cognitive decline based on the

neuropsychological test battery [18]. However, the preDIVA and MAPT trials failed to show a significant effect on dementia risk or cognitive function [19, 20]. Nevertheless, in the MAPT trial, individuals at increased risk for dementia, based on the presence of Aβ on PET imaging and a CAIDE score ≥ 6, had a reduced risk for dementia when receiving the multidomain intervention. These findings combined with the lack of efficacy of interventions not targeting at-risk individuals, raised the question of classifying patients at preclinical stages in different risk groups for which preventive measures would be tailored to.

5.2.3. Limitation of the ATN classification system in classifying at risk individuals

One response was to harmonise the definition of individuals along the AD spectrum using the ATN classification with the aim of tailoring interventions to a particular group of individuals [21]. In this classification, biomarkers are then classified into three categories: A stands for β amyloid markers (Aβ 42 in the CSF or amyloid PET), T for tau biomarkers (phosphorylated tau in the CSF or tau PET) and N for biomarkers of neurodegeneration/ neuronal injury (total tau in the CSF, FDG PET or MRI structural changes). Recently, analysis from the SCIENCe project which included 693 participants showed that individuals with a particular ATN classification (A–T+N+, A+T–N–, A+T+N–, and A+T+N+) had increased risk for cognitive decline after 3 years [22]. Similarly, in 262 individuals from ADNI, individuals without dementia diagnosis at baseline and showing first changes in the "N" category (brain atrophy, positive FDG PET) showed faster cognitive decline than individuals showing first elevation of biomarkers from the "A" or "T" categories [23]. However, one major limitation with this classification system is that measurement of these biomarkers can only be done in specialised centres such as Memory Clinics and relies on invasive techniques (lumbar puncture) or PET imaging, which are expensive and expose to radiation. Although this classification system helps to characterise clinical trial participants better, it would be difficult to implement in primary care routine. However, the involvement of primary care physicians will be essential for the success of large-scale public health dementia prevention strategies. Experience from cardiology shows that effective primary or secondary preventive strategies rely on the identification of at-risk individuals through widely accessible testing at the primary care setting [24]. For instance, the Framingham risk score, which is used to classify individuals who would benefit from statin therapy as primary prevention, uses clinical markers, patient's history and laboratory markers; all these can be easily applied in primary care practice [25].

5.3. miRNAs represent a strong biomarker candidate in neurodegenerative diseases

Compared to other biomarkers of neurodegeneration, miRNA offer several advantages.

5.3.1. Advantage 1: miRNAs can easily be measured in the blood using qPCR analysis

One major advantage of miRNAs is that they can be measured in any body fluid or tissue. Consequently, miRNAs can be measured in the blood and do not necessitate highly invasive techniques, such as lumbar puncture, to measure their expression levels; this contrasts with current classical biomarkers of neurodegeneration, such as Aβ and tau, which are measured in the CSF and requires a lumbar puncture. While growing body of evidence have investigated blood levels auf Aβ and tau, concentrations between CSF levels and blood levels may be up to 100 fold lower than in the CSF, hindering their application in preclinical stages of the disease where elevations may be very subtle [26]. Recently, a multiplexed electrical sensing platform detecting Aβ42, Aβ40, p-tau and t-tau in the blood attracted increased attention. Although the sensitivity and specificity of this platform reached over 90% in detecting individuals with AD, these findings will need to be validated on a large scale and the cost-effectiveness of this approach will need to be confirmed [27]. In this regard, miRNAs provide a serious alternative. Indeed, in the last decades, a wide variety of techniques such as RT-qPCR, microarrays, Northern blot hybridization, or next-generation sequencing have been used to quantify miRNA expression levels. Several of these techniques are widely used and rely on validated methods developed several decades ago and continuously improved over the years. The most frequent used method, RT-qPCR, was developed over 30 years ago and constitutes a gold standard in molecular diagnostics with a wide range of indications [28]. Recently for example, due to its wide availability and proven efficacy, RT-qPCR was selected as the gold standard for the detection of SARS-COV-2 during the 2020-2021 pandemic [29]. PCR testing revealed to be an essential cost-effective ally for public health strategies aiming at reducing SARS-CoV-2 transmission in the US; saliva based PCR were reported to cost between 1.29$ to 4.30$ [30]. Because qPCR testing is available in many laboratories, qPCR analyses of miRNAs are considered cost-effective [31, 32].

5.3.2. Advantage 2: miRNAs regulate different biological pathways

Owing to our incomplete understanding of AD pathogenesis, the prioritisation of laboratory measurements on a single blood-based biomarker, known to influence different actors in AD pathomechanisms could be very useful. Indeed, I have shown in chapter 4 that SNPs surrounding *MIR29C* are associated with CSF alterations of Aß, BACE1 activity and sTREM2 levels. As a result, I could hypothesise that measuring downregulation of miR-29c in the blood of a patient presenting with minor changes in cognitive function, would signal ongoing neuro-inflammation and amyloid deposition and prompt more advanced testing, such as PET or CSF measurements. It could be tempting to discuss the potential of miR-29c measured in the blood to replace Aβ, BACE1 activity and sTREM2 measurements in the CSF. However, further studies in a larger cohort are needed to confirm my findings particularly because Aβ, BACE1 activity and sTREM2 in the CSF show added values in terms of predicting clinical course; this has still to be confirmed for miR-29c. Nevertheless, combining this blood-based miRNA with clinical (e.g neuropsychological assessment) or imaging could provide additional benefits. Recently, a cross sectional analysis of 120 patients with multiple sclerosis, revealed that reduced expression of hsa-miR-143-3p was negatively correlated with T1:T2 ratio and therefore was a biomarker of myelin integrity. Two other miRNAs, hsa-miR-375 and hsa-miR-629-5p were negatively associated with brain volume. All in all, these findings confirmed the role of different miRNAs at different stages of multiple sclerosis and highlight their importance when combined with imaging techniques [33]. I envisage a similar role for miRNA biomarkers in AD. Moreover, although I did not have longitudinal miRNA measurements for the CHARIOT-PRO cohort, I would anticipate that after progression of the disease, another miRNA profile would emerge, reflecting downstream or subsequent pathomechanisms. Therefore, a blood-based miRNA signature could be used to stratify individuals at different risk and disease stages.

5.3.3. Advantage 3: miRNAs focus on the pathobiology rather than the disease entity

Despite our growing understanding of the spectrum of neurodegenerative diseases, questions are still unanswered. The recent description of a novel disease entity, LATE (limbic-predominant age-related TDP-43 encephalopathy) reveals how heterogeneous neurodegenerative diseases are in terms of clinical presentation [34]. Moreover, some typical hallmarks of AD are also described in PD and Lewy body disorders suggesting an overlap

between these pathologies [35, 36]. PD is defined by the degeneration of dopamine neurons in the substantia nigra leading to rigor, tremor, akinesia and cognitive impairment. However the clinical presentation varies between individuals and may often lead to under-recognition of the disease [37]. AD and PD patients may share similar symptoms. For example, similar alterations in domains such as orientation, naming, verbal fluency was reported in patients with either PD or AD [38]. Moreover, experimental studies conducted in mice reported how α-synuclein can influence APP and vice versa [39]. A previous study conducted in more than 600 individuals with AD and PD revealed the presence of loss of function variants within the *ABCA7* gene. The latter has also been associated with increased AD risk [40]. More interestingly, the analysis of miRNAs in the brain, blood or CSF of AD and PD patients revealed further overlap in biological pathways involved in both diseases. Indeed, we previously discussed that top miRNAs dysregulated in AD and PD, according to systematic reviews and meta-analyses, target the same genes such as *MAPK1*, *APP*, *FAS* or *CDK5R1* [41]. For instance, miR-152-p and miR-132-3p, which are dysregulated in AD and PD respectively, repress *MAPK1*. Noticeably, genes targeted by miRNAs dysregulated in both diseases are involved in regulating cell death, organising inflammatory reaction to aberrant protein accumulation, and activating axon guidance. Based on these findings, it could be hypothesized that targeting these genes or targeting miRNAs which alter these genes' expression, could represent a novel therapeutic opportunity.

5.4. miRNAs: role in AD therapy

As discussed previously, miRNAs involved in AD and PD alter the expression of the same genes, such as *MAPK1*, *APP*, *FAS* or *CDK5R1*. Consequently, targeting any of these miRNAs may affect the expression of both genes. While this approach has never been taken so far in animal models of AD or PD, experience from other neurological diseases offers an insight on the possible role miRNAs could play. For instance, *FAS* is involved in the caspase pathway which regulates cell death. FAS activates CASP8 which induces a cascade of events resulting in apoptotic signal [42]. Interestingly, caspases have been investigated as direct therapeutic target in a model of stroke where the intracellular administration of XBir3, a caspase-9 specific inhibitor, reduced apoptosis of neuronal cells [43]. Recently, it was shown that Aβ stimulates

caspase mediated cleavage of APP resulting in the production of C31, a peptide inducing synaptic loss [44]. More importantly, administration of a caspase inhibitor was available to restore synaptic architecture and function. Similarly, the administration of a L1CAM analogue stimulated MAPK phosphorylation in an animal model with spinal cord injury and led to increased axonal growth [45]. Finally, as I showed in the previous chapter, the analysis of miRNA expression can reveal novel interplay between different key players in AD pathogenesis. Indeed, analysis of SNPs within *MIR29C* showed a correlation between BACE1 activity and sTREM2 in the CSF. For instance, considering the correlation between BACE1 activity and sTREM2 levels in the CSF, one could hypothesize that microglia might have played an important role in mediating an individual's response to the different BACE1 inhibitors tested in clinical trials. As a result, miRNAs could bring a new perspective to understand why previous AD drug trials failed.

5.5. Future directions and conclusion

MiRNAs are a potentially valuable class of novel biomarkers, the further development and positioning of which should be considered carefully within the broad spectrum of AD clinical practice. A number of limitations need to be addressed in future studies, in order to validate their possible role and application.

First, while the main advantage of miRNAs in AD is that they are measured in the blood, evidence shows that miRNAs may not necessarily reflect the tissue's alteration. For example, in rats, levels of brain miRNAs correlated best with miRNA levels measured in arterial rather than venous blood [46]. Ideally, further studies should examine the relationship between miRNA expression in blood and brain samples from the same individuals. Nevertheless, this is undoubtedly difficult to conduct *in vivo* as it would involve a brain biopsy, which poses ethical issues. Indeed, while brain biopsies may be performed in dementia cases, they remain very seldom, due to the increasing diagnostic performance of non-invasive techniques and due to the non-negligible risk of complications which can reach up to 20% [47]. In the last decade, miRNA-based imaging techniques have been developed at the molecular level which have enabled investigators to explore miRNA activity *in vivo* [48]. We could imagine that identifying

a tracer targeting a particular miRNA in the brain would offer a novel non-invasive opportunity to correlate expression of a single miRNA in the brain and in the blood.

Second, there is so far no gold standard for miRNA measurements. Furthermore, different normalization protocols are described for different platforms and experimental designs [49-51]. For instance, for qPCR analyses, the cut-off for the Cq value, i.e. the value representing the number of cycles needed to detect a signal, may vary according to the manufacturers, with the majority suggesting a cut-off of 35 [52]. The lack of universal consensus on a gold standard normalization and quality control check hampers the reproducibility of the results. A state-of-the-art recommendation issued by a panel of experts in the field is therefore urgently needed.

Third, while I did show in previous chapters how dysregulated miRNAs affect pathways involved in the pathogenesis of AD, I also identified biological pathways not yet related to AD or whose role in AD is still discussed. This highlights one major limitation of miRNA as they are expressed in several tissues. For instance, a search of the Human microRNA Disease Database shows that hsa-miR-144 is reported in 111 diseases in addition to AD, among which diabetes mellitus or metabolic syndrome which can be comorbid to AD. Also, in 2006, the evidence presented on the role of miR-134 in dendrite development and synaptogenesis in rat hippocampal neurons suggested miR-134 is a brain specific miRNA [53]. Since then, however, studies have reported that miR-134 is expressed in other tissues, including the prostate gland, where it is involved in oncogenesis [54]. As such, I believe that when considering miRNAs as biomarker of AD, the expression levels should be combined with other biomarkers such as *APOE* status, clinical findings (e.g. neuropsychological assessments) and appropriate brain imaging modalities. In this respect, experience from oncological clinical scores combining genetic, pathological and clinical parameters can be used as an example. In lung cancer, targeted therapy is based on radiological findings (size, lymph node involvement, presence of metastasis) but also histopathological tumour type (adenocarcinoma, squamous cell, large cell, small cell) and molecular markers (for example presence of *EGFR* mutation) [55]. This concept of personalised and stratified medicine is taking increasing importance and should be evaluated as an option for AD patients. This would not only guide preventive strategies or therapies but would also be used as a prognostic marker.

Fourth, to my knowledge, there has been no clinical trial investigating a miRNA-based therapy in neurodegenerative diseases. This can be seen as surprising when considering the abundance of literature on dysregulated miRNAs in AD. Moreover, several clinical trials based on anti-microRNA (anti-miRs) or miRNA mimics have been launched for other complex diseases such as hepatitis C, type 2 diabetes or cancers [56]. Yet, the investigation of miRNA therapeutics in AD is hindered by several points. First, the pathogenesis is still not fully understood and actors of the neurodegenerative process can be a friend or a foe depending on the stage of the disease [57]. Second, the drug once administered needs to pass the blood brain barrier which controls the delivery to the brain [58]. Third, the targeted cells need to be appropriately defined and reached; the latter might be challenging with the evolving environment surrounding amyloid plaques over the course of the disease (for instance the development of gliosis). Finally, miRNAs need to overcome the immune reaction resulting from their presence [59] (*Figure 1*). Taken together, further studies are needed to evaluate the role of miRNAs as disease modifying treatment for AD.

To conclude, my work shows that miRNAs measured in the blood can be a solid ally in the quest for understanding the pathogenesis of AD in early stages of the disease. Furthermore, my results are a potent advocate for considering miRNAs as a novel biomarker to be applied in defining risk groups for preventive strategies.

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Supplementary table 1 : Overview of the included studies for the meta-analysis								
PMID	First author	Year	Country	Total	AD*	Controls*	Region	# miRNA
17314675	Lukiw [1]	2007	USA; CAN	10	5	5	Hippocampus (CA1)	4
18234899	Wang [2]	2008	USA	12	6	6	Cortex	2
18434550	Hebert [3]	2008	FRA (S1)	10	5	5	Anterior temporal cortex or cerebellum	323
			FRA (S2)	32	11	21		2
18525125	Cogswell [4]	2008	NLD (S1)	17	10	7	Hippocampus, cerebellum or medial frontal gyrus	67
			USA (S2)	16	7	9	CSF	59
18801740	Lukiw [5]	2008	USA; CAN	46	23	23	Hippocampus	1
19110058	Hebert [6]	2009	FRA	30	19	11	Anterior temporal cortex or cerebellum	2
19406203	Sethi [7]	2009	USA; CAN	12	6	6	Temporal lobe cortex (BA22)	4
20126538	Nunez-Iglesias [8]	2010	USA	8	4	4	Parietal lobe cortex	29
20202123	Shioya [9]	2010	JPN	11	7	4	Frontal lobe cortex	2
20347935	Pogue [10]	2010	USA; CAN	12	6	6	Temporal lobe cortex (BA22)	1
20507594	Faghihi [11]	2010	USA (S1)	70	35	35	Entorhinal cortex	1
			USA (S2)	10	5	5	Parietal lobe cortex	1
20660113	Hebert [12]	2010	FRA	18	8	10	Anterior temporal cortex	4
20937840	Cui [13]	2010	USA	66	36	30	Superior temporal lobe neocortex (BA22)	2
20451302	Persengiev [14]	2011	NLD; DEU	4	2	2	Frontal lobe cortex	2
21062284	Smith [15]	2011	FRA	22	11	11	Anterior temporal cortex	3
21548758	Villa [16]	2011	ITA	631	287	344	PBMC	1
21686130	Culpan [17]	2011	UK	18	12	6	Temporal lobe cortex (BA22)	6
21994399	Geekiyanage [18]	2011	USA	14	7	7	Neocortex	5
22160687	Agostini [19]	2011	UK	49	29	20	Hippocampus	1
22155483	Geekiyanage [20]	2012	USA	14	7	7	Serum	8
22509485	Lukiw [21]	2012	USA	10	5	5	Temporal lobe cortex (BA22)	12
22610069	Lehmann [22]	2012	DEU	24	13	11	CSF	1
22660168	Lukiw [23]	2012	USA	10	5	5	CSF	13
22733824	Long [24]	2012	USA	20	10	10	Frontal cortex (BA9)	1
22926857	Lee [25]	2012	USA	8	4	4	Temporal lobe cortex	1
23403535	Hebert [26]	2013	USA (S1)	4	2	2	Sup/middle temporal gyri (BA21/22) (GM)	465
			CAN (S2)	16	8	8	Sup/middle temporal gyri (BA21/22) (GM)	2
23408966	Yan [27]	2013	USA	16	8	8	Hippocampus / Frontal Cortex	1
23435408	Villa [28]	2013	ITA	53	28	25	PBMC	2

23462268	Zhao [29]	2013	USA	6	3	3	Hippocampus (CA1)	5
23585551	Wong [30]	2013	USA	32	16	16	Temporal cortex	2
23895045	Leidinger [31]	2013	USA; CAN	70	48	22	Whole blood	369
23922807	Kumar [32]	2013	USA (S1)	31	11	20	Plasma	7
			USA (S2)	37	20	17	Plasma	7
24014289	Lau [33]	2013	NLD (S1)	12	6	6	Prefrontal cortex	84
			UK (S2)	64	41	23	Hippocampus	34
23962497	Muller [34]	2014	NLD (S1)	21	10	11	Hippocampus	8
			NLD (S2)	42	20	22	CSF	2
24027266	Absalon [35]	2013	USA	18	10	8	Temporal lobe cortex	2
24064186	Tiribuzi [36]	2014	ITA	71	34	37	Monocytes	1
24139697	Tan [37]	2014	CHN	255	105	150	Serum	6
24157723	Kiko [38]	2014	JPN	20	10	10	CSF	6
				20	10	10	Plasma	6
24212398	Frigerio [39]	2013	SWE (S1)	16	8	8	CSF	90
			SWE (S2)	33	15	18	CSF	1
			SWE (S3)	39	20	19	CSF	1
24304186	Ubhi [40]	2014	USA			7 (3/4)	Frontal cortex	539
24352696	Long [41]	2014	USA	20	15	5	Frontal cortex (BA9)	2
24550773	Bhatnagar [42]	2014	CAN	163	78	85	Plasma	2
24577456	Tan [43]	2014	CHN (S1)	100	50	50	Serum	5
			CHN (S2)	100	50	50	Serum	6
			CHN (S3)	313	158	155	Serum	6
24797360	Burgos [44]	2014	USA (S1)	115	53	62	Serum	20
			USA (S2)	127	62	65	CSF	40
25001178	Banzhaf-Strathmann [45]	2014	DEU			15 (10/5)	Frontal cortex (BA6/8)	7
25024331	Galimberti [46]	2014	ITA (S1)	13	7	6	Serum	75
			ITA (S2)	27	15	12	Serum	3
			ITA (S3)	27	15	12	CSF	3
24827165	Liu [47]	2014	CHN (S1)	95	45	50	Plasma	1
			CHN (S2)	14	7	7	CSF	1
25119742	Liu [48]	2014	CHN (S1)	102	51	51	Serum	1
			CHN (S2)	14	7	7	CSF	1
25152461	Liu [49]	2014	CHN (S1)	10	5	5	CSF	3
			CHN (S2)	68	38	30	Serum	3
25349172	Cheng [50]	2014	AUS	46	23	23	Serum	17

25378159	Zhang [51]	2014	USA	16	8	8	Temporal lobe cortex	1
25742200	Wang [52]	2014	CHN	178	97	81	Plasma	1
25574843	Santa-Maria [53]	2015	USA	27	7	20	Frontal cortex (BA9)	1
25667669	Zhu [54]	2015	CHN (S1)	68	26	42	CSF	1
			CHN (S2)	68	26	42	Serum	1
25815896	Yang [55]	2015	CHN	60	30	30	CSF	1
25895659	Müller [56]	2015	NLD	38	18	20	CSF	3
25955795	Yang [57]	2015	CHN	60	30	30	Whole blood	3
25973041	Lei [58]	2015	CHN	60	31	29	Frontal cortex	1
25992776	Denk [59]	2015	DEU	50	22	28	CSF	278
26078483	Dong [60]	2015	CHN (S1)	96	48	48	Serum	12
			CHN (S2)	96	48	48	Serum	4
			CHN (S3)	154	79	75	Serum	4
26362250	Smith [61]	2015	CAN (S1)	23	10	13	Hippocampus	1
			USA (S2)	22	11	11	Temporal lobe cortex	1
26402772	van Harten [62]	2015	NLD	38	19	19	CSF	3
26426747	Lugli [63]	2015	USA	70	35	35	Plasma	20
26497032	Ren [64]	2015	CHN (S1)	8	4	4	PBMC	60
			CHN (S2)	8	4	4	PBMC	9
			CHN (S3)	86	45	41	PBMC	9
26497684	Gui [65]	2015	CHN (S1)	55	28	27	CSF	18
			CHN (S2)	55	28	27	CSF	7
			CHN (S3)	88	53	35	CS	8
26594146	Weinberg [66]	2015	USA (S1)	22	10	12	Frontal cortex	82
			USA (S2)	22	10	12	Inferior temporal cortex	6
26792551	Zhu [67]	2016	NLD	37	13	24	Nucleus basalis of Meynert	1
26806387	Keller [68]	2016	DEU	104	49	55	Whole blood	475
26842588	Moon [69]	2016	KOR	20	11	9	Anterior nasal septum mucosa	1
26856603	Zhang [70]	2016	CHN	14	7	7	Hippocampus	1
26973465	Ragusa [71]	2016	ITA	80	40	40	Plasma	3
27027823	Jia [72]	2016	CHN	146	84	62	Serum	3
27104900	Müller [73]	2016	NLD, ITA, BEL	97	57	40	CSF	4
27235866	Sarkar [74]	2016	USA (S1)	19	10	9	Temporal lobe cortex	2
			USA (S2)	19	10	9	Temporal lobe cortex	3
27239545	Guedes [75]	2016	PRT	72	36	36	Blood derived monocytes	7
27277332	Xing [76]	2016	CHN	60	30	30	Whole blood	1

27298190	Briley [77]	2016	USA	10	6	4	Hippocampus	6
27446280	Zhang [78]	2016	CHN	50	25	25	Whole blood	1
27501295	Yilmaz [79]	2016	TUR	281	172	109	Whole blood	7
27520374	Liu [80]	2016	CHN	10	5	5	Temporal lobe cortex	1
27545218	Li [81]	2016	CHN (S1)	88	48	40	CSF	1
			CHN (S2)	88	48	40	Serum	1
27631879	Cosin-Tomas [82]	2016	ESP (S1)	42	21	21	Plasma	9
			ESP (S2)	30	15	15	Plasma	2
27738874	Dangla-Valls [83]	2016	ESP	68	37	31	CSF	8
27816213	Pichler [84]	2016	DEU (S1)	64	39	25	Temporal lobe cortex	101
			NLD (S2)	312	225	87	Prefrontal cortex	2
27929395	Zhao [85]	2016	USA	18	12	6	Temporal lobe cortex and hippocampus (CA1)	4
27814298	Lusardi [86]	2017	USA	99	50	49	CSF	36
28137310	Hara [87]	2017	JPN (S1)	45	27	18	Serum	3
			JPN (S2)	58	36	22	Serum	3
			JPN (S3)	45	27	18	Temporal lobe cortex	1
28179587	Nagaraj [88]	2017	POL (S1)	13	7	6	Plasma	15
			POL (S2)	22	13	9	Plasma	15
28626163	Wu [89]	2017	CHN	85	45	40	Serum	10
28934394	Kumar [90]	2017	USA (S1)	29	11	18	Serum	7
			USA (S2)	11	6	5	Frontal lobe cortex	4
28849039	Zeng [91]	2017	CHN	60	30	30	Serum	1
28269782	Riancho [92]	2017	ESP (S1)	20	10	10	CSF	14
			ESP (S2)	36	18	18	CSF	3
28871468	Llorens [93]	2017	ESP	44	25	19	Entorhinal cortex	4
28947385	Ma [94]	2017	USA	19	9	10	Brain	1
29207665	Gong [95]	2017	CHN	75	40	35	Frontal cortex	1
29253717	Akhter [96]	2017	USA	43	21	22	Hippocampus	4
29371969	An [97]	2017	CHN, MNG	70	35	35	Brain	1
29523845	Annese [98]	2018	USA, UK	12	6	6	Hippocampus	4
29036829	Manzine [99]	2018	BRA	38	21	17	Whole blood	19
29527164	Kumar [100]	2018	USA (S1)	42	27	15	Frontal cortex (BA10)	1
			USA (S2)	16	6	10	Lymphocytes	1
29603092	McKeever [101]	2018	USA, CAN (S1)	25	13	12	CSF	4

			USA, CAN (S2)	29	17	12	CSF	5
29635818	Wang [102]	2018	CHN	40	20	20	Plasma	13
29901156	Jin [103]	2018	CHN	48	24	24	CSF	1
29855513	Hadar [104]	2018	ISR, ITA (S1)	35	24	11	Lymphocytes	3
			UK (S2)	34	14	20	Olfactory bulb	2
30011310	Derkow [105]	2018	DEU	21	11	10	CSF	5
29966198	Dias [106]	2018	DEU	20	10	10	Plasma	3
29746584	Denk [107]	2018	DEU (S1)	92	48	44	CSF	10
			DEU (S2)	85	47	38	Serum	30

Abbreviations AD = Alzheimer Disease, BA = Brodmann Area, CSF = Cerebrospinal fluid, GM = Gray Matter, HC = Healthy Control, PBMC = Peripheral blood mononuclear cell, S = Sample

*Max number of AD/HC in each study

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Supplementary Table 2: Pathway enrichment analysis of the 25 significantly dysregulated miRNAs in the brain of AD patients

pathway name	database code	cluster	P value FDR	genes intersection	n	Up/ Down
actin filament-based transport	GO:0099515	cellular transport	3.967E-02	MYO19,MYO6,WASL,MYO5A,SYNE2,MYO1C,MYO1B,SUN2	8	up
activated notch1 transmits signal to the nucleus	REAC:R-HSA-2122948	NOTCH signalling	4.504E-02	NUMB,NOTCH1,DTX4,ADAM17,MIB1,JAG1,DLL1,UBB,RPS27A,UBC,NCSTN	11	up
activated ntrk3 signals through pi3k	REAC:R-HSA-9603381	PI3k signalling	4.447E-02	NTRK3,IRS1,PIK3R1,SRC	4	up
activated tak1 mediates p38 mapk activation	REAC:R-HSA-450302	MAPK signalling	1.012E-05	MAPK14,IRAK2,TRAF6,IRAK1,UBE2V1,MAPKAPK2,MAP2K3,TAB3,MAP3K7,RIPK2,NOD1,UBB,RPS27A,UBC,TAB2	15	up
activation of atr in response to replication stress	REAC:R-HSA-176187	cellular response to external stimuli	5.309E-03	CHEK1,ORC4,CDC25A,CLSPN,CDK2,CDC25C,MCM4,MCM2,MCM7,MCM10,MCM6,MCM3,MCM5,RFC2,ORC1	15	up
activation of bad and translocation to mitochondria	REAC:R-HSA-111447	mitochondrial activity	1.052E-02	BID,YWHAG,AKT1,BCL2,AKT2,AKT3,PPP3R1,YWHAE,YWHAB	9	both
activation of bh3-only proteins	REAC:R-HSA-114452	protein metabolism	2.485E-05	TP63,BID,YWHAG,PPP1R13B,AKT1,PMAIP1,BCL2,BBC3,AKT2,AKT3,PPP3R1,BCL2L11,TP53,TFDP2,YWHAE,YWHAB	16	both
activation of caspases through apoptosome-mediated cleavage	REAC:R-HSA-111459	caspase signalling pathway	4.144E-04	XIAP,CASP7,CASP3,CASP9,CYCS,APAF1	6	up
activation of cysteine-type endopeptidase activity involved in apoptotic process	GO:0006919	endopeptidase activity	2.581E-06	CDKN2A,BCL2L13,JAK2,S100A8,BBC3,TNF,TNFRSF10B,Fas,HSPD1,FADD,ROBO1,SMAD3,BCL2L11,RET,F3,SENP1,DIABLO,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,TRAF2,BAX,NOD1,FASLG,CFLAR,CASP8,APAF1,CASP10,DLC1,EGLN3	32	up
activation of cysteine-type endopeptidase activity involved in apoptotic process by cytochrome c	GO:0008635	endopeptidase activity	4.660E-03	DIABLO,CASP9,CYCS,BAX,APAF1	5	up
activation of gene expression by srebf (srebp)	REAC:R-HSA-2426168	gene expression	2.620E-02	MTF1,CREBBP,MED1,LSS,FASN,CARM1,TBL1XR1,SP1,NCOA1,DHCR7,CYP51A1,PPARA,NFYB,SC5D	14	up
activation of irf3/irf7 mediated by tbk1/ikk epsilon	REAC:R-HSA-936964	IRF signalling	4.903E-02	IRF7,TLR4,TRAF3,TANK,UBB,RPS27A,UBC	7	up
activation of mapk activity	GO:0000187	MAPK signalling	1.847E-06	MAP3K2,DUSP6,TNF,MAP3K11,MAPK14,PIK3CB,NTRK3,CXCR4,CD40LG,IRAK2,TRAF6,IRAK1,TLR4,FGF2,TGFA,S1PR2,MAP3K9,TAOK1,UBE2V1,PRKAA1,MAPKAPK2,MAP2K3,CDK1,INSR,TAB3,MAP4K2,RET,MAP3K7,PEA15,MAPK3,MAP2K1,SAA1,RIPK2,KIT,NOD1,DUSP5,MAP2K4,UBB,MAPK1,RPS27A,UBC,THBS1,TAB2	43	up
activation of nf-κb-inducing kinase activity	GO:0007250	Nfκ	3.317E-04	TNFRSF10B,COPS8,TRAF6,IRAK1,CARD10,MAP3K7,TNFRSF10A,TRAF2,TIRAP,TLR3	10	up
activation of protein kinase activity	GO:0032147	protein kinase activity	4.990E-02	DUSP9,PRKAR2A,PAK2,MAPK1,MAPK14,PRKCD,MAP3K13,EMP2,RET,MAP2K2,IGF1,PAK5,TAOK3,MAP3K2,PDPK1,TAOK1,MAP3K11,AKT1,UBE2V1,MAP2K7,TGFBR1,TGFBR2,KIT,ADCY9,DUSP5,VEGFA,ZFP91,PRKAR1A,TNFRSF10B,FRS2,CRKL,TNFRSF10A,IL4,GADD45A,CRK,TRAF7,ERN1,IKBKG,EIF2AK2,MUC20,IRAK2,PLCE1,THBS1,WNT5A,MINK1,S1PR2,TAOK2,PAK4	48	both
activation of puma and translocation to mitochondria	REAC:R-HSA-139915	mitochondrial activity	4.467E-02	TP53,BBC3,E2F1,TP73,TP53BP2	5	up
activation of the pre-replicative complex	REAC:R-HSA-68962	cell cycle	3.056E-02	ORC4,POLE4,CDK2,MCM4,MCM2,MCM7,PRIM1,MCM10,MCM6,MCM3,MCM5,ORC1	12	up
actomyosin structure organisation	GO:0031032	cell organisation	1.925E-02	NF2,NEBL,SMAD4,ABL1,RHOA,ROCK1,WASF2,SFRP1,PHLDB2,NRP1,PAK2,CUL3,VPS4A,RACGAP1,AMOT,PIK3R1,CGNL1,CDC42,SLC9A1,STMN1,EPB41L3,ITGB1,MET,EPB41L2,TPM1,ACTG1,SRC,PDGFRB,PDGFRA,TMOD3,CFLAR,TMOD2,ACTC1,F11R,EDN1,DLC1,MYH11,CSRP1,EPB41L4B,ACTA1	40	up
acute myeloid leukemia	KEGG:05221	cancer	2.579E-02	MYC,MAPK1,MAP2K2,CCND1,EIF4EBP1,CEBPA,NFKB1,RARA,AKT1,KIT,KRAS,PER2,CCNA2,AKT2,AKT3,STAT3,IKBKG	17	both
adaptive thermogenesis	GO:1990845	cellular response to external stimuli	8.208E-03	IRF4,EHMT1,PCTP,JAK2,IP6K1,NRDC,IGF1R,APC,CXCR4,DECR1,KDM6B,TLR4,NOTCH1,LNPEP,ADAM17,VEGFA,OGT,FLCN,RBPJ,NOVA2,TRPV2,CPT2,CEBPB,ACSL1,FH,MFN2,CIDEA,SIRT6,TLE3,PER2,BMP8A,GRB10,ZBTB7B,THRA,CD36,ADAMTS5,IL15,FFAR4	38	up
adherens junction	KEGG:04520	cell adhesion and migration	9.935E-04	MAPK1,YES1,CDH1,EP300,PARD3,IGF1R,SNAI2,TGFBR1,TGFBR2,SSX2IP,NLK,CTNND1,CDC42,SMAD3,WASL,MET,RHOA,CTNNB1,CSNK2A1,ACTG1,ACTN4,CREBBP	22	both
adherens junction assembly	GO:0034333	cell adhesion and migration	1.813E-03	VCL,PAK2,SMAD7,CTNNB1,PIP5K1C,ACTB,ZNF703	7	up
adipocytokine signalling pathway	KEGG:04920	signalling pathways	1.034E-02	STAT3,JAK2,AKT1,TNF,PRKAG1,NFKB1,IRS1,PRKAA1,CHUK,AKT3,SLC2A4,ACSL4,ACSL1,ACSL6,TRAF2,TNFRSF1A,PPARA,G6PC,SOCS3,CD36,POMC	21	up
adp metabolic process	GO:0046031	metabolic process	5.456E-04	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,POM121C,LDHA,GPI,NUP62,TIGAR,NUP98,RAE1,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	32	up
advanced glycosylation endproduct receptor signalling	REAC:R-HSA-879415	signalling pathways	6.696E-04	S100A12,AGER,APP,CAPZA2,MAPK3,SAA1,HMGB1,MAPK1,PRKCSH	9	up
age-rage signalling pathway in diabetic complications	KEGG:04933	signalling pathways	1.681E-05	MAPK1,MAPK14,PRKCD,COL1A1,FOXO1,CCND1,CASP3,SERPINE1,NFKB1,AKT1,TGFBR1,TGFBR2,KRAS,IL1A,VCAM1,BCL2,COL1A2,COL4A1,CDC42,COL3A1,MMP2,COL4A2,JUN,AKT2,AKT3,VEGFA,SMAD2,SMAD3,CDKN1B,STAT3,ICAM1,PLCD3,PLCE1	33	both
aging	GO:0007568	senescence	2.422E-03	CDKN2A,STAT3,SMC6,TP53,BBC3,ULK3,NPM1,MAPK14,HMGA2,HMGA1,MIF,CDKN1A,DKK1,WNT1,HLA-G,PDCD4,CHEK1,CDK6,PRKCD,AGER,AKT3,APP,KRT33B,ATM,SIRT1,MAP2K1,YBX1,MAPKAPK5,PRNP,CHEK2,ROMO1,TERF2,B2M,SOD2,TWIST1	35	both
akt phosphorylates targets in the cytosol	REAC:R-HSA-198323	phosphorylation	3.248E-02	AKT1,CDKN1A,CDKN1B,CHUK,AKT3,GSK3B,MDM2,CASP9,AKT1S1	9	both
aldosterone-regulated sodium reabsorption	KEGG:04960	endocrine system	4.177E-02	SCNN1A,PIK3CB,PIK3CD,SLC9A3R2,IRS1,KRAS,PIK3R3,INSR,PIK3R1,SFN,MAPK3,MAPK1	12	up

α-β t cell differentiation	GO:0046632	cell differentiation	4.002E-02	CBFB,IRF4,STAT3,PRDM1,CD80,IL6,RSAD2,IL23R,MYB,SMAD7,SOCS5,NLRP3,TOX,LEF1,TGFBR2,HMGB1,NKAP,ZBTB7B,ATP7A	19	up
α-protein kinase 1 signalling pathway	REAC:R-HSA-9645460	protein kinase activity	6.225E-03	TRAF6,TAB3,MAP3K7,UBB,RPS27A,UBC,TAB2	7	up
alzheimer disease	KEGG:05010	AD	2.696E-02	ND6,FZD4,KLC2,GRIN2A,FRAT2,AKT1,COX7C,SDHB,BACE2,TNF,ADRM1,VDAC1,PIK3CB,PSMB1,APC,Fas,RAF1,PIK3CD,FZD6,CSNK2A1,COX2,NFKB1,FADD,PTGS2,NOS1,IL6,CASP7,WNT2B,CSF1,DKK1,IRS1,WNT1,KRAS,ADAM17,FZD5,ATG14,PIK3R3,KIF5B,Bace1,WNT7A,CHUK,TUBB,AGER,ITPR1,INSR,PIK3R1,WIPI2,AKT3,AXIN2,TUBB2A,APP,GSK3B,FZD9,RTN4,PSMB5,MAPK3,KLC1,CASP3,MAP2K1,CTNNB1,HSD17B10,CASP9,CYCS,TRAF2,BECN1,PPP3R1,TNFRSF1A,CAPN1,CYBB,CASP8,APAF1,NRAS,CDK5R1,UQCRFS1,GNAQ,MAPK1,NRBF2,UQCRB,NCSTN,PLCB1	80	up
ameboidal-type cell migration	GO:0001667	cell adhesion and migration	3.073E-02	DDR2,SEMA6B,SEMA6A,GLUL,RAB13,GDNF,PRKX,SEMA3E,NR2F2,EMP2,SP1,NOTCH1,DUSP10,BMPR2,ADAM17,HMGB1,PDPK1,PFN2,ADGRA2,SIRT1,SEMA4C,SOX9,HIF1A,ROCK2,AKT1,ZEB2,PTK2,CAPN7,PPARG,VASH1,MECP2,PTEN,KIT,PHOX2B,PLPP3,ETS1,ARF6,MAP3K3,ITGB1,SPARC,ENPP2,KLF4,AKT3,VEGFA,ACVR1C,SEMA7A,APPL1,CYP1B1,MET,RHOA,IL4,AMOT,ROCK1,MAPRE2,GADD45A,KANK2,RREB1,NF1,SEMA4G,GIPC1,TBXA2R,ATOH8,LPXN,SRF,EGF,PHACTR4,SYNJ2BP,ANGPT4,RRAS,THBS1,WNT5A,ARSB,PFN1	73	both
ampk signalling pathway	KEGG:04152	signalling pathways	9.540E-03	SCD5,RAB10,PCK1,IGF1,PDPK1,CPT1A,FOXO1,RAB11B,CCND1,SIRT1,EIF4EBP1,AKT1,IGF1R,PPARG,PPP2R5E,SCD,ULK1,PRKAB2,CCNA2,HMGCR,AKT2,CREB5,AKT3,CAB39,ELAVL1,FOXO3,CPT1B,PPARGC1A	28	both
amplification of signal from unattached kinetochores via a mad2 inhibitory signal	REAC:R-HSA-141444	cell cycle	4.284E-02	AURKB,PPP2CA,RANBP2,NUP37,CENPP,NSL1,RCC2,KIF2C,TAOK1,PAFAH1B1,BIRC5,DYNLL2,PPP2R5C,RANGAP1,ERCC6L,CDC20,CKAP5,KIF2A,PPP1CC,NUP43,INCENP,DYNC1LI2,CLIP1,DSN1,SKA2	25	up
amplification of signal from the kinetochores	REAC:R-HSA-141424	cell cycle	4.284E-02	AURKB,PPP2CA,RANBP2,NUP37,CENPP,NSL1,RCC2,KIF2C,TAOK1,PAFAH1B1,BIRC5,DYNLL2,PPP2R5C,RANGAP1,ERCC6L,CDC20,CKAP5,KIF2A,PPP1CC,NUP43,INCENP,DYNC1LI2,CLIP1,DSN1,SKA2	25	up
amyloid fibril formation	GO:1990000	AD	3.967E-02	CDKN2A,LDLR,FKBP1A,CLU,APP,MDM2,CD36,B2M	8	up
amyloid-β clearance	GO:0097242	AD	4.002E-02	TNF,IGF1R,ROCK1,LRP2,ITGB2,LDLR,INSR,CLU,HDAC1,CYP51A1,TREM2,CD36	12	up
anatomical structure homeostasis	GO:0060249	homeostasis	4.095E-02	VCL,SMC6,TNFAIP3,AURKB,CNGB1,CDH5,PFKM,CLDN12,TNKS1BP1,DRAM2,PARP1,SPP1,BGLAP,IL6,HAAO,TLR4,NOTCH1,HSP90AA1,CCT6A,VEGFA,TAOK1,CHMP4B,PRKAA1,WNK3,HNRNPA1,HMBOX1,RIF1,POLE4,LAMC1,HNRNPA2B1,BSG,ZNF365,ITGB1,CHMP2B,ATM,MYC,MRE11,POLD1,ACTG1,MAPK3,SRC,STRAP,FEN1,PRIM1,PPP1R10,CCT3,ITGB3,XRN1,TJP2,RAD51,CSF1R,BAG3,SIRT6,S1PR1,SLX4,F11R,RAB3D,MAPKAPK5,MAPK1,RFC2,TPP1,TERF2,ERCC4,UBASH3B,SMG1,SLC39A8,SIGLEC15,B2M,ACTB,CTC1,HNRNPC	71	up
angiogenesis	GO:0001525	organogenesis	5.917E-03	ETS1,E2F7,SPHK1,PKM,STAT3,ERBB2,AKT1,TNFAIP3,ANGPT2,TNF,STARD13,ENPEP,CDH5,MED1,PLXND1,PIK3CB,TMEM2,RNH1,NRARP,PIK3CD,HMGA2,ALOX5,HK2,FGFR2,E2F2,PLXDC1,RHOA,ROCK1,PTGS2,STAT1,SFRP1,BRCA1,CARD10,IL6,CXCL8,ROBO1,NOTCH1,ITGA5,HLA-G,FGF2,KLF4,AGO2,NRP1,PIK3R3,ITGB8,VEGFA,SPRED1,MECP2,AGO1,RECK,EFNB2,HOXA3,RBPJ,AMOT,AKT3,AMOTL1,TGFBR3,KDR,RTN4,RHOB,F3,SP1,ITGB1,JAG1,DLL1,ACTG1,PDGFRB,PDGFRA,SIRT1,TGFBR2,MTDH,RRAS,CD40,GATA4,ITGB3,PLCG1,CTNNB1,EPHA2,FASLG,PRKD1,SIRT6,CASP8,AGTR1,S1PR1,GATA6,PKNOX1,SASH1,HOXB3,CLIC4,ACVR1,BTG1,HOXA5,ADM2,PTPRB,PRKD2,EMP2,THBS1,COL4A1,TWIST1,ADAMTS9,HIPK1	101	up
anoikis	GO:0043276	apoptosis	4.173E-02	NOTCH1,AKT1,PTK2,SNAI2,BCL2,MCL1,ITGB1,ANKRD13C,IKBKG,PTRH2	10	both
antifolate resistance	KEGG:01523	drug resistance	1.001E-02	SHMT1,TNF,SLC19A1,ABCC4,ABCC1,NFKB1,IL6,ALOX12,CHUK,MTHFR,TYMS,SLC46A1	12	up
antigen processing and presentation of exogenous peptide antigen via mhc class i, tap-independent	GO:0002480	adaptive immune system	2.287E-02	LNPEP,HLA-A,HLA-G,HLA-C,B2M	5	up
antigen processing and presentation of exogenous peptide antigen via mhc class ii	GO:0019886	adaptive immune system	2.287E-02	SEC24A,KLC2,KIF22,OSBPL1A,KIF2C,AP2B1,DCTN5,KIF23,RACGAP1,KIF3B,DYNLL2,CANX,CAPZA2,AP2A1,KIF11,KLC1,CAPZB,KIF4A,AP2M1,AP2A2,KIF2A,ARF1,CLTA,DYNC1LI2,ACTR1A	25	up
antigen processing and presentation of peptide antigen via mhc class ii	GO:0002495	adaptive immune system	2.019E-02	SEC24A,KLC2,KIF22,OSBPL1A,KIF2C,AP2B1,DCTN5,KIF23,RACGAP1,KIF3B,DYNLL2,CANX,CAPZA2,AP2A1,KIF11,KLC1,CAPZB,KIF4A,AP2M1,AP2A2,TREM2,KIF2A,ARF1,CLTA,DYNC1LI2,ACTR1A	26	up
antigen processing and presentation of peptide or polysaccharide antigen via mhc class ii	GO:0002504	adaptive immune system	1.231E-02	SEC24A,KLC2,KIF22,OSBPL1A,KIF2C,AP2B1,DCTN5,KIF23,RACGAP1,KIF3B,DYNLL2,CANX,CAPZA2,AP2A1,KIF11,KLC1,CAPZB,KIF4A,AP2M1,AP2A2,TREM2,KIF2A,ARF1,CLTA,DYNC1LI2,THBS1,ACTR1A	27	up
antiviral mechanism by ifn-stimulated genes	REAC:R-HSA-1169410	viral of bacterial infection	4.670E-05	NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,KPNB1,ISG15,STAT1,MX2,OASL,IFIT1,KPNA4,ARIH1,NUP50,KPNA1,KPNA3,POM121C,MAPK3,NUP62,PLCG1,EIF4G1,RAE1,NUP43,UBB,RPS27A,UBC,NUP54,UBA7,KPNA2,PPM1B	31	up
apc/c:cdc20 mediated degradation of cyclin b	REAC:R-HSA-174048	cyclin signalling pathway	1.671E-02	ANAPC16,CDK1,CDC27,CDC20,ANAPC5,CDC23,CCNB1,UBB,RPS27A,UBC	10	up
apelin signalling pathway	KEGG:04371	signalling pathways	5.811E-03	SPHK1,AKT1,APLN,PRKAG1,RAF1,SMAD4,SPP1,NOS1,MYLK,SMAD2,CCND1,PRKCE,KRAS,SMAD3,RPS6KB1,GABARAPL1,PRKAA1,GNB1,ITPR1,AKT3,GABARAP,GNG12,SLC9A1,MEF2C,RRAS2,JAG1,TFAM,MAPK3,RRAS,MAP2K1,PIK3CG,BECN1,AGTR1,NRAS,GNAQ,MAPK1,PLCB1	37	up
apoptosis	KEGG:04210	apoptosis	6.386E-12	PARP1,MAPK1,XIAP,MAP2K2,BID,PDPK1,CASP3,NFKB1,AKT1,ATM,KRAS,PMAIP1,BCL2,BBC3,MCL1,FOS,JUN,AKT2,AKT3,CASP8,TNFRSF10B,ITPR1,BCL2L11,LMNA,TNFRSF10A,GADD45A,LMNB2,TRAF1,ERN1,TP53,IKBKG,DFFA,ACTG1,DFFB,BIRC5,PARP2,CYCS,CTSS	38	both
apoptosis	REAC:R-HSA-109581	apoptosis	6.386E-12	PARP1,MAPK1,XIAP,MAP2K2,BID,PDPK1,CASP3,NFKB1,AKT1,ATM,KRAS,PMAIP1,BCL2,BBC3,MCL1,FOS,JUN,AKT2,AKT3,CASP8,TNFRSF10B,ITPR1,BCL2L11,LMNA,TNFRSF10A,GADD45A,LMNB2,TRAF1,ERN1,TP53,IKBKG,DFFA,ACTG1,DFFB,BIRC5,PARP2,CYCS,CTSS	38	both
apoptosis - multiple species	KEGG:04215	apoptosis	1.097E-02	BECN1,XIAP,BID,CASP3,PMAIP1,BCL2,BBC3,CASP8,BCL2L11,BIRC5,CYCS	11	both
apoptotic cleavage of cellular proteins	REAC:R-HSA-111465	apoptosis	3.056E-02	APC,ROCK1,CASP7,PRKCD,CLSPN,CASP3,DSP,SPTAN1,CTNNB1,TJP2,CASP6,CASP8,BIRC2	13	both
apoptotic dna fragmentation	GO:0006309	apoptosis	2.508E-03	CDKN2A,KPNB1,IL6,DICER1,KPNA1,CASP3,HMGB1,AIFM1,CIDEA,BAX,DFFA	11	up
apoptotic execution phase	REAC:R-HSA-75153	apoptosis	3.264E-03	APC,KPNB1,ROCK1,CASP7,PAK2,PRKCD,KPNA1,CLSPN,HIST1H1E,CASP3,DSP,SPTAN1,CTNNB1,TJP2,HMGB1,DFFA,CASP6,CASP8,BIRC2	19	both
apoptotic factor-mediated response	REAC:R-HSA-111471	apoptosis	3.774E-05	CDKN2A,XIAP,BAK1,CASP7,MAPK3,CASP3,DIABLO,CASP9,CYCS,BAX,APAF1,MAPK1	12	up
apoptotic mitochondrial changes	GO:0008637	mitochondrial activity	1.618E-02	CDKN2A,PMAIP1,BMF,TP53,BBC3,AKT1,BCL2,BAK1,HSPD1,HK2,ERBB4,PLAUR,YWHAB,BCL2L11,YWHAQ,YWHAH,CLU,GSK3B,FZD9,E2F1,SFN,HRK,BNIP3,TP73,BAX,BIK,PPP3R1,NOL3,CIDEB,CASP8,MOAP1,BCL2L1,TP53BP2,MFF,TIMM50,SOD2	36	both

apoptotic nuclear changes	GO:0030262	apoptosis	3.293E-03	CDKN2A,KPNB1,IL6,DICER1,KPNA1,CASP3,HMGB1,AIFM1,CIDEA,BAX,DFFA,BLCAP,TOP2A	13	up
apoptotic signalling pathway	GO:0097190	apoptosis	2.606E-03	PMAIP1,ZMYND11,BMF,BCL3,TP53,JAK2,S100A8,BBC3,AKT1,TNFAIP3,EPO,BCL2,TNF,ZNF385A,CDKN2D,BAK1,IL6R,SORT1,RPS7,TNFRSF10B,PIK3CB,ERBB3,SGPL1,Fas,CD44,MCL1,DYRK2,ABL1,MUC1,CSNK2A1,IFI27,MIF,FADD,CDKN1A,BCL2A1,SFRP1,BRCA1,BCLAF1,TLR4,CXCL12,PLAUR,ICAM1,FGFR3,PPARD,YWHAB,PTEN,SMAD3,TMEM109,ZNF622,BCL2L11,DDX3X,CHAC1,PAK2,CUL3,DNAJA1,PRKCD,CUL2,ITPR1,CYLD,RNF41,GABARAP,YWHAQ,YWHAH,BCL2L12,CLU,PPP2R5C,GSK3B,FZD9,RET,HYOU1,DNAJC10,FBXW7,MDM2,E2F1,ATM,MAZ,ITGA6,SFN,PEA15,SENP1,SRC,CASP3,SIRT1,AR,CEBPB,MAGEA3,IFNB1,BIRC6,DIABLO,GATA4,HRK,BNIP3,CASP9,BAG6,CRADD,CD24,TP73,AIFM1,TNFRSF10A,TRAF2,SNAI1,BECN1,BAX,EPHA2,BIK,PPP3R1,LTBR,FASLG,TNFRSF1A,NOL3,CIDEB,BAG3,DAPK1,BCL10,NR4A2,CD70,CFLAR,CASP8,CD27,MOAP1,BCL2L1,APAF1,TP53BP2,CASP10,USP28,AEN,MFF,TLR3,DDIT4,UBB,CHEK2,TCF7L2,JMY,ACVR1,NACC2,TIMM50,SOD2,THBS1,HIPK1	139	both
appendage development	GO:0048736	organogenesis	6.521E-03	BMPR1B,CREBBP,FGFR2,DKK1,SKI,WNT7A,TFAP2A,CYP26B1,SALL1,ZNRF3,HDAC1,ITGA6,LNPK,CTNNB1,SOX4,SOX11,CHD7,SMOC1,MBNL1,KREMEN1,ECE1,TWIST1	22	up
appendage morphogenesis	GO:0035107	organogenesis	3.073E-02	BMPR1B,CREBBP,FGFR2,SKI,WNT7A,TFAP2A,CYP26B1,SALL1,HDAC1,CTNNB1,SOX4,SOX11,MBNL1,ECE1,TWIST1	15	up
assembly of the hiv virion	REAC:R-HSA-175474	viral of bacterial infection	4.903E-02	FURIN,VPS37B,VPS37A,VPS37D,UBB,RPS27A,UBC	7	up
atrioventricular valve development	GO:0003171	organogenesis	2.335E-02	SMAD4,NOTCH1,HEYL,MDM4,TGFBR2,GATA4,SOX4,BMPR1A,ACVR1	9	up
atrioventricular valve morphogenesis	GO:0003181	organogenesis	1.235E-02	SOX4,NOTCH1,BMPR2,TGFBR2,ZFPM1,MDM4,HEYL,BMPR1A	8	both
autophagic cell death	GO:0048102	autophagy	3.859E-02	TP53INP1,CDKN2D,CDKN1B,ATG7,TREM2	5	up
autophagosome assembly	GO:0000045	autophagy	2.006E-02	TP53INP1,MTMR3,PIP4K2C,ATG9A,PACS2,ATG14,RAB1B,CHMP4B,GABARAPL1,STX17,RAB23,TBC1D14,WIPI2,GABARAP,SMURF1,RAB3GAP2,ATG5,UBQLN2,MFN2,RALB,BECN1,ATG7,UBXN2B,RAB1A	24	up
autophagosome organisation	GO:1905037	cell organisation	2.283E-02	TP53INP1,MTMR3,PIP4K2C,ATG9A,PACS2,ATG14,RAB1B,CHMP4B,GABARAPL1,STX17,RAB23,TBC1D14,WIPI2,GABARAP,SMURF1,RAB3GAP2,ATG5,UBQLN2,MFN2,RALB,BECN1,ATG7,UBXN2B,RAB1A	24	up
autophagy	GO:0006914	autophagy	1.213E-02	LARP1,TRIM27,ABL2,SNAP29,BECN1,FBXL2,CALCOCO2,EI24,CHMP3,TP53INP1,SESN3,RRAGC,UFM1,EP300,SPTLC2,TRIM13,SLC38A9,HMGB1,PIK3C3,TRIM38,TECPR1,FOXO1,S100A9,SNX5,TP53INP2,CASP3,IL10RA,SIRT1,AKT1,DRAM1,TGFBRAP1,ATM,WDFY3,CHMP2B,BCL2,ULK1,TSG101,SMCR8,ATG2B,GAPDH,MCL1,PRKAB2,FZD5,HUWE1,SH3GLB1,WDR45B,STAT3,RAB3GAP2,ITPR1,PIP4K2C,RRAGD,HSPA8,UBXN2A,FOXO3,MET,CHMP4B,IL4,ROCK1,EXOC8,LRSAM1,RAB7A,CSNK2A1,LIX1L,ERN1,TP53,PACS2,TRIM65,IKBKG,ATP6V0D2,PGAM5,QSOX1,TMEM59,AMBRA1,CLU,GNAI3,TPCN2,UFC1,GSK3B,UBQLN4,FOXK2,RAB3GAP1,CAPNS1,ATG2A	83	both
autophagy	GO:0006914	autophagy	1.213E-02	LARP1,TRIM27,ABL2,SNAP29,BECN1,FBXL2,CALCOCO2,EI24,CHMP3,TP53INP1,SESN3,RRAGC,UFM1,EP300,SPTLC2,TRIM13,SLC38A9,HMGB1,PIK3C3,TRIM38,TECPR1,FOXO1,S100A9,SNX5,TP53INP2,CASP3,IL10RA,SIRT1,AKT1,DRAM1,TGFBRAP1,ATM,WDFY3,CHMP2B,BCL2,ULK1,TSG101,SMCR8,ATG2B,GAPDH,MCL1,PRKAB2,FZD5,HUWE1,SH3GLB1,WDR45B,STAT3,RAB3GAP2,ITPR1,PIP4K2C,RRAGD,HSPA8,UBXN2A,FOXO3,MET,CHMP4B,IL4,ROCK1,EXOC8,LRSAM1,RAB7A,CSNK2A1,LIX1L,ERN1,TP53,PACS2,TRIM65,IKBKG,ATP6V0D2,PGAM5,QSOX1,TMEM59,AMBRA1,CLU,GNAI3,TPCN2,UFC1,GSK3B,UBQLN4,FOXK2,RAB3GAP1,CAPNS1,ATG2A	83	both
autophagy	REAC:R-HSA-9612973	autophagy	1.213E-02	LARP1,TRIM27,ABL2,SNAP29,BECN1,FBXL2,CALCOCO2,EI24,CHMP3,TP53INP1,SESN3,RRAGC,UFM1,EP300,SPTLC2,TRIM13,SLC38A9,HMGB1,PIK3C3,TRIM38,TECPR1,FOXO1,S100A9,SNX5,TP53INP2,CASP3,IL10RA,SIRT1,AKT1,DRAM1,TGFBRAP1,ATM,WDFY3,CHMP2B,BCL2,ULK1,TSG101,SMCR8,ATG2B,GAPDH,MCL1,PRKAB2,FZD5,HUWE1,SH3GLB1,WDR45B,STAT3,RAB3GAP2,ITPR1,PIP4K2C,RRAGD,HSPA8,UBXN2A,FOXO3,MET,CHMP4B,IL4,ROCK1,EXOC8,LRSAM1,RAB7A,CSNK2A1,LIX1L,ERN1,TP53,PACS2,TRIM65,IKBKG,ATP6V0D2,PGAM5,QSOX1,TMEM59,AMBRA1,CLU,GNAI3,TPCN2,UFC1,GSK3B,UBQLN4,FOXK2,RAB3GAP1,CAPNS1,ATG2A	83	both
autophagy	REAC:R-HSA-9612973	autophagy	1.213E-02	LARP1,TRIM27,ABL2,SNAP29,BECN1,FBXL2,CALCOCO2,EI24,CHMP3,TP53INP1,SESN3,RRAGC,UFM1,EP300,SPTLC2,TRIM13,SLC38A9,HMGB1,PIK3C3,TRIM38,TECPR1,FOXO1,S100A9,SNX5,TP53INP2,CASP3,IL10RA,SIRT1,AKT1,DRAM1,TGFBRAP1,ATM,WDFY3,CHMP2B,BCL2,ULK1,TSG101,SMCR8,ATG2B,GAPDH,MCL1,PRKAB2,FZD5,HUWE1,SH3GLB1,WDR45B,STAT3,RAB3GAP2,ITPR1,PIP4K2C,RRAGD,HSPA8,UBXN2A,FOXO3,MET,CHMP4B,IL4,ROCK1,EXOC8,LRSAM1,RAB7A,CSNK2A1,LIX1L,ERN1,TP53,PACS2,TRIM65,IKBKG,ATP6V0D2,PGAM5,QSOX1,TMEM59,AMBRA1,CLU,GNAI3,TPCN2,UFC1,GSK3B,UBQLN4,FOXK2,RAB3GAP1,CAPNS1,ATG2A	83	both
autophagy - animal	KEGG:04140	autophagy	2.021E-10	AKT1,ZFYVE1,BCL2,PPP2CA,MTMR3,IGF1R,PIK3CB,RAF1,PIK3CD,MTMR4,TRAF6,SQSTM1,ATG9A,IRS1,KRAS,ATG14,PIK3R3,PTEN,RUBCN,RPS6KB1,GABARAPL1,STX17,LAMP2,PRKAA1,PRKCD,ITPR1,PIK3R1,WIPI2,AKT3,GABARAP,MAP3K7,RRAS2,MAPK3,RRAS,ATG5,MAP2K1,RRAGD,RRAGA,ATG4B,ATG4C,BNIP3,HMGB1,ATG4D,BECN1,ATG7,DAPK1,ATG4A,CFLAR,BCL2L1,NRAS,TANK,DDIT4,MAPK1,NRBF2,AKT1S1,RAB1A	56	both
autophagy - other	KEGG:04136	autophagy	1.322E-02	PPP2CA,ATG9A,GABARAPL1,WIPI2,GABARAP,ATG5,ATG4B,ATG4C,ATG4D,BECN1,ATG7,ATG4A	12	up
autophagy of mitochondrion	GO:0000422	mitochondrial activity	3.519E-02	VDAC1,HUWE1,HK2,SQSTM1,ATG9A,FZD5,ATG14,GABARAPL1,WIPI2,GABARAP,HAX1,FBXW7,ATG5,MFN2,BNIP3,BECN1,ATG7,SREBF1	18	up
axon development	GO:0061564	organogenesis	2.949E-02	SEMA4C,ZSWIM6,SEMA4B,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,PIK3CD,ABL1,EPHA7,FGFR2,CXCR4,RHOA,LAMC2,PARD6B,ACTBL2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,HSP90AA1,NPTX1,B4GALT5,NRP1,ALCAM,PTEN,VEGFA,PAFAH1B1,KIF5B,WNT7A,GRB2,EFNB2,PAK2,SLC9A6,SPTBN1,PIK3R1,ARHGDIA,APP,GSK3B,RET,RTN4,BSG,ARTN,ITGB1,SEMA3A,EFNB1,MAPK3,SRC,SPTAN1,PLCG1,ANK3,EPHA5,MAP1B,EPHA2,GDI1,GFRA3,CTTN,ADNP,GAP43,CDK5R1,PLXNA3,NFIB,GRB10,MAPK1,CAMSAP2,RPS6KA5,RHOH,ENAH,UNC5C,FRS2,ACTB,RAB10,PAK3,EMB	78	both
axon guidance	GO:0007411	neuronal architecture	2.648E-03	SEMA4C,ZSWIM6,SEMA4B,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,PIK3CD,EPHA7,CXCR4,LAMC2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,NRP1,ALCAM,VEGFA,KIF5B,GRB2,EFNB2,SPTBN1,PIK3R1,APP,RET,BSG,ARTN,SEMA3A,EFNB1,MAPK3,SRC,SPTAN1,PLCG1,EPHA5,EPHA2,GFRA3,GAP43,CDK5R1,PLXNA3,NFIB,GRB10,MAPK1,RPS6KA5,RHOH,ENAH,UNC5C,FRS2,EMB	52	both
axon guidance	GO:0007411	neuronal architecture	2.648E-03	SEMA4C,ZSWIM6,SEMA4B,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,PIK3CD,EPHA7,CXCR4,LAMC2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,NRP1,ALCAM,VEGFA,KIF5B,GRB2,EFNB2,SPTBN1,PIK3R1,APP,RET,BSG,ARTN,SEMA3A,EFNB1,MAPK3,SRC,SPTAN1,PLCG1,EPHA5,EPHA2,GFRA3,GAP43,CDK5R1,PLXNA3,NFIB,GRB10,MAPK1,RPS6KA5,RHOH,ENAH,UNC5C,FRS2,EMB	52	both
axon guidance	KEGG:04360	neuronal architecture	2.648E-03	SEMA4C,ZSWIM6,SEMA4B,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,PIK3CD,EPHA7,CXCR4,LAMC2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,NRP1,ALCAM,VEGFA,KIF5B,GRB2,EFNB2,SPTBN1,PIK3R1,APP,RET,BSG,ARTN,SEMA3A,EFNB1,MAPK3,SRC,SPTAN1,PLCG1,EPHA5,EPHA2,GFRA3,GAP43,CDK5R1,PLXNA3,NFIB,GRB10,MAPK1,RPS6KA5,RHOH,ENAH,UNC5C,FRS2,EMB	52	both
axon guidance	KEGG:04360	neuronal architecture	2.648E-03	SEMA4C,ZSWIM6,SEMA4B,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,PIK3CD,EPHA7,CXCR4,LAMC2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,NRP1,ALCAM,VEGFA,KIF5B,GRB2,EFNB2,SPTBN1,PIK3R1,APP,RET,BSG,ARTN,SEMA3A,EFNB1,MAPK3,SRC,SPTAN1,PLCG1,EPHA5,EPHA2,GFRA3,GAP43,CDK5R1,PLXNA3,NFIB,GRB10,MAPK1,RPS6KA5,RHOH,ENAH,UNC5C,FRS2,EMB	52	both
b cell activation involved in immune response	GO:0002312	leukocyte activation	1.029E-02	SUPT6H,HSPD1,CD40LG,LFNG,IL6,NOTCH2,DOCK11,RNF168,RIF1,POU2AF1,CD180,DLL1,CD40,TFRC,IFNB1,IL10,CCR6	17	up

b cell differentiation	GO:0030183	cell differentiation	2.017E-02	IKZF3,CEBPG,LFNG,SFRP1,IL6,NOTCH2,ADAM17,KLF6,PTPRJ,DOCK11,TCF3,POU2AF1,ITGB1,ATM,DLL1,TPD52,IFNB1,KIT,IL10,ADGRG3,CD27,FNIP1,DNAJB9,RAG1,ZBTB7A	25	up
b cell proliferation	GO:0042100	cell proliferation	2.196E-02	CDKN2A,CD320,IKZF3,BCL2,RASGRP1,HSPD1,CD40LG,MIF,TCF3,CD180,MEF2C,ATM,VAV3,CD40,TFRC,IFNB1,TNFRSF21,IL10,CD70,TIRAP,TNFRSF13C	21	up
b cell receptor signalling pathway	KEGG:04662	signalling pathways	3.302E-03	AKT1,PIK3CB,RAF1,PIK3CD,FOS,NFKB1,IFITM1,SOS1,KRAS,SOS2,PIK3R3,VAV2,GRB2,CHUK,PIK3R1,AKT3,GSK3B,VAV3,MAPK3,MAP2K1,PPP3R1,BCL10,LILRA2,NRAS,MAPK1	25	up
bacterial invasion of epithelial cells	KEGG:05100	viral of bacterial infection	2.233E-03	VCL,PIK3CB,PIK3CD,RHOA,WASF2,WASL,ITGA5,PIK3R3,ACTR3B,ACTR2,CRKL,PIK3R1,CD2AP,CDC42,CRK,ITGB1,MET,ACTG1,CLTB,SRC,CTNNB1,CTTN,CLTA,ARHGEF26,ACTB	25	up
basal cell carcinoma	KEGG:05217	cancer	3.859E-03	FZD4,TP53,BAK1,SMO,APC,FZD6,GLI1,CDKN1A,WNT2B,WNT1,FZD5,WNT7A,AXIN2,GSK3B,FZD9,LEF1,CTNNB1,GADD45A,BAX,TCF7,TCF7L2	21	up
β-catenin destruction complex disassembly	GO:1904886	Wnt signalling	5.888E-04	APC,CSNK1A1,AMER1,LRP6,FZD5,FRAT2,CTNNB1,DVL3,GSK3B,PPP1CA,DVL1	11	down
β-catenin-tcf complex assembly	GO:1904837	Wnt signalling	2.329E-03	CREBBP,KMT2D,CDC73,TLE4,AXIN2,MYC,HDAC1,LEF1,CTNNB1,SMARCA4,TLE3,TCF7,TCF7L2	13	up
bh3-only proteins associate with and inactivate anti-apoptotic bcl-2 members	REAC:R-HSA-111453	apoptosis	1.456E-03	BID,PMAIP1,BCL2,BBC3,STAT3,BCL2L11	6	both
binding of tcf/lef:ctnnb1 to target gene promoters	REAC:R-HSA-4411364	gene expression	4.654E-03	AXIN2,MYC,LEF1,CTNNB1,TCF7,TCF7L2	6	up
biological process involved in interaction with host	GO:0051701	viral of bacterial infection	1.042E-02	VPS4B,CHMP3,EXOC7,KPNB1,CXCR4,TRIM22,IFITM3,IFITM1,IFIT1,CXCL8,KPNA4,VPS37B,CHMP4B,TRIM35,GRB2,VPS4A,INSR,KPNA1,KPNA3,BSG,CHMP2B,MET,THOC2,SNX3,SRC,TPCN2,ATG5,RRAGA,ITGB3,CTNNB1,AXL,ATG7,CASP8,BCL2L1,PABPN1,KPNA2	36	up
bladder cancer	KEGG:05219	cancer	4.920E-04	MYC,RASSF1,MAPK1,CDH1,MAP2K2,RPS6KA5,CCND1,KRAS,MMP2,MDM2,VEGFA,CDKN1A,TP53,EGF,THBS1,E2F3	16	both
blood vessel endothelial cell migration	GO:0043534	cell adhesion and migration	3.576E-02	ETS1,AKT1,ANGPT2,TNF,STARD13,CDH5,RHOA,PTGS2,CARD10,ROBO1,NOTCH1,ADAM17,FGF2,KLF4,NRP1,PIK3R3,VEGFA,MECP2,MAP2K3,EFNB2,AMOT,AKT3,KDR,MEF2C,SP1,ITGB1,STAT5A,SIRT1,CD40,PLCG1,HMGB1,GADD45A,EPHA2,PRKD1,NUS1,PRKD2,PDGFB,EMP2,THBS1	39	up
bmal1:clock,npas2 activates circadian gene expression	REAC:R-HSA-1368108	gene expression	4.503E-02	CREBBP,MED1,CLOCK,BHLHE40,CARM1,TBL1XR1,NAMPT,NCOA1,PPARA,ARNTL2	10	up
bmp signalling pathway	GO:0030509	signalling pathways	6.303E-04	BMPR1B,XIAP,CDH5,SMAD4,FBN1,LRP2,SMAD2,NOTCH1,WNT1,UBE2D3,SKI,PDCD4,SMAD3,CRIM1,RUNX2,RBPJ,ACVR2A,TMEM100,TGFBR3,SMAD7,USP15,SMURF1,MAPK3,BMP7,GDF5,POU5F1,HIVEP1,BMPR1A,SLC33A1,BMP8A,SOX11,DAND5,PCSK6,SPART,ACVR1,LEFTY1,TRIM33	37	up
bone cell development	GO:0098751	organogenesis	6.405E-04	ZNF385A,MED1,FBN1,NOTCH2,PAFAH1B1,FBXW7,SRC,KIT,SH2B3,SIGLEC15	10	up
bone development	GO:0060348	organogenesis	3.228E-02	BMPR1B,TP53,ZNF385A,MED1,MMP13,FBN1,FGFR2,RHOA,BGLAP,NOTCH2,WNT1,FGFR3,SKI,PAFAH1B1,RAB23,TFAP2A,CYP26B1,FBXW7,MEF2C,SRC,KIT,SH2B3,SIGLEC15,TWIST1	24	up
bone resorption	GO:0045453	organogenesis	2.736E-02	TNFAIP3,SPP1,BGLAP,IL6,SRC,ITGB3,CSF1R,S1PR1,RAB3D,TPP1,UBASH3B,SIGLEC15	12	up
branching involved in blood vessel morphogenesis	GO:0001569	organogenesis	3.023E-02	NRARP,NRP1,VEGFA,KDR,TGFBR2,CTNNB1,SIRT6,COL4A1	8	up
breast cancer	KEGG:05224	cancer	2.924E-05	E2F3,FZD4,TP53,ERBB2,FRAT2,AKT1,BAK1,IGF1R,PIK3CB,APC,RAF1,PIK3CD,FZD6,EGFR,E2F2,FOS,CDKN1A,BRCA2,BRCA1,CCND1,NOTCH2,SOS1,NOTCH1,WNT2B,WNT1,KRAS,FZD5,SOS2,FGF2,PIK3R3,PTEN,CDK4,CDK6,RPS6KB1,WNT7A,GRB2,PIK3R1,AKT3,HEYL,AXIN2,GSK3B,FZD9,SP1,E2F1,MYC,JAG1,DLL1,LEF1,NCOA1,MAPK3,MAP2K1,CTNNB1,GADD45A,BAX,KIT,TCF7,NRAS,TCF7L2,MAPK1,ESR1	60	both
budding and maturation of hiv virion	REAC:R-HSA-162588	viral of bacterial infection	2.479E-02	VPS4B,CHMP3,VPS37B,VPS37A,CHMP4B,VPS4A,CHMP2B,VPS37D,UBB,RPS27A,UBC	11	up
c-type lectin receptor signalling pathway	KEGG:04625	signalling pathways	2.044E-02	BCL3,AKT1,TNF,MAPK14,PIK3CB,RAF1,PIK3CD,RHOA,NFKB1,PTGS2,STAT1,IL6,KRAS,PIK3R3,MAPKAPK2,CHUK,PRKCD,ITPR1,CYLD,PIK3R1,AKT3,NLRP3,RRAS2,MDM2,MAPK3,SRC,CCL22,RRAS,MAP3K14,CASP1,PPP3R1,IL10,BCL10,CASP8,NRAS,STAT2,MAPK1,IRF1	38	both
ca2+ pathway	REAC:R-HSA-4086398	homeostasis	9.163E-03	FZD4,FZD6,TNRC6B,AGO3,FZD5,TNRC6A,AGO2,AGO1,GNB1,AGO4,ITPR1,MAP3K7,GNG12,LEF1,MOV10,CTNNB1,PPP3R1,TCF7,TCF7L2,PLCB1	20	up
calnexin/calreticulin cycle	REAC:R-HSA-901042	protein metabolism	1.429E-02	SEL1L,EDEM1,GANAB,MAN1B1,EDEM3,CANX,UBB,RPS27A,UBC,PRKCSH,DERL2	11	up
canonical wnt signalling pathway	GO:0060070	Wnt signalling	1.669E-02	TMEM9,FZD4,XIAP,FRAT2,SFRP5,WNK1,PSMB1,APC,EMD,NRARP,FZD6,USP8,PPP1CA,EGFR,GLI1,FGFR2,DKK3,NFKB1,SFRP1,SOX2,WNT2B,DKK1,WNT1,FZD5,PTEN,WNT7A,DDX3X,PPM1A,BTRC,CUL3,AMER1,CCDC88C,KANK1,NKD1,CYLD,TLE4,AXIN2,GSK3B,FZD9,TBL1XR1,PLPP3,ZNRF3,PSMB5,LATS2,TMEM64,HDAC1,LEF1,CTNNB1,USP47,POU5F1,NR4A2,TLE3,TCF7,SOX4,GNAQ,TCF7L2,MCC,CAPRIN2,KREMEN1,WWTR1,STK4,ZNF703,TMEM170B,LIMD1,PPM1B	65	up
carbohydrate biosynthetic process	GO:0016051	metabolic process	4.606E-02	IGF2,AKT1,SIRT7,SLC25A1,PTH1R,DYRK2,CD244,NFKB1,IRS1,SIK1,SORD,OGT,B3GNT2,TPI1,EPM2AIP1,SLC25A12,INSR,B4GALT1,EXT1,GSK3B,AP2A1,GPI,GYG1,SIRT1,AKR1B1,EXT2,FUT8,PPP1R3D,PER2,SLC39A14,G6PC,GRB10,ARPP19,PDGFB,HAS2,HS2ST1	36	up
carbohydrate catabolic process	GO:0016052	catabolic process	2.118E-03	PKM,SCARB2,STAT3,TP53,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,NEU1,HK2,NDC1,ENTPD5,SORD,PHKA1,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,PGD,APP,TKTL1,POM121C,NUDT5,LDHA,GPI,NUP62,PYGB,TIGAR,NUP98,FUT8,RAE1,FUT10,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	43	up
carbohydrate metabolic process	GO:0005975	metabolic process	3.334E-04	PMAIP1,PKM,SCARB2,STAT3,IGF2,TP53,AKT1,NUP93,SIRT7,NUP205,SLC25A1,IPPK,RANBP2,PTH1R,NUP37,PRKAG1,PFKM,MAN1B1,NEU1,DYRK2,HK2,CD244,NDC1,ST6GAL2,NFKB1,ENTPD5,PRKCE,IRS1,SIK1,SORD,PPARD,PTEN,SLC2A3,PHKA1,FOXK1,OGT,PRKAA1,PPIP5K2,B3GNT2,OCRL,TPI1,EPM2AIP1,CBFA2T3,SLC25A12,INSR,NUP50,B4GALT1,PGD,APP,EXT1,GSK3B,TKTL1,POM121C,SLC2A4,CYB5A,AP2A1,NUDT5,LDHA,GPI,AKR7A2,GYG1,SIRT1,AKR1B1,NUP62,GALNT7,EXT2,PYGB,TIGAR,NUP98,RPIA,FUT8,RAE1,AKR1A1,FUT10,ME1,PPARA,SPAM1,IMPA1,NUP43,PGAM4,PPP1R3D,PER2,GCNT3,CHST1,SLC39A14,G6PC,ZBTB7A,GRB10,GNPTAB,NUP54,EIF6,ARPP19,MIDN,PDGFB,HAS2,HS2ST1	96	up
carboxylic acid transmembrane transport	GO:1905039	cellular transport	3.482E-02	SLC7A1,AKT1,SLC19A1,SLC25A1,SLC7A6,LRP2,ARL6IP1,SLC38A2,SLC25A12,SLC25A22,SLC25A29,SLC7A5,ITGB1,CPT2,ACSL1,SLC1A5,PER2,SLC25A32,SLC38A9,MID1IP1,LRRC8D,ABCD2,SLC46A1,CD36,SLC16A1,THBS1,EMB	27	up
cardiac chamber development	GO:0003205	organogenesis	5.423E-03	SMAD4,FGFR2,LRP2,ROBO1,NOTCH2,NOTCH1,NRP1,RBPJ,HEYL,FKBP1A,TGFBR3,SMAD7,SALL1,MEF2C,JAG1,TPM1,MDM4,TGFBR2,DSP,GATA4,PKP2,BMP7,SOX4,BMPR1A,GATA6,SOX11,DAND5,ACVR1	28	up
cardiac epithelial to mesenchymal transition	GO:0060317	organogenesis	9.646E-03	NOTCH1,PDCD4,RBPJ,HEYL,TGFBR3,JAG1,TGFBR2,SNAI1,ACVR1,HAS2	10	up

cardiac muscle tissue development	GO:0048738	organogenesis	1.812E-03	NEBL,SMAD4,GLI1,FGFR2,ERBB4,LRP2,KDM6B,NOTCH1,DKK1,SIK1,FGF2,VEGFA,EFNB2,RBPJ,FKBP1A,TGFBR3,SMAD7,PIM1,MEF2C,ITGB1,TPM1,PDGFRB,PDGFRA,DSP,PKP2,TP73,BMP7,ACTC1,S1PR1,BMPR1A,CBY1,EDN1,ACVR1,MYH11,FRS2,VGLL4,ADAMTS9	37	up
cardiac septum development	GO:0003279	organogenesis	1.619E-03	SMAD4,FGFR2,LRP2,ROBO1,NOTCH2,NOTCH1,NRP1,HEYL,TGFBR3,SMAD7,SALL1,JAG1,MDM4,TGFBR2,GATA4,BMP7,SOX4,BMPR1A,GATA6,SOX11,DAND5,ACVR1	22	up
cardiac ventricle development	GO:0003231	organogenesis	2.076E-03	SMAD4,FGFR2,LRP2,ROBO1,NOTCH1,RBPJ,HEYL,FKBP1A,TGFBR3,SMAD7,SALL1,MEF2C,JAG1,TPM1,MDM4,TGFBR2,DSP,GATA4,PKP2,SOX4,BMPR1A,SOX11,DAND5,ACVR1	24	up
cardiac ventricle morphogenesis	GO:0003208	organogenesis	1.487E-03	SMAD4,FGFR2,LRP2,NOTCH1,RBPJ,HEYL,FKBP1A,TGFBR3,SMAD7,MEF2C,JAG1,TPM1,TGFBR2,DSP,GATA4,PKP2,SOX4,BMPR1A,SOX11	19	up
cardiocyte differentiation	GO:0035051	cell differentiation	2.539E-02	NEBL,REST,SMAD4,EGFR,KDM6B,NOTCH1,DKK1,SIK1,PDCD4,VEGFA,EFNB2,RBPJ,TGFBR3,MEF2C,ITGB1,JAG1,PDGFRB,PDGFRA,GATA4,POU5F1,ACTC1,GATA6,CBY1,EDN1,ACVR1,MYH11,FRS2	27	up
cargo recognition for clathrin-mediated endocytosis	REAC:R-HSA-8856825	endocytosis	1.197E-02	SCARB2,FZD4,EGFR,COPS8,LRP2,STON2,LDLR,TGFA,AP2B1,CFTR,AP2A1,VAMP2,CLTB,AP2M1,SYT1,UBQLN2,TFRC,AP2A2,STAM2,AREG,AGTR1,TOR1B,CLTA,UBB,RPS27A,IGF2R,UBC,EREG,SGIP1,COPS7B	30	up
casp8 activity is inhibited	REAC:R-HSA-5218900	caspase signalling pathway	3.238E-03	TNFRSF10B,Fas,FADD,TNFRSF10A,TRAF2,FASLG,CASP8	7	up
caspase activation via death receptors in the presence of ligand	REAC:R-HSA-140534	caspase signalling pathway	1.052E-02	TNFRSF10B,Fas,FADD,TLR4,TNFRSF10A,TRAF2,FASLG,CASP8	8	up
caspase activation via extrinsic apoptotic signalling pathway	REAC:R-HSA-5357769	caspase signalling pathway	1.052E-02	TNFRSF10B,Fas,FADD,TLR4,CASP3,CASP9,TNFRSF10A,TRAF2,FASLG,DAPK1,CASP8	11	up
cd163 mediating an anti-inflammatory response	REAC:R-HSA-9662834	signalling pathways	4.467E-02	MAPK14,IL6,FURIN,ADAM17,IL10	5	up
cd28 co-stimulation	REAC:R-HSA-389356	signalling pathways	4.504E-02	AKT1,GRAP2,CD80,PIK3R3,PAK2,PIK3R1,AKT3,CDC42,MAP3K14,RICTOR,PAK3	11	up
cd4-positive, α-β t cell activation	GO:0035710	leukocyte activation	4.034E-02	CBFB,IRF4,STAT3,CD80,IL6,RSAD2,IL23R,CD274,VSIR,AGER,MYB,SMAD7,SOCS5,NLRP3,TOX,LEF1,TGFBR2,HMGB1,ZBTB7B,ATP7A	20	up
cd40 signalling pathway	GO:0023035	signalling pathways	4.808E-02	TNFAIP3,CD40LG,ITGA5,ITGB1,CD40,TREM2	6	up
cell adhesion mediated by integrin	GO:0033627	cell adhesion and migration	1.765E-02	WNK1,PODXL,LIF,MUC1,FBN1,ITGBL1,CCL5,ITGB2,ITGA5,ADAM17,ITGB8,ITGA2,RET,PLPP3,ITGB1,ITGA11,ITGB3,PIK3CG,EPHA2	19	up
cell aging	GO:0007569	senescence	1.301E-03	CDKN2A,SMC6,TP53,ULK3,NPM1,MAPK14,HMGA2,HMGA1,MIF,CDKN1A,WNT1,HLA-G,PDCD4,CHEK1,CDK6,PRKCD,AKT3,ATM,SIRT1,MAP2K1,YBX1,MAPKAPK5,CHEK2,ROMO1,TERF2,B2M,TWIST1	27	both
cell cycle	KEGG:04110	cell cycle	1.391E-04	MYC,CDK6,E2F5,WEE1,EP300,MCM4,YWHAG,CCND1,CCND3,ATM,STAG1,CDC23,MDM2,CCNA2,CCND2,SMAD2,SMAD3,CDKN1B,CHEK1,SKP2,BUB1,SMC3,GADD45A,CDKN1A,CDC27,TP53,ESPL1,TFDP2,YWHAE,GSK3B,YWHAB,CREBBP,ORC6,MCM5,E2F3	35	both
cell cycle arrest	GO:0007050	cell cycle	2.075E-10	CDKN2A,TP53INP1,E2F7,TP53,ARID3A,ZNF385A,CDKN2D,PRKAG1,BTG2,APC,TNKS1BP1,HMGA2,ABL1,MUC1,DUSP1,MIF,CDKN1A,CDKN3,BRCA1,CNOT6L,CXCL8,CCND1,NOTCH2,NOTCH1,SOX2,STRADB,RBM38,CDKN1B,CNOT4,CDK4,CDK6,SMAD3,PRKAA1,PPM1A,CARM1,CDK1,TBRG1,CAB39,PPP2R5C,FZD9,CDK2,MDM2,E2F1,ATM,MYC,CDC25C,SFN,MDM4,MAP2K1,RRAGD,RRAGA,CRADD,GADD45A,TP73,CDKN2C,BAX,CNOT2,SOX4,AURKA,GATA6,CCNB1,RPL23,SLC38A9,CHEK2,CNOT1,TCF7L2,IRF1,HBP1,JMY,DHCR24,THBS1,CRLF3	72	both
cell cycle checkpoint	GO:0000075	cell cycle	6.139E-06	E2F7,TP53,ARID3A,AURKB,RFWD3,ZNF385A,BTG2,APC,TNKS1BP1,HMGA2,MUC1,DUSP1,CDKN1A,BRCA1,CNOT6L,CCND1,RBM38,CLOCK,CDKN1B,CNOT4,CHEK1,TAOK1,WEE1,VPS4A,CARM1,CDK1,PPP2R5C,CLSPN,CDK2,MDM2,E2F1,ATM,MRE11,CDC25C,MRNIP,SFN,MDM4,CDC20,FZR1,FOXN3,IK,PPP1R10,CDC5L,CRADD,GADD45A,DGKZ,BAX,BCL2L1,CNOT2,SOX4,USP28,AURKA,CCNB1,SOX11,NABP1,CHEK2,CNOT1,ORC1,TOP2A	59	both
cell cycle checkpoints	REAC:R-HSA-69620	cell cycle	2.826E-04	CDKN2A,TP53,CCNE1,AURKB,PPP2CA,ZNF385A,RANBP2,NUP37,PSMB1,ANAPC16,CENPP,CDKN1A,BRCA1,NSL1,CCNA2,RCC2,KIF2C,CDKN1B,YWHAB,CHEK1,TAOK1,PAFAH1B1,WEE1,BIRC5,ORC4,CDK1,CDC25A,CDC27,RNF168,DYNLL2,YWHAQ,YWHAH,CCNE2,PPP2R5C,PSMB5,CLSPN,CDK2,MDM2,RANGAP1,ATM,MRE11,CDC25C,ERCC6L,SFN,MDM4,MCM4,CDC20,MCM2,MCM7,MCM10,ANAPC5,MCM6,HIST1H2BJ,CKAP5,MCM3,KIF2A,CDC23,PPP1CC,MCM5,NUP43,CCNB1,INCENP,DYNC1LI2,UBB,CHEK2,RPS27A,UBC,RFC2,ORC1,CLIP1,DSN1,HERC2,SKA2	73	up
cell cycle dna replication	GO:0044786	cell cycle	2.947E-02	E2F7,BRCA2,MCMDC2,POLE4,POLD1,MCM4,MCM2,MCM7,FEN1,PRIM1,MCM6,MCM3,MCM5,NUGGC,CHEK2,RFC2,TERF2	17	up
cell cycle g1/s phase transition	GO:0044843	cell cycle	7.548E-15	MYC,DCUN1D3,SOX4,CDK6,WEE1,DDX3X,LSM10,TP63,ARID3A,FAM107A,EP300,ADAM17,MCM4,ZNF655,FAM83D,CCND1,MAP3K11,EIF4EBP1,EZH2,AKT1,CCND3,RPA1,ATM,CUL5,PTEN,KMT2E,LATS2,CARM1,NASP,BTG2,ITGB1,MDM2,CCNA2,KLF4,CNOT6,CCND2,CDKN1B,SKP2,APPL1,RFWD3,GADD45A,CDKN1A,KANK2,TP53,CDC73,MDM4,PRIM2,RBM38,PRIM1,GSPT1,TFDP2,BACH1,BCAT1,ORC6,EIF4E,MCM5,AURKA,E2F3	58	both
cell division	GO:0051301	cell cycle	2.491E-02	CDKN2A,VPS4B,E2F7,CHMP3,MYO19,AURKB,PIK3CB,APC,USP8,HDGF,FGFR2,RHOA,ROCK1,NUMB,PRKCE,CEP55,TXNIP,ZFYVE26,PAFAH1B1,CHMP4B,CUL3,FLCN,VPS4A,KIF23,RACGAP1,TUBB,SPTBN1,CDC27,CDC42,STMN1,RHOB,TAL1,CHMP2B,ECT2,MYC,DLL1,SFN,RAB11FIP4,KIF4A,NUP62,BIRC6,SON,SEPT7,ANK3,MAP4,BECN1,POU5F1,CDC23,BCL2L1,AURKA,INCENP,OR2A4,TRIM36,KLHL21,SPART,CDK2AP2,CSPP1,KIF13A,WWTR1,SKA2,RAB10	61	both
cell fate commitment	GO:0045165	cell proliferation	7.260E-03	IRF4,STAT3,PRDM1,APC,MCL1,FGFR2,CDC73,SMAD2,IL6,NOTCH2,SOX2,WNT2B,IL23R,DKK1,GAS1,WNT1,FGF2,KLF4,NRP1,WNT7A,RBPJ,TCF3,CYP26B1,MEF2C,PAX6,ITGB1,TAL1,TOX,JAG1,DLL1,GATA4,NANOG,POU5F1,GATA6,ESRP1,PDPN,TCF7L2,ACVR1,RAB10	39	up
cell fate determination	GO:0001709	cell proliferation	3.967E-02	MCL1,NOTCH2,KLF4,CYP26B1,MEF2C,JAG1,DLL1,POU5F1	8	up
cell growth	GO:0016049	cell proliferation	1.275E-02	DCUN1D3,SEMA6B,SEMA6A,DDX3X,SLC25A33,ACSL4,EI24,SEMA3E,SORBS2,MAP3K13,FAM107A,BMPR2,L1CAM,ADAM17,IGF1,PAK5,FGFR1OP,S100A9,BCL11A,SIRT1,SEMA4C,SOX9,AKT1,CCAR2,TGFBR1,RNF6,CAPRIN2,DCBLD2,BCL2,RPS6KA3,ULK1,IL2,CDC42,ITGB1,SGK1,PPT1,VEGFA,CDKN2AIP,SMAD3,CDKN1B,SEMA7A,NET1,KIAA1109,CTTN,SERTAD2,CTNNB1,FOXM1,CDKN1A,HSP90AB1,CRK,SEMA4G,CSNK2A1,TP53,NDRG3,EXOSC2,SERTAD1,WT1,SLIT1,ZNF639,ITCH,NPR1,PLCE1,GSK3B,TMEM97,DCUN1D5,TAOK2,PAK4	67	both
cell morphogenesis involved in neuron differentiation	GO:0048667	organogenesis	2.351E-03	SEMA6B,EPHB2,PAK2,NPTN,MAPK1,SEMA6A,RAB10,RNF165,NTNG2,NSMF,METRN,LRTM1,BRSK1,GDNF,VLDLR,SEMA3E,UNC5D,CAPRIN1,NPTX1,MAP3K13,NOTCH1,RET,ZDHHC15,SLITRK4,L1CAM,RPS6KA5,TIAM2,NTNG1,EFNB1,LHX9,PARD3,NFIB,BCL11A,SEMA4C,PTK2,CDH2,RELN,UNC5B,PTEN,RNF6,PHOX2B,CAPRIN2,NOTCH2,RHOG,ULK1,HECW2,SIPA1L1,BTBD3,CDC42,HECW1,ITGB1,TIAM1,VEGFA,LAMC2,UNC5C,WASL,SEMA7A,PTPRD,FRS2,MYPN,TUBB3,CTTN,C8orf37,RHOA,HSP90AB1,SEMA4G,NRXN3,FBXW8,ARHGDIA,KIF3A,KIF5C,SLIT1,LLGL1,WNT5A,MINK1,GSK3B,TAOK2,DVL1,ZSWIM4	79	both
cell proliferation involved in kidney development	GO:0072111	organogenesis	3.844E-02	IL6R,STAT1,FLCN,MYC,PDGFRB,BMP7,PDGFB	7	up
cell surface receptor signalling pathway involved in cell-cell signalling	GO:1905114	signalling pathways	6.899E-03	WNT4,NLGN2,SOX4,RSPO1,DDX3X,ESR1,NR4A2,APC,GNAQ,PSMB9,CPE,CHRFAM7A,AGO3,TRABD2A,XIAP,KREMEN1,TNRC6B,ZNF703,DAB2,HMGXB4,AGO4,BICC1,COL1A1,GID8,TERT,ADGRA2,SOX9,NFKB1,AKT1,CBY1,CCAR2,SNAI2,AGO1,RELN,FERMT2,FOXL1,PTEN,CCDC88C,CAPRIN2,CSNK1A1,LATS2,ARRB2,PLPP3,GSKIP,TBL1XR1,NLK,CTNND1,IGFBP1,CDC42,HECW1,AMFR,AMER1,WWTR1,OTULIN,CTNNBIP1,LRP6,FZD5,TIAM1,FZD4,FRAT2,TMEM237,NLGN4X,PPP3R1	88	both

				,SKI,SOX2,PRICKLE1,RHOA,CTNNB1,CSNK2A1,ITGA3,CDC73,DVL3,EGF,FZD7,USP34,WNK1,SHISA2,PSMC4,MAGI2,WNT5A,TMEM170B,GSK3B,PSMD3,RAB3GAP1,UBE2B,PPP1CA,PFN1,DVL1		
cell surface receptor signalling pathway involved in heart development	GO:0061311	organogenesis	1.033E-02	NOTCH2,NOTCH1,DKK1,RBPJ,HEYL,JAG1,CTNNB1,SNAI1,POU5F1,BMPR1A,ACVR1	11	up
cell-cell signalling by wnt	GO:0198738	Wnt signalling	4.889E-03	WNT4,SOX4,RSPO1,DDX3X,ESR1,NR4A2,APC,GNAQ,PSMB9,CPE,AGO3,TRABD2A,XIAP,KREMEN1,TNRC6B,ZNF703,DAB2,HMGXB4,AGO4,BICC1,COL1A1,GID8,TERT,ADGRA2,SOX9,NFKB1,CBY1,CCAR2,SNAI2,AGO1,FERMT2,FOXL1,PTEN,CCDC88C,CAPRIN2,CSNK1A1,LATS2,ARRB2,PLPP3,GSKIP,TBL1XR1,NLK,CTNND1,IGFBP1,CDC42,HECW1,AMFR,AMER1,WWTR1,OTULIN,CTNNBIP1,LRP6,FZD5,TIAM1,FZD4,FRAT2,TMEM237,PPP3R1,SKI,SOX2,PRICKLE1,RHOA,CTNNB1,CSNK2A1,ITGA3,CDC73,DVL3,EGF,FZD7,USP34,WNK1,SHISA2,PSMC4,MAGI2,WNT5A,TMEM170B,GSK3B,PSMD3,UBE2B,PPP1CA,PFN1,DVL1	82	both
cell-matrix adhesion	GO:0007160	cell adhesion and migration	9.502E-03	CDKN2A,VCL,NF2,PIK3CB,CD44,ABL1,RHOA,GPM6B,ROCK1,ITGBL1,SFRP1,ITGB2,L1CAM,CSF1,PHLDB2,RCC2,NRP1,PTEN,VEGFA,CDK6,PTPRJ,CASK,ITGA2,MINK1,KDR,GSK3B,SLC9A1,ITGB1,JAG1,ITGA11,ACTG1,SRC,RRAS,ITGB3,MKLN1,CTTN,ADAM15,DLC1,CD36,LYPD3,PLET1,EMP2,ITGA1,THBS1,ADAMTS9	45	up
cell-substrate adhesion	GO:0031589	cell adhesion and migration	1.564E-03	CDK6,NTNG2,LIMS1,PRKX,SEMA3E,EMP2,NOTCH1,DEFB118,FAM107A,L1CAM,NTNG1,SPRY4,SERPINE1,ROCK2,PTK2,FERMT2,PTEN,VCAM1,CDC42,COL3A1,ITGB1,FGG,RCC2,FGB,FGA,PHLDB2,TIAM1,FZD4,ITGA6,VEGFA,NEDD9,LAMC1,LYVE1,CTTN,DLC1,CRKL,RHOA,ROCK1,MKLN1,ARL2,PARVB,CRK,RREB1,NF1,ITGA3,LPXN,MYADM,ACTG1,TYRO3,FZD7,BVES,PDPN,RRAS,THBS1,MINK1,GSK3B,ACTN4,TAOK2,HOXD3,ATXN3	60	both
cell-substrate junction assembly	GO:0007044	cell adhesion and migration	3.855E-02	LIMS1,FAM107A,ROCK2,PTK2,FERMT2,PTEN,RCC2,PHLDB2,ITGA6,VEGFA,LAMC2,LAMC1,CTTN,DLC1,RHOA,ROCK1,DST,ACTG1,THBS1,TAOK2	20	both
cell-substrate junction organisation	GO:0150115	cell organisation	2.111E-02	LIMS1,FAM107A,ROCK2,PTK2,FERMT2,PTEN,ARF6,RCC2,PHLDB2,ITGA6,VEGFA,LAMC2,LAMC1,CTTN,DLC1,RHOA,ROCK1,MAPRE2,DST,ACTG1,THBS1,TAOK2	22	both
cellular carbohydrate metabolic process	GO:0044262	metabolic process	3.016E-02	PMAIP1,SCARB2,STAT3,IGF2,TP53,AKT1,SIRT7,IPPK,PTH1R,DYRK2,CD244,PRKCE,IRS1,SIK1,SORD,PTEN,PHKA1,FOXK1,OGT,PPIP5K2,B3GNT2,OCRL,TPI1,EPM2AIP1,CBFA2T3,INSR,B4GALT1,PGD,EXT1,GSK3B,GYG1,SIRT1,EXT2,PYGB,TIGAR,PPARA,IMPA1,PPP1R3D,PER2,G6PC,GRB10,GNPTAB,ARPP19,MIDN,HAS2,HS2ST1	46	up
cellular component disassembly involved in execution phase of apoptosis	GO:0006921	apoptosis	6.165E-03	CDKN2A,KPNB1,IL6,DICER1,KPNA1,CASP3,HMGB1,AIFM1,CIDEA,BAX,DFFA,BLCAP,TOP2A	13	up
cellular copper ion homeostasis	GO:0006878	homeostasis	3.339E-02	APP,ARF1,ATOX1,PRNP,SLC31A1,ATP7A	6	up
cellular response to abiotic stimulus	GO:0071214	cellular response to external stimuli	2.952E-02	MYC,PARP1,NEUROD2,MAPK14,DDX3X,NSMF,CLOCK,FMR1,USP28,YY1,EP300,METAP1,MAP3K2,RAB11B,SIRT1,YAP1,SOX9,NFKB1,MMP3,ATM,PTEN,NMT2,HMGA2,ZFP36L1,LRRC8D,RHBDD1,MMP2,MDM2,REST,CCND2,CASP8,MAP3K1,SDE2,TNFRSF10B,CHEK1,NET1,CAB39,BCL10,CRY2,TNFRSF10A,GADD45A,CDKN1A,NUCKS1,TP53,HUS1,RAD51,CREBBP,PIEZO1	48	both
cellular response to biotic stimulus	GO:0071216	cellular response to external stimuli	3.865E-03	TP53,TNFAIP3,TNF,MAPK14,RHOA,TRAF6,NFKB1,TLR2,CDC73,IRAK1,CD80,IL6,CCL5,CXCL8,PRKCE,TLR4,TXNIP,FZD5,CD274,PDCD4,GSK3B,CD180,NLRP3,MEF2C,CXCL2,CCL3,MTDH,CXCL9,TIGAR,AXL,CASP1,HMGB1,IL10,BCL10,APAF1,NUGGC,LILRA2,TIRAP,SLX4,SASH1,TMCO1,CD36,PABPN1,TNIP3	44	up
cellular response to chemical stress	GO:0062197	cellular response to external stimuli	8.555E-03	PRDX2,TP53,AKT1,TNFAIP3,EPO,REST,Fas,MCL1,ABL1,ALOX5,EGFR,PARP1,FOS,MYLK,IL6,TLR4,ZNF622,PRKAA1,DDX3X,WNK3,DNAJA1,CHUK,PRKCD,CPEB2,PLEKHA1,CAB39,LANCL1,ALDH3B1,RHOB,FOXO3,FBXW7,FOXO1,CDK2,ECT2,ATM,MET,TPM1,PYCR1,MAPK3,PDGFRA,SIRT1,AKR1B1,DIABLO,GATA4,TXNRD1,CYCS,AIFM1,BMP7,SESN2,ATG7,NOL3,PRKD1,DAPK1,IL10,CYBB,LETM1,LRRC8D,ROMO1,MAPK1,SOD2,ATP7A	61	up
cellular response to decreased oxygen levels	GO:0036294	oxygen levels	1.620E-02	PMAIP1,TP53,SUV39H1,BBC3,EPO,CREBBP,BACH1,PIK3CB,PSMB1,PTGS2,SFRP1,NOTCH1,NDRG1,VEGFA,RBPJ,CUL2,CPEB2,HIGD1A,HYOU1,RTN4,PSMB5,MDM2,MYC,MDM4,SIRT1,TIGAR,BNIP3,AIFM1,BMP7,NOL3,DDAH1,CPEB4,HP1BP3,GATA6,UBB,RPS27A,UBC,EGLN3,LIMD1,TWIST1	40	both
cellular response to environmental stimulus	GO:0104004	cellular response to external stimuli	2.952E-02	MAP3K2,BMF,TP53,EPO,AURKB,CNGB1,BAK1,CREBBP,REST,NPM1,MAPK14,TNFRSF10B,MMP2,Fas,TNKS1BP1,HMGA2,PARP1,NFKB1,RHO,FADD,CDKN1A,MYLK,TLR4,CCND2,CLOCK,PTEN,CHEK1,TMEM109,N4BP1,NUCKS1,DDX3X,GRB2,GNB1,WNK3,CDC25A,GNAT1,CAB39,YAP1,SLC9A1,RHOB,FBXW7,MDM2,ECT2,ATM,MYC,YY1,POLD1,MAPK3,SIRT1,AKR1B1,METAP1,CD40,MAP3K14,MAP3K1,RAD51,BNIP3,CASP1,CASP9,CRADD,GADD45A,TNFRSF10A,USP47,LTBR,TNFRSF1A,BCL10,CASP8,NEUROD2,USP28,LETM1,TLR3,TANK,F11R,MAP2K4,LRRC8D,IRF1,HABP4,ERCC4	77	both
cellular response to external stimulus	GO:0071496	cellular response to external stimuli	3.147E-11	PMAIP1,VDR,MAP3K2,TP53,ZFYVE1,MTMR3,SIK2,BAK1,PRKAG1,TNFRSF10B,Fas,FES,CYP24A1,NFKB1,FADD,CDKN1A,SFRP1,TLR4,SIK1,ATG14,SESN3,CHEK1,GABARAPL1,LAMP2,PRKAA1,FLCN,HSPA8,HNRNPA1,WIPI2,GABARAP,PIM1,SLC9A1,FOXO3,FOXO1,NCOA1,MAPK3,SIRT1,CD40,MAP3K14,ATG5,RRAGD,RRAGA,MAP3K1,EIF4G1,INHBB,BNIP3,CASP1,CRADD,GADD45A,AIFM1,TNFRSF10A,DCTPP1,RALB,BECN1,SESN2,ATG7,LTBR,TNFRSF1A,PRKD1,BCL10,NR4A2,PPARA,ADNP,CASP8,FNIP1,CPEB4,TLR3,F11R,MAP2K4,MAPK1,IRF1,HABP4,KCNB1,SESN1,SREBF1	75	both
cellular response to glucose starvation	GO:0042149	cellular response to external stimuli	1.206E-02	PMAIP1,TP53,MTMR3,SIK2,PRKAG1,SIK1,ATG14,SESN3,PRKAA1,HNRNPA1,FOXO3,BECN1,SESN2,CPEB4,SESN1	15	up
cellular response to heat	GO:0034605	cellular response to external stimuli	1.931E-03	NUP98,MAPK1,EP300,NUP62,NUP205,POLR2D,DNAJB6,BAG4,SIRT1,BAG1,CCAR2,RPA1,ATM,IL1A,POM121C,HSPA8,NUP50,NUP210,HSP90AB1,NUP35,CHORDC1,CLPB,NUP85,THBS1,YWHAE,GSK3B,HSBP1,CREBBP,ATXN3	29	both
cellular response to heat stress	REAC:R-HSA-3371556	cellular response to external stimuli	1.804E-03	MAPK1,EP300,NUP62,NUP205,DNAJB6,BAG4,SIRT1,BAG1,CCAR2,RPA1,ATM,POM121C,HSPA8,NUP50,NUP210,HSP90AB1,NUP35,NUP85,YWHAE,GSK3B,HSBP1,CREBBP	22	both
cellular response to insulin stimulus	GO:0032869	cellular response to external stimuli	4.984E-03	PKM,IGF2,AKT1,SIK2,IGF1R,APC,PARP1,STAT1,SOS1,IRS1,RAB12,PIK3R3,RPS6KB1,RAB15,OGT,MYO5A,NUCKS1,GRB2,KANK1,PRKCD,CPEB2,INSR,PIK3R1,GSK3B,FOXO3,FOXO1,SLC2A4,VAMP2,SIRT1,ATP6V1E1,INHBB,INSIG1,SLC39A14,ATP6V1C1,ATP6V1B2,GRB10,ATP6V0E1,ZBTB7B,ATP6V0D1,SNX5,RAB31,RAB10	42	up
cellular response to interleukin-12	GO:0071349	cellular response to external stimuli	1.376E-02	JAK2,RPLP0,MIF,PDCD4,PAK2,HNRNPDL,HNRNPA2B1,CDC42,CFL1,SNRPA1,MTAP,AIP,IL10,ARF1,SOD2,PLCB1	16	up
cellular response to ionizing radiation	GO:0071479	cellular response to external stimuli	1.531E-02	TP53,MAPK14,TNKS1BP1,HMGA2,CDKN1A,CCND2,CLOCK,TMEM109,NUCKS1,GRB2,YAP1,RHOB,MDM2,ECT2,ATM,SIRT1,RAD51,GADD45A,TANK	19	both
cellular response to lipid	GO:0071396	lipid metabolism	1.298E-03	CBFB,VDR,NCOR2,FZD4,TNFAIP3,TNF,MED1,REST,MAPK14,SMO,STRN3,KMT2D,FES,CYP24A1,EGFR,RHOA,TRAF6,NFKB1,CDC73,IRAK1,CD80,SPP1,SFRP1,BRCA1,IL6,CCL5,CXCL8,PRKCE,TLR4,IRS1,CLOCK,CD274,PDCD4,ABL2,BCL2L11,CARM1,PAGR1,ABHD2,HEYL,YWHAH,CLU,RET,PIM1,CD180,YAP1,NLRP3,MEF2C,CXCL2,CFTR,CCL3,ATM,HDAC1,SRC,SIRT1,AR,MTDH,CXCL9,PER1,SMARCA4,AXL,CASP1,HMGB1,AIFM1,BMP7,IL10,BCL10,CNOT2,RBFOX2,NUGGC,INSIG1,LILRA2,ADAM15,SASH1,LCOR,CREB1,TMF1,PMEPA1,CNOT1,ZBTB7A,SSTR2,ESR1,CD36,ARID1A,PABPN1,TNIP3,SSTR1,ZNF703	87	up
cellular response to molecule of bacterial origin	GO:0071219	cellular response to external stimuli	2.514E-02	TNFAIP3,TNF,MAPK14,RHOA,TRAF6,NFKB1,TLR2,CDC73,IRAK1,CD80,IL6,CCL5,CXCL8,PRKCE,TLR4,FZD5,CD274,PDCD4,CD180,NLRP3,MEF2C,CXCL2,CCL3,MTDH,CXCL9,AXL,CASP1,HMGB1,IL10,BCL10,NUGGC,LILRA2,TIRAP,SASH1,CD36,PABPN1,TNIP3	37	up
cellular response to nutrient levels	GO:0031669	cellular response to external stimuli	5.079E-05	PMAIP1,VDR,TP53,ZFYVE1,MTMR3,SIK2,PRKAG1,Fas,FES,CYP24A1,CDKN1A,SFRP1,SIK1,ATG14,SESN3,GABARAPL1,LAMP2,PRKAA1,FLCN,HSPA8,HNRNPA1,WIPI2,GABARAP,PIM1,FOXO3,FOXO1,NCOA1,MAPK3,SIRT1,ATG5,RRAGD,RRAGA,EIF4G1,INHBB,AIFM1,RALB,BECN1,SESN2,ATG7,PRKD1,PPARA,FNIP1,CPEB4,MAPK1,KCNB1,SESN1,SREBF1	47	up
cellular response to organic cyclic compound	GO:0071407	cellular response to external stimuli	1.853E-03	CBFB,VDR,STAT3,NCOR2,TNF,GABRB3,MED1,REST,NPM1,SMO,STRN3,KMT2D,FES,ABL1,CYP24A1,EGFR,SPP1,STAT1,SFRP1,BRCA1,CCL5,IFIT1,CASP7,CLOCK,COLEC12,HSP90B1,IGFBP5,GABPA,PDE4D,BCL2L11,GNAL,GNB1,CARM1,PAGR1,ZCCHC3,ABHD2,HEYL,YWHAH,CLU,GSK3B,PIM1,DIAPH1,YAP1,SLC9A1,MEF2C,CFTR,CCL3,HDAC1,MAPK3,SRC,CASP3,SIRT1,AR,LARP1,IFNB1,PER1,CTNNB1,SMARCA4,RAD51,AIFM1,RALB,BMP7,CASP6,CNOT2,RBFOX2,INSIG1,LCOR,TMF1,PMEPA1,CNOT1,ZBTB7A,MAVS,MAPK1,SSTR2,ESR1,ARID1A,PDGFB,SSTR1,ACTB,ZNF703	80	up

cellular response to oxygen levels	GO:0071453	oxygen levels	3.381E-03	PMAIP1,TP53,SUV39H1,BBC3,EPO,CREBBP,BACH1,PIK3CB,PSMB1,Fas,PTGS2,SFRP1,NOTCH1,NDRG1,VEGFA,RBPJ,CUL2,CPEB2,HIGD1A,HYOU1,RTN4,PSMB5,FOXO1,MDM2,MYC,MDM4,SIRT1,TIGAR,BNIP3,AIFM1,BMP7,ATG7,NOL3,DDAH1,CPEB4,HP1BP3,GATA6,UBB,RPS27A,UBC,EGLN3,ATP6V0D1,CCDC115,LIMD1,TWIST1	45	up
cellular response to radiation	GO:0071478	cellular response to external stimuli	1.666E-03	BMF,TP53,AURKB,CNGB1,BAK1,CREBBP,NPM1,MAPK14,MMP2,TNKS1BP1,HMGA2,PARP1,RHO,CDKN1A,CCND2,CLOCK,CHEK1,TMEM109,N4BP1,NUCKS1,GRB2,GNB1,CDC25A,GNAT1,YAP1,RHOB,FBXW7,MDM2,ECT2,ATM,MYC,YY1,POLD1,SIRT1,METAP1,RAD51,CASP9,GADD45A,USP47,USP28,TANK,ERCC4	42	up
cellular response to tumor necrosis factor	GO:0071356	cellular response to external stimuli	4.904E-02	SPHK1,TP53,JAK2,AKT1,TNFAIP3,TNF,PSMB1,CD40LG,TRAF6,STAT1,SFRP1,BRCA1,CCL5,CXCL8,ADAM17,CCL4,TNFSF9,CPNE1,CHUK,BAG4,CYLD,PSMB5,FOXO3,SPPL2A,CCL3,TRAIP,TNFRSF6B,BIRC3,SIRT1,CCL22,CD40,MAP3K14,TRAF3,HIST1H2BJ,CASP1,TRAF2,TNFRSF21,RBCK1,LTBR,FASLG,TNFRSF1A,LTA,CD70,CASP8,CD27,BIRC2,TANK,TNFRSF13C,ERBIN,F2RL1,HAS2,HIPK1	52	up
cellular response to type i interferon	GO:0071357	cellular response to external stimuli	4.002E-02	IRF4,IFI27,IFIT3,FADD,IRAK1,ISG15,IFITM3,IFITM1,STAT1,IRF7,MX2,OASL,RSAD2,IFIT1,HLA-A,HLA-G,HLA-C,TTLL12,IFNB1,NLRC5,STAT2,MAVS,IRF1	23	up
cellular response to unfolded protein	GO:0034620	cellular response to external stimuli	2.539E-02	BBC3,EXTL3,EDEM1,BAK1,YOD1,HDGF,HSPD1,SRPRB,CXCL8,HSP90B1,CREBRF,SRPRA,BCL2L11,HSPA8,TM7SF3,PIK3R1,CANX,HYOU1,PDIA6,GFPT1,TATDN2,BAX,BAG3,BFAR,HSPA13,FICD,DNAJB9,TMEM33,PPP1R15B,ATP6V0D1,TPP1,KLHDC3,DERL2	33	up
cellular response to uv	GO:0034644	cellular response to external stimuli	3.226E-02	BMF,TP53,AURKB,BAK1,CREBBP,NPM1,MMP2,PARP1,CDKN1A,CHEK1,N4BP1,CDC25A,FBXW7,MYC,YY1,POLD1,SIRT1,CASP9,USP47,USP28,ERCC4	21	up
cellular senescence	REAC:R-HSA-2559583	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	REAC:R-HSA-2559583	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	REAC:R-HSA-2559583	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	KEGG:04218	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	KEGG:04218	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	KEGG:04218	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	GO:0090398	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	GO:0090398	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
cellular senescence	GO:0090398	senescence	2.356E-02	CDK6,SLC30A10,MAPK14,TP63,TWIST1,PRKCD,TERF2,TERT,HMGA1,SIRT1,VASH1,HMGA2,MAP3K3,AKT3,B2M,PNPT1,CDKN1A,TP53,SRF,MAPKAPK5	20	both
central carbon metabolism in cancer	KEGG:05230	cancer	8.139E-09	MYC,MAPK1,RET,MAP2K2,PDGFRA,SLC7A5,HIF1A,AKT1,PTEN,KIT,KRAS,PDGFRB,AKT2,AKT3,MET,TP53,PKM	17	both
centrosome cycle	GO:0007098	cell cycle	1.462E-03	CCP110,KIF3B,RTTN,BRSK1,SLC16A1,CHMP3,CNTLN,NUP62,PCM1,SIRT1,ROCK2,NIN,SSX2IP,CHMP2B,CEP68,CHEK1,HAUS8,KIF11,CHMP4B,CTNNB1,ARL2,XPO1,CHMP1B,HAUS3,KIF3A,CHORDC1,NDEL1,NDE1,XRCC2,WDR62,CCNF,AURKA	32	down
chagas disease	KEGG:05142	diseases	1.449E-02	AKT1,PPP2CA,TNF,MAPK14,PIK3CB,Fas,PIK3CD,FOS,TRAF6,NFKB1,TLR2,FADD,IRAK1,TGFB1,SMAD2,IL6,CCL5,CXCL8,TLR4,PIK3R3,GNAL,CHUK,PIK3R1,AKT3,CCL3,MAPK3,TGFBR2,IFNB1,FASLG,TNFRSF1A,IL10,CFLAR,CASP8,MAP2K4,GNAQ,MAPK1,PLCB1	37	both
chaperone mediated autophagy	REAC:R-HSA-9613829	autophagy	1.240E-02	EEF1A1,HSP90AA1,LAMP2,HSPA8,CFTR,PLIN3,UBB,RPS27A,UBC,PCNT	10	up
chemokine (c-x-c motif) ligand 2 production	GO:0072567	cell adhesion and migration	4.808E-02	TNF,TLR4,KLF4,HMGB1,TIRAP,F2RL1	6	up
chemokine signalling pathway	KEGG:04062	signalling pathways	4.293E-03	STAT3,JAK2,AKT1,PIK3CB,RAF1,PIK3CD,CXCR4,RHOA,ROCK1,NFKB1,CCR9,STAT1,CCL5,CXCL8,SOS1,CXCL12,KRAS,SOS2,PIK3R3,CCL4,VAV2,GRB2,GNB1,CHUK,PRKCD,CRKL,PIK3R1,AKT3,CDC42,GSK3B,CRK,GNG12,FOXO3,CXCL2,CCL3,VAV3,MAPK3,SRC,CCL22,CXCL9,MAP2K1,PLCG1,PIK3CG,NRAS,STAT2,GNAQ,MAPK1,CCR6,PLCB1	49	up
chk1/chk2(cds1) mediated inactivation of cyclin b:cdk1 complex	REAC:R-HSA-75035	cyclin signalling pathway	7.909E-05	YWHAB,CHEK1,WEE1,CDK1,YWHAQ,YWHAH,CDC25C,SFN,CCNB1,CHEK2	10	up
chl1 interactions	REAC:R-HSA-447041	signalling pathways	4.467E-02	NRP1,HSPA8,ITGA2,ITGB1,ITGA1	5	up
choline metabolism in cancer	KEGG:05231	cancer	9.530E-04	PLA2G4F,AKT1,EIF4EBP1,PIK3CB,RAF1,PIK3CD,EGFR,FOS,WASF2,SOS1,KRAS,SOS2,PIK3R3,RPS6KB1,GRB2,PIK3R1,AKT3,PLPP3,SP1,MAPK3,PDGFRB,PDGFRA,MAP2K1,PLCG1,DGKZ,NRAS,PIP5K1C,MAPK1,PDGFB,DGKB,DGKI	31	up
chordate embryonic development	GO:0043009	organogenesis	8.858E-03	SOX4,TWIST1,BMPR2,IGF1,SIX1,EOMES,PDGFRA,COL1A1,SEMA4C,SOX9,MTHFD1L,TGFBR1,TGFBR2,CDX2,NASP,ITGB1,LRP6,VEGFA,CASP8,ACVR1C,SKI,BCL10,PRICKLE1,HOXA9,DLC1,CTNNB1,DVL3,SRF,HOXB3,EIF4A3,C6orf141,ALX1,PHACTR4,WNT5A,HOXD3,TFAP2A,DVL1,BMPR1A	38	both
chromatin disassembly	GO:0031498	chromatin organisation	3.018E-03	SMARCD2,HMGA1,SET,SUPT16H,SMARCD1,SMARCC2,SMARCA4,SMARCC1,ARID1A,GRWD1	10	up
chromatin modifying enzymes	REAC:R-HSA-3247509	chromatin organisation	4.283E-02	KMT2A,ELP2,RBBP4,NCOA1,HIST1H2BJ,EPC1,CLOCK,MTA3,HIST1H2AH,EP300,PHF21A,KAT6B,MCRS1,MEAF6,CCND1,EED,EZH2,NFKB1,KDM5C,SUZ12,HIST1H2BK,KDM5A,KMT2E,ATXN7,PBRM1,NSD2,SUV39H2,CARM1,TBL1XR1,RCOR1,MORF4L1,DNMT3A,KDM6B,DOT1L,KDM5B,KMT5C,MORF4L2,REST,DR1,SMARCD1,USP22,MSL2,SETD7,KDM2A,CREBBP,BRPF3,KMT2B,HCFC1	48	down
chromatin organisation	REAC:R-HSA-4839726	chromatin organisation	4.283E-02	KMT2A,ELP2,RBBP4,NCOA1,HIST1H2BJ,EPC1,CLOCK,MTA3,HIST1H2AH,EP300,PHF21A,KAT6B,MCRS1,MEAF6,CCND1,EED,EZH2,NFKB1,KDM5C,SUZ12,HIST1H2BK,KDM5A,KMT2E,ATXN7,PBRM1,NSD2,SUV39H2,CARM1,TBL1XR1,RCOR1,MORF4L1,DNMT3A,KDM6B,DOT1L,KDM5B,KMT5C,MORF4L2,REST,DR1,SMARCD1,USP22,MSL2,SETD7,KDM2A,CREBBP,BRPF3,KMT2B,HCFC1	48	down
chromatin remodeling	GO:0006338	chromatin organisation	3.838E-03	CDKN2A,SMARCD2,SUV39H1,PHF8,NPM1,HMGA2,CENPP,HMGA1,MTA2,KDM6B,JARID2,DNMT1,BAZ2B,SETDB1,BAZ2A,EZH1,HCFC2,MYB,TADA2B,SMARCD1,NASP,MYC,HDAC1,TFAM,NUDT5,SMARCC2,SIRT1,CBX3,SMARCA4,SATB2,SMARCC1,HMGB1,POU5F1,SIRT6,KDM4A,ANP32E,BPTF,ATF7IP,SMARCA5,ARID1B,GATAD2B,ZBTB7A,ESR1,TET1,ARID1A,NPM3,OIP5,ACTB,BAHD1,HNRNPC	50	up

chromosome segregation	GO:0007059	cell cycle	2.198E-02	BECN1,DDX3X,APC,KNSTRN,BOD1,ATRX,DUSP1,TTL,NUP62,FAM83D,PLSCR1,RAN,HFM1,ATM,INCENP,STAG1,KIF2C,CHMP2B,NAA50,NCAPG,HECW2,CDC23,CDC42,RIOK3,OIP5,RCC2,MMS19,RMDN1,KIF23,PUM2,PUM1,PDS5A,SLX4,BUB1,CHMP4B,MCMBP,SMC3,DSN1,CTNNB1,CDC27,CSNK2A1,HASPIN,DYNC1H1,KNL1,ESPL1,HJURP,CHMP1B,MRE11,ARL8B,NDEL1,NDE1,FANCD2,SPAG5,CENPK	54	both
chronic myeloid leukemia	KEGG:05220	cancer	1.521E-13	CDKN2A,E2F3,TP53,AKT1,BAK1,GAB2,PIK3CB,RAF1,PIK3CD,SMAD4,ABL1,E2F2,NFKB1,CDKN1A,TGFB1,CCND1,SOS1,KRAS,SOS2,CDKN1B,PIK3R3,CDK4,CDK6,SMAD3,GRB2,CHUK,CRKL,PIK3R1,AKT3,CRK,MDM2,E2F1,STAT5A,MYC,HDAC1,MAPK3,TGFBR2,MAP2K1,GADD45A,BAX,BCL2L1,NRAS,MAPK1	43	both
circadian clock	REAC:R-HSA-400253	endocrine system	3.513E-04	CREBBP,MED1,CRTC1,PPP1CA,SIK1,CLOCK,BTRC,BHLHE40,CARM1,TBL1XR1,MEF2C,NAMPT,NCOA1,SIRT1,PER1,PPP1CC,PPARA,CREB1,ARNTL2,PER2,UBB,RPS27A,UBC,SREBF1	24	both
circadian rhythm	GO:0007623	endocrine system	4.042E-02	KMT2A,ZFHX3,CLOCK,GNAQ,PPARA,RORA,EP300,GFPT1,CPT1A,SIRT1,EZH2,SERPINE1,ROCK2,CCAR2,PPARG,PTEN,KDM5A,PER2,SUV39H2,ID4,PER1,ID3,HUWE1,PPP1CB,PPP1CC,KLF10,FBXL3,CRY2,PPARGC1A,TP53,RBM4B,GSK3B,KDM2A,PPP1CA	34	down
clathrin-dependent endocytosis	GO:0072583	endocytosis	3.516E-03	PIK3CB,WASL,AP2B1,CANX,AP2A1,DLL1,CLTB,AP2M1,UBQLN2,AP2A2,CLTA,PIP5K1C,GPR107,SGIP1,KIAA1107	15	up
clathrin-mediated endocytosis	REAC:R-HSA-8856828	endocytosis	2.065E-03	SCARB2,FZD4,EGFR,COPS8,LRP2,STON2,LDLR,WASL,TGFA,AP2B1,ACTR2,OCRL,HSPA8,TRIP10,CFTR,AP2A1,VAMP2,ACTG1,CLTB,AP2M1,SYT1,UBQLN2,TFRC,AP2A2,ARF6,STAM2,AREG,CTTN,GAPVD1,AGTR1,TOR1B,CLTA,PIP5K1C,RAB5B,UBB,RPS27A,IGF2R,UBC,EREG,SGIP1,ACTB,COPS7B	42	up
coagulation	GO:0050817	diseases	1.685E-03	VCL,JAK2,PABPC4,PIK3CB,RAF1,EHD1,CD40LG,IL6,PRKCE,TLR4,PLAUR,VAV2,ALOX12,DOCK11,RCOR1,PRKAR2A,GNB1,MAFK,PRKCD,ENTPD1,ITPR1,PIK3R1,ITGA2,CDC42,STXBP3,CAPZA2,F3,MYL9,HDAC1,VAV3,HNF4A,ACTG1,VPS45,MAPK3,SRC,PDGFRA,CAPZB,METAP1,CD40,IFNB1,GATA4,ITGB3,MFN2,AXL,PIK3CG,SAA1,DGKZ,GGCX,SH2B3,GATA6,F11R,PDPN,AKAP10,GNAQ,MAPK1,EDN1,IRF1,ENPP4,TRPC3,F2RL1,CD36,UBASH3B,PDGFB,CBX5,CSRP1,CYP4F11,ACTB,THBS1,DGKB,DGKI,LMAN1	71	up
cold-induced thermogenesis	GO:0106106	cellular response to external stimuli	5.917E-03	IRF4,EHMT1,PCTP,JAK2,IP6K1,NRDC,IGF1R,APC,CXCR4,DECR1,KDM6B,TLR4,NOTCH1,LNPEP,ADAM17,VEGFA,OGT,FLCN,RBPJ,NOVA2,TRPV2,CPT2,CEBPB,ACSL1,FH,MFN2,CIDEA,SIRT6,TLE3,PER2,GRB10,ZBTB7B,THRA,CD36,ADAMTS5,IL15,FFAR4	37	up
colorectal cancer	KEGG:05210	cancer	5.928E-06	MYC,MAPK1,APC,MAP2K2,CCND1,CASP3,AKT1,TGFBR1,TGFBR2,KRAS,PMAIP1,BCL2,EREG,BBC3,FOS,JUN,AKT2,AKT3,SMAD2,SMAD3,BCL2L11,APPL1,RHOA,CTNNB1,GADD45A,CDKN1A,TP53,EGF,BIRC5,CYCS,GSK3B	31	both
columnar/cuboidal epithelial cell differentiation	GO:0002065	cell differentiation	1.489E-02	FGFR2,CLOCK,CDK6,GSK3B,YAP1,IL6ST,PAX6,DLL1,SRC,CEBPB,GATA4,WDR77,SOX4,GATA6,SOX11	15	up
competing endogenous rnas (cernas) regulate pten translation	REAC:R-HSA-8948700	PTEN expression	4.627E-04	TNRC6B,AGO3,TNRC6A,AGO2,AGO1,AGO4,MOV10	7	up
condensation of prometaphase chromosomes	REAC:R-HSA-2514853	cell cycle	2.727E-02	SMC2,CSNK2A1,CDK1,NCAPG,CCNB1,NCAPD2	6	up
constitutive signalling by aberrant pi3k in cancer	REAC:R-HSA-2219530	cancer	3.447E-03	ERBB2,PIK3CB,PIK3CD,EGFR,CD80,IRS1,FGF2,PIK3R3,TGFA,FGFR4,PIK3R1,MET,SRC,PDGFRB,PDGFRA,KLB,KIT,AREG,EREG,ESR1,PDGFB,FRS2	22	up
constitutive signalling by akt1 e17k in cancer	REAC:R-HSA-5674400	cancer	1.456E-03	AKT1,CDKN1A,CDKN1B,CHUK,AKT3,GSK3B,FOXO3,FOXO1,MDM2,CASP9,RICTOR,CREB1,AKT1S1	13	both
constitutive signalling by ligand-responsive egfr cancer variants	REAC:R-HSA-1236382	EGFR signalling	6.489E-03	EGFR,SOS1,HSP90AA1,PIK3R1,PLCG1,NRAS,UBB,RPS27A,UBC	9	up
constitutive signalling by notch1 hd domain mutants	REAC:R-HSA-2691232	NOTCH signalling	1.052E-02	NOTCH1,ADAM17,MIB1,JAG1,DLL1,UBB,RPS27A,UBC	8	up
constitutive signalling by notch1 hd+pest domain mutants	REAC:R-HSA-2894862	NOTCH signalling	2.698E-02	NCOR2,CREBBP,NOTCH1,ADAM17,RBPJ,CDK8,HEYL,MIB1,TBL1XR1,MYC,JAG1,HDAC1,DLL1,UBB,RPS27A,UBC,NCSTN,MAMLD1	18	up
constitutive signalling by notch1 pest domain mutants	REAC:R-HSA-2644606	NOTCH signalling	2.698E-02	NCOR2,CREBBP,NOTCH1,ADAM17,RBPJ,CDK8,HEYL,MIB1,TBL1XR1,MYC,JAG1,HDAC1,DLL1,UBB,RPS27A,UBC,NCSTN,MAMLD1	18	up
constitutive signalling by overexpressed erbb2	REAC:R-HSA-9634285	ERB signalling	4.467E-02	ERBB2,SOS1,HSP90AA1,NRAS,ERBIN	5	up
copper ion homeostasis	GO:0055070	homeostasis	2.731E-02	XIAP,APP,ARF1,ATOX1,PRNP,SLC31A1,ATP7A	7	up
coronary vasculature development	GO:0060976	organogenesis	3.962E-02	APLN,LRP2,NOTCH1,NRP1,VEGFA,SPRED1,TGFBR3,PDGFRB,GATA6	9	up
coronary vasculature morphogenesis	GO:0060977	organogenesis	7.119E-03	LRP2,NOTCH1,NRP1,VEGFA,SPRED1,TGFBR3,PDGFRB	7	up
coronavirus disease - covid-19	KEGG:05171	viral of bacterial infection	1.177E-03	STAT3,TNF,RPL29,RPS12,RPL3,IL6R,RPS7,MAPK14,PIK3CB,RPS3A,RPLP0,PIK3CD,RPL35A,EGFR,RPS28,FOS,TRAF6,NFKB1,TLR2,IRAK1,ISG15,STAT1,MX2,IL6,CXCL8,TLR4,ADAM17,NRP1,PIK3R3,CHUK,RPL14,PIK3R1,RPL10,MAP3K7,RPL36,RPS5,IL6ST,NLRP3,MAPK3,RPL37,RPS2,IFNB1,PLCG1,TRAF3,CASP1,TNFRSF1A,CYBB,AGTR1,RPL9,STAT2,TLR3,RPL23,RPL24,RPS15A,RPL4,MAVS,MAPK1,RPS27A,RPS14,TAB2	60	up
cotranslational protein targeting to membrane	GO:0006613	protein metabolism	3.204E-02	RPL29,RPS12,RPL3,RPS7,RPS3A,RPLP0,RPL35A,RPS28,ARL6IP1,SRPRA,SEC61A1,RPL14,TRAM1,RPL10,RPL36,RPS5,RPL37,RPS2,RPL9,RPL23,RPL24,RPS15A,RPL4,RPS27A,RPS14	25	up
covalent chromatin modification	GO:0016569	chromatin organisation	5.751E-05	KMT2A,WDR82,RYBP,EPC1,TWIST1,FMR1,PRKCD,MTA3,ATRX,RIF1,DTX3L,EP300,KAT6B,RPS6KA5,MCRS1,MEAF6,SIRT1,EZH2,KDM5C,INCENP,KDM5A,KMT2E,PER2,ELK4,ATXN7,SUV39H2,NAA50,HMGA2,CARM1,TBL1XR1,RCOR1,BAZ2A,MORF4L1,KDM6B,DNMT3B,DOT1L,KDM5B,PER1,NAA40,KMT5C,MORF4L2,CCNA2,HUWE1,REST,TET3,TET2,VEGFA,PRDM4,CHEK1,BCOR,PCGF2,LMNA,JARID2,DR1,MTF2,CTNNB1,PPARGC1A,HASPIN,CDC73,USP22,MSL2,BMI1,RNF40,KDM2A,CREBBP,UBE2B,HELLS,BRPF3,ZBTB7B,KMT2B,HCFC1	71	both
cranial skeletal system development	GO:1904888	organogenesis	3.860E-02	TWIST1,COLEC10,SIX1,PDGFRA,MTHFD1L,TGFBR1,TGFBR2,EIF4A3,TFAP2A	9	down
creb phosphorylation	REAC:R-HSA-199920	phosphorylation	1.500E-02	RPS6KA1,MAPKAPK2,RPS6KA3,CREB1,RPS6KA5	5	up
crmps in sema3a signalling	REAC:R-HSA-399956	signalling pathways	4.903E-02	FES,NRP1,GSK3B,SEMA3A,CDK5R1,PLXNA3,DPYSL2	7	up
cushing syndrome	KEGG:04934	endocrine system	3.014E-04	CDKN2A,E2F3,FZD4,CCNE1,KMT2D,APC,FZD6,USP8,EGFR,E2F2,CDKN1A,CCND1,LDLR,WNT2B,WNT1,FZD5,CDKN1B,CDK4,CDK6,WNT7A,ITPR1,AXIN2,CCNE2,GSK3B,FZD9,CDK2,SP1,E2F1,SCARB1,LEF1,MAPK3,MAP2K1,FH,CTNNB1,CDKN2C,AIP,AGTR1,TCF7,CREB1,GNAQ,TCF7L2,MAPK1,POMC,MC2R,PLCB1	45	up

cyclin d associated events in g1	REAC:R-HSA-69231	cyclin signalling pathway	1.249E-04	CDKN2A,E2F3,JAK2,PPP2CA,CDKN2D,ABL1,E2F2,CDKN1A,CCND1,CCND2,CDKN1B,CDK4,CCND3,CDK6,E2F1,E2F5,CDKN2C,UBB,RPS27A,UBC	20	up
cysteine and methionine metabolism	KEGG:00270	nucleotide metabolism	4.137E-02	CBS,GOT1,DNMT3A,DNMT3B,AHCY,MAT2A,KYAT3,ADI1,AGXT2,MRI1,AHCYL2,BCAT1,AMD1	13	down
cytochrome c-mediated apoptotic response	REAC:R-HSA-111461	apoptosis	6.696E-04	XIAP,CASP7,MAPK3,CASP3,DIABLO,CASP9,CYCS,APAF1,MAPK1	9	up
cytokinesis	GO:0000910	cell cycle	8.760E-03	VPS4B,E2F7,CHMP3,MYO19,AURKB,APC,USP8,RHOA,ROCK1,PRKCE,CEP55,ZFYVE26,CHMP4B,CUL3,FLCN,VPS4A,KIF23,RACGAP1,SPTBN1,CDC42,STMN1,RHOB,CHMP2B,ECT2,RAB11FIP4,KIF4A,NUP62,BIRC6,SON,SEPT7,ANK3,BECN1,BCL2L1,AURKA,INCENP,OR2A4,TRIM36,KLHL21,CSPP1,KIF13A	40	up
cytoskeleton-dependent cytokinesis	GO:0061640	cytoskeleton	3.976E-02	VPS4B,CHMP3,AURKB,APC,USP8,RHOA,ROCK1,CEP55,CHMP4B,VPS4A,KIF23,RACGAP1,SPTBN1,STMN1,RHOB,CHMP2B,ECT2,KIF4A,NUP62,SON,SEPT7,ANK3,INCENP,TRIM36	24	up
dap12 interactions	REAC:R-HSA-2172127	signalling pathways	1.292E-02	PIK3CB,GRAP2,CD300LB,SOS1,VAV2,PIK3R1,VAV3,PLCG1,TREM2,NRAS,KLRD1,SIGLEC15,B2M	13	up
dap12 signalling	REAC:R-HSA-2424491	signalling pathways	1.052E-02	PIK3CB,GRAP2,SOS1,VAV2,PIK3R1,VAV3,PLCG1,TREM2,NRAS,KLRD1,B2M	11	up
ddx58/ifih1-mediated induction of interferon-α/β	REAC:R-HSA-168928	interferon signalling	5.836E-07	TNFAIP3,PCBP2,CREBBP,NKIRAS2,TRAF6,NFKB1,FADD,ISG15,SIKE1,IRF7,S100A12,UBE2D3,CHUK,AGER,CYLD,APP,ATG5,IFNB1,MAP3K1,TRAF3,SAA1,HMGB1,TRAF2,NLRC5,CASP8,CASP10,TANK,UBB,MAVS,RNF125,RPS27A,UBC,UBE2D2,UBA7	34	up
deactivation of the β-catenin transactivating complex	REAC:R-HSA-3769402	Wnt signalling	1.023E-03	XIAP,AKT1,KMT2D,APC,SOX2,BTRC,TLE4,HDAC1,LEF1,CTNNB1,TLE3,TCF7,SOX4,UBB,CBY1,TCF7L2,RPS27A,UBC	18	up
death receptor signalling	REAC:R-HSA-73887	apoptosis	1.219E-05	XIAP,TNFAIP3,TNF,TNFRSF10B,Fas,PLEKHG5,RHOA,TRAF6,NFKB1,FADD,IRAK1,SQSTM1,SOS1,ADAM17,SOS2,VAV2,BCL2L11,CHUK,BAG4,PRDM4,CYLD,TAB3,ARHGDIA,MAP3K7,RTN4,SPPL2A,ECT2,HDAC1,VAV3,BIRC3,CASP3,TNFRSF10A,TRAF2,RBCK1,RIPK2,FASLG,TNFRSF1A,CFLAR,CASP8,BIRC2,CASP10,OTUD7B,UBB,ARHGEF26,RPS27A,UBC,NCSTN,TAB2	48	up
death-inducing signalling complex assembly	GO:0071550	apoptosis	2.287E-02	TNF,FADD,TRAF2,TNFRSF1A,CASP8	5	up
defective tpr may confer susceptibility towards thyroid papillary carcinoma (tpc)	REAC:R-HSA-5619107	cancer	3.007E-02	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,NUP62,RAE1,NUP43,NUP54	11	up
defense response to symbiont	GO:0140546	cellular response to external stimuli	4.563E-05	PMAIP1,ZMYND11,TNFAIP3,BCL2,PCBP2,IFI27,IFIT5,IFIT3,FADD,ISG15,IFITM3,IFITM1,IFI44L,STAT1,IRF7,MX2,OASL,IL6,RSAD2,IFIT1,IL23R,TARBP2,ZCCHC3,USP15,C6orf106,MOV10,BIRC3,IFNLR1,PUM2,CD40,MAP3K14,IFNB1,TRAF3,BNIP3,ATG7,NLRC5,BCL2L1,BIRC2,NLRP9,APOBEC3F,STAT2,TLR3,AGBL5,DDIT4,MAVS,IRF1,SERINC3,RNF125,F2RL1,G3BP1,DTX3L,PPM1B	52	up
dendritic spine development	GO:0060996	organogenesis	1.765E-02	WASL,PTEN,PAFAH1B1,WNT7A,SLC9A6,CPEB3,CDC42,MEF2C,CAPRIN1,ZNF365,CFL1,LLPH,ARF6,SLC12A5,CDK5R1,DLG5,CAPRIN2,ARC,PAK3	19	up
dendritic spine organisation	GO:0097061	cell organisation	4.497E-02	IGF1R,WASL,PTEN,PAFAH1B1,WNT7A,INSR,CDC42,CAPRIN1,ZNF365,CFL1,MTMR2,ARF1,CDK5R1,PRNP,CAPRIN2,ARC,PAK3	17	up
dephosphorylation	GO:0016311	phosphorylation	1.342E-02	CTDSP1,PPP1R37,MTMR12,ZFYVE1,PPP2CA,DUSP6,TNF,MTMR3,WNK1,CDH5,CSRNP2,PTBP1,MFHAS1,PPP1CA,MTMR4,DUSP1,ROCK1,PPP1R11,HSP90B1,PPP6R1,YWHAB,PLPP4,PTEN,SPRED1,PTPRJ,PTPRD,RPRD1B,PPM1A,BTRC,OCRL,PRKCD,PPP6R3,FKBP1A,PPP2R5C,GSK3B,PPP6C,PIP4P1,PLPP3,SSU72,MEF2C,SGPP1,RRP1B,MTMR2,CAMTA1,SRC,PDGFRB,RBM26,MTMR9,FKBP1B,PPP1CC,IMPA1,CNEP1R1,MTMR10,DUSP5,WDR81,PPP1R7,MASTL,PTPN4,PPP1R15B,TIMM50,DLC1,PTPRG,DUSP18,ACP6,PTPRB,UBASH3B,ARPP19,ITGA1,ELL,PPM1B	70	up
deregulated cdk5 triggers multiple neurodegenerative pathways in alzheimer's disease models	REAC:R-HSA-8862803	AD	8.874E-03	PRDX2,BCL2L11,CDC25A,APP,FOXO3,CDC25C,FASLG,CAPN1,CDK5R1,SOD2	10	up
deubiquitination	REAC:R-HSA-5688426	ubiquitination	2.328E-03	TP53,TNFAIP3,ADRM1,VDAC1,PSMB1,YOD1,APC,USP8,SMAD4,RHOA,TRAF6,USP48,SMAD2,BRCA1,CCNA2,PTEN,USP42,RAD23B,SMAD3,FOXK1,OGT,OTUB1,CDK1,CDC25A,CYLD,AXIN2,SMAD7,USP15,TADA2B,ASXL1,MAP3K7,USP3,PSMB5,CLSPN,NLRP3,MDM2,CFTR,MYC,YY1,MDM4,CDC20,FKBP8,BIRC3,HIST1H2AC,SNX3,AR,TGFBR2,TRAF3,HIST1H2BJ,HIST1H2AH,USP47,TRAF2,STAM2,BECN1,RIPK2,NOD1,MBD6,BIRC2,USP28,OTUD7B,UBB,MAVS,USP13,RPS27A,UBC,OTUD3,ESR1,TNIP3,ACTB,OTUD7A	70	up
developmental growth	GO:0048589	organogenesis	8.914E-03	WDR11,SEMA4C,STAT3,BMPR1B,SEMA4B,DUSP6,SIX1,KMT2D,ABL1,ARIH2,GLI1,FGFR2,CDKN1A,ERBB4,L1CAM,NOTCH1,HSP90AA1,GAS1,FGFR3,FGF2,CDKN1B,NRP1,ALCAM,PTEN,VEGFA,PAFAH1B1,CPNE1,RBPJ,SLC9A6,NKD1,INSR,TGFBR3,APP,GSK3B,SMURF1,FZD9,SALL1,PIM1,RTN4,MEF2C,LATS2,ITGB1,STAT5A,SEMA3A,DLL1,SYT1,GATA4,CTNNB1,TP73,LLPH,MAP1B,CTTN,CFLAR,ADNP,S1PR1,GAP43,BMPR1A,EDN1,EREG,GHSR,NLGN4X,PLCB1,AKIRIN1,VGLL4	64	up
developmental induction	GO:0031128	organogenesis	3.844E-02	SIX1,ROBO1,DKK1,WNT1,FZD5,SALL1,POU5F1	7	up
digestive system development	GO:0055123	organogenesis	3.061E-02	SFRP5,TNF,SMO,GLI1,FGFR2,RARB,CXCL8,RET,SALL1,YAP1,IL6ST,SRC,PDGFRA,GATA4,KIT,GATA6,SOX11,AHI1	18	up
digestive tract development	GO:0048565	organogenesis	2.282E-02	SFRP5,TNF,SMO,GLI1,FGFR2,RARB,CXCL8,RET,SALL1,YAP1,IL6ST,SRC,PDGFRA,GATA4,KIT,GATA6,SOX11,AHI1	18	up
dimerization of procaspase-8	REAC:R-HSA-69416	caspase signalling pathway	3.238E-03	TNFRSF10B,Fas,FADD,TNFRSF10A,TRAF2,FASLG,CASP8	7	up
disassembly of the destruction complex and recruitment of axin to the membrane	REAC:R-HSA-4641262	signalling pathways	4.124E-02	APC,PPP2R5E,CSNK1A1,AMER1,LRP6,FZD5,FRAT2,CTNNB1,DVL3,GSK3B,DVL1	11	down
diseases of programmed cell death	REAC:R-HSA-9645723	apoptosis	5.440E-03	CDKN2A,PRDX2,BCL2L11,CDC25A,APP,FOXO3,CDC25C,FASLG,CAPN1,CDK5R1,SOD2	11	up
diseases of signal transduction by growth factor receptors and second messengers	REAC:R-HSA-5663202	signalling pathways	1.157E-02	MYC,KLB,MAPK1,ESR1,ETV6,KIAA1549,APC,PSMB9,NOTCH1,EP300,KREMEN1,MAP2K2,ADAM17,FGFR1OP,PDGFRA,PDPK1,POLR2D,FOXO1,BAG4,MAP3K11,AKT1,POLR2E,FGF19,TGFBR1,TGFBR2,FKBP1A,PTEN,KIT,KRAS,PPP2R5E,CSNK1A1,ARRB2,RHOG,RAP1B,TBL1XR1,PEBP1,EREG,FGG,AMER1,PDGFRB,LRP6,MDM2,FZD5,FGB,FGA,FZD4,AKT2,AKT3,SMAD2,SMAD3,CDKN1B,STAT3,FRS2,BCL2L11,LMNA,FOXO3,MET,QKI,CTNNB1,CDKN1A,NF1,SPRED3,EGF,ACTG1,HEYL,PSMC4,GSK3B,PSMD3,ZC3HAV1,YWHAB,CREBBP,NCSTN	72	both
dna catabolic process, endonucleolytic	GO:0000737	cell cycle	2.316E-02	CDKN2A,KPNB1,IL6,DICER1,KPNA1,CASP3,HMGB1,AIFM1,CIDEA,BAX,DFFA	11	up
dna damage checkpoint	GO:0000077	cell cycle	8.586E-04	SOX4,CLOCK,BRSK1,ARID3A,USP28,EP300,TAOK3,TAOK1,CCND1,CCAR2,FEM1B,ATM,TOPBP1,HMGA2,CARM1,BTG2,DOT1L,TIPRL,MDM2,CNOT6,CDKN1B,CHEK1,DONSON,RFWD3,GADD45A,CDKN1A,TP53,MDM4,RBM38,MRNIP,MRE11,HUS1,TFDP2,TAOK2,FANCD2,AURKA	36	both

dna damage induced protein phosphorylation	GO:0006975	phosphorylation	2.287E-02	ABL1,CHEK1,ATM,MAPK3,CHEK2	5	up
dna damage response, signal transduction by p53 class mediator	GO:0030330	cell cycle	9.185E-11	CDKN2A,PMAIP1,E2F7,BCL3,TP53,ARID3A,ZNF385A,NPM1,BTG2,CD44,TNKS1BP1,MUC1,MIF,CDKN1A,BRCA1,MYO6,CNOT6L,RBM38,CDKN1B,CNOT4,NDRG1,SPRED1,CARM1,CDK1,PPP2R5C,CDK2,MDM2,E2F1,ATM,CDC25C,SFN,MDM4,SIRT1,CRADD,GADD45A,SNAI1,SESN2,BAX,CNOT2,SOX4,AURKA,CCNB1,CHEK2,CNOT1,DYRK1A,TWIST1	46	both
dna geometric change	GO:0032392	cell cycle	3.519E-02	TP53,HMGA1,PARP1,MCMDC2,RAD23B,PURA,HNRNPA2B1,MRE11,MCM4,MCM2,MCM7,MCM6,RAD51,HMGB1,UBB,RPS27A,UBC,TOP2A	18	up
dna integrity checkpoint	GO:0031570	cell cycle	1.457E-06	E2F7,TP53,ARID3A,RFWD3,ZNF385A,BTG2,TNKS1BP1,HMGA2,MUC1,CDKN1A,BRCA1,CNOT6L,CCND1,RBM38,CLOCK,CDKN1B,CNOT4,CHEK1,TAOK1,CARM1,CDK1,PPP2R5C,CLSPN,CDK2,MDM2,E2F1,ATM,MRE11,CDC25C,MRNIP,SFN,MDM4,FZR1,FOXN3,PPP1R10,CDC5L,CRADD,GADD45A,DGKZ,BAX,CNOT2,SOX4,USP28,AURKA,CCNB1,CHEK2,CNOT1,ORC1,TOP2A	49	both
dna modification	GO:0006304	cell cycle	3.376E-02	MYC,UNG,PARP1,KMT2A,ATRX,EXOSC6,APOBEC3C,PPM1D,MECP2,KMT2E,BAZ2A,DNMT3A,DNMT3B,FOS,TDG,OTUD4,TET3,TET2,MGMT,APOBEC3F,PARP2,WT1,HELLS	23	down
dna recombination	GO:0006310	cell cycle	5.513E-04	SMC6,SUPT6H,RFWD3,FUS,HSPD1,PARP1,CD40LG,FANCM,BRCA2,BRCA1,ZFYVE26,MCMDC2,CHEK1,ACTR2,NUCKS1,RNF138,RNF168,KLHL15,RIF1,AP5Z1,TCF3,KPNA1,ZNF365,ATM,MRE11,ZSWIM7,YY1,HIST1H1E,MRNIP,MCM4,POLL,MCM2,MCM7,FEN1,CD40,TSN,TFRC,FIGN,MCM6,XRCC1,RAD51,HMGB1,MMS19,MCM3,SIRT6,IL10,MCM5,POLQ,REV3L,SLX4,NABP1,RAG1,ZNF711,CCR6,TERF2,ERCC4,KLHDC3,KPNA2,TOP2A,XRCC2	60	up
dna replication	GO:0006260	cell cycle	3.965E-04	E2F7,PDS5A,PPP2CA,SIRT7,RFWD3,EGFR,HMGA1,GLI1,SET,FANCM,BRCA2,BRCA1,FAF1,CCNA2,MCMDC2,CHEK1,ATAD5,RBBP6,NUCKS1,PURA,ORC4,CDK1,TBRG1,POLE4,CLSPN,CDK2,ZNF365,ATM,MRE11,POLD1,TRAIP,MCM4,POLL,MCM2,DDX21,MCM7,FEN1,MCMBP,PRIM1,MCM10,CDAN1,MCM6,RAD51,PTMS,MCM3,DUT,MCM5,NUGGC,POLQ,REV3L,CHEK2,RFC2,ORC1,EREG,TERF2,PCLAF,GRWD1,CTC1	58	up
dna replication initiation	GO:0006270	cell cycle	1.789E-02	MCMDC2,PURA,ORC4,POLE4,MCM4,MCM2,MCM7,PRIM1,MCM10,MCM3,MCM5,ORC1	12	up
dna unwinding involved in dna replication	GO:0006268	cell cycle	1.022E-02	HMGA1,MCMDC2,PURA,MCM4,MCM2,MCM7,MCM6,RAD51	8	up
dna-dependent dna replication	GO:0006261	cell cycle	3.859E-02	E2F7,SIRT7,RFWD3,HMGA1,FANCM,BRCA2,MCMDC2,NUCKS1,PURA,ORC4,POLE4,ZNF365,MRE11,POLD1,TRAIP,MCM4,MCM2,DDX21,MCM7,FEN1,MCMBP,PRIM1,MCM10,MCM6,RAD51,MCM3,MCM5,NUGGC,POLQ,REV3L,CHEK2,RFC2,ORC1,TERF2	34	up
dna-templated transcription, initiation	GO:0006352	cell cycle	2.750E-04	ESR1,HNF4G,NR4A2,TWIST1,TEAD3,GTF2H5,PPARA,NOTCH1,GTF2H1,RORA,THRB,HMGB1,POLR2D,CCND1,YAP1,SOX9,RARA,FOSL1,POLR2E,NR3C1,PPARG,PPM1D,MECP2,NOTCH4,PTEN,NOTCH2,NR6A1,RSF1,MAZ,WWTR1,ZNF45,JUN,MITF,TAF13,DR1,MED17,CTNNB1,CDKN1A,PPARGC1A,POLR1E,TP53,MED16,TAF8,SRF,MED7,CRCP,CD3EAP,NR2F6,POLR1A,PSMC4,CREBBP,E2F3	52	both
double-strand break repair via break-induced replication	GO:0000727	cell cycle	7.119E-03	MCMDC2,MCM4,MCM2,MCM7,MCM6,MCM3,MCM5	7	up
double-strand break repair via homologous recombination	GO:0000724	cell cycle	4.218E-04	RFWD3,FUS,PARP1,FANCM,BRCA2,BRCA1,ZFYVE26,MCMDC2,CHEK1,ACTR2,NUCKS1,RNF138,KLHL15,RIF1,AP5Z1,ZNF365,MRE11,ZSWIM7,YY1,MRNIP,MCM4,POLL,MCM2,MCM7,FEN1,FIGN,MCM6,XRCC1,RAD51,MMS19,MCM3,SIRT6,MCM5,POLQ,REV3L,SLX4,NABP1,ERCC4,XRCC2	39	up
downregulation of erbb2 signalling	REAC:R-HSA-8863795	ERB signalling	6.595E-03	ERBB2,AKT1,USP8,EGFR,HSP90AA1,AKT3,RNF41,UBB,RPS27A,UBC,EREG,ERBIN	12	up
downregulation of erbb2:erbb3 signalling	REAC:R-HSA-1358803	ERB signalling	2.113E-03	ERBB2,AKT1,USP8,AKT3,RNF41,UBB,RPS27A,UBC	8	up
downregulation of smad2/3:smad4 transcriptional activity	REAC:R-HSA-2173795	SMAD activity	1.012E-05	NCOR2,SMAD4,PARP1,SMAD2,UBE2D3,SKI,SMAD3,PPM1A,HDAC1,TGIF2,UBB,RPS27A,UBC,TRIM33,TGIF1	15	up
downregulation of tgf-β receptor signalling	REAC:R-HSA-2173788	TGF signalling	1.149E-04	PPP1CA,MTMR4,SMAD2,SMAD3,SMAD7,USP15,SMURF1,STRAP,TGFBR2,PPP1CC,PMEPA1,UBB,RPS27A,UBC	14	up
downstream signal transduction	REAC:R-HSA-186763	signalling pathways	3.438E-04	STAT3,PIK3CB,STAT1,SOS1,CRKL,PIK3R1,CRK,STAT5A,SRC,PDGFRB,PDGFRA,PLCG1,NRAS,PDGFB	14	up
dsrna processing	GO:0031050	cell cycle	2.400E-04	ESR1,AGO3,MAP2K2,AGO4,TERT,AGO1,DICER1,MYCN,SMAD2,SMAD3,TSNAX,STAT3,DDX5,PUM2,PUM1,HNRNPA2B1,LIN28A,TP53,DGCR8	19	both
early endosome to late endosome transport	GO:0045022	cellular transport	4.850E-02	CHMP3,SNX16,SNX12,MTMR2,MAPK3,SNX3,SRC,MAP2K1,BECN1,WDR81,MAPK1,EMP2	12	up
egfr interacts with phospholipase c-gamma	REAC:R-HSA-212718	EGFR signalling	4.467E-02	EGFR,TGFA,PLCG1,AREG,EREG	5	up
egfr tyrosine kinase inhibitor resistance	KEGG:01521	EGFR signalling	3.925E-03	STAT3,ERBB2,JAK2,AKT1,BCL2,EIF4EBP1,IL6R,IGF1R,PIK3CB,ERBB3,EIF4E,RAF1,PIK3CD,EGFR,FGFR2,IL6,SOS1,KRAS,FGFR3,SOS2,FGF2,PIK3R3,TGFA,PTEN,VEGFA,RPS6KB1,BCL2L11,GRB2,PIK3R1,AKT3,KDR,GSK3B,FOXO3,MET,MAPK3,SRC,PDGFRB,PDGFRA,MAP2K1,PLCG1,AXL,BAX,BCL2L1,NRAS,MAPK1,PDGFB	46	both
embryo development	GO:0009790	organogenesis	7.185E-07	SEMA4C,E2F7,EHMT1,IGF2,TNF,STOX2,NES,WNK1,SIX1,CREBBP,SMO,PIK3CB,MMP2,TRIM71,LBX2,HMGA2,FBN1,TDG,FGFR2,DUSP1,KDM2B,ROCK1,CDC73,MICAL2,ERBB4,LRP2,LFNG,RARB,SMAD2,BRCA1,MYO6,KDM6B,ITGB2,CXCL8,NOTCH1,SOX2,DNMT1,RAB14,DKK1,PHLDB2,WNT1,ITGA5,FZD5,B4GALT5,MYO3A,FGF2,KLF4,SKI,VEGFA,PAFAH1B1,WNT7A,TET3,TFAP2A,CUL3,FLCN,NOLC1,HOXA3,RBPJ,LUZP1,RACGAP1,CDK1,NR2C2,NKD1,INSR,ITGA2,CYP26B1,KDR,UBR3,RPL10,SALL1,MTHFR,MEF2C,ITGB1,TAL1,CFL1,NASP,HDAC1,DLL1,PDGFRA,TGFBR2,SEPT7,GATA4,ITGB3,MFN2,CTNNB1,TCOF1,NANOG,BAG6,RICTOR,YBX1,FUT8,SNAI1,BMP7,POU5F1,KIT,WDR77,IL10,BCL10,CASP8,SOX4,DUSP5,BMPR1A,SH2B3,UGDH,SOX11,HOXB3,CHD7,GPR161,ACVR1,DLC1,MBNL1,TET1,AHI1,ZNF281,ECE1,PDGFB,PLCB1,SIX3,TWIST1	119	both
embryo development ending in birth or egg hatching	GO:0009792	organogenesis	2.722E-02	SOX4,TWIST1,BMPR2,IGF1,SIX1,EOMES,PDGFRA,COL1A1,CELF1,SEMA4C,SOX9,MTHFD1L,TGFBR1,TGFBR2,CDX2,NASP,ITGB1,LRP6,VEGFA,CASP8,ACVR1C,SKI,BCL10,PRICKLE1,HOXA9,DLC1,CTNNB1,DVL3,SRF,HOXB3,EIF4A3,C6orf141,USP22,ALX1,PHACTR4,WNT5A,HOXD3,TFAP2A,DVL1,BMPR1A	40	both
embryonic cranial skeleton morphogenesis	GO:0048701	organogenesis	3.134E-03	TWIST1,SIX1,PDGFRA,MTHFD1L,TGFBR1,TGFBR2,EIF4A3,TFAP2A	8	down
embryonic epithelial tube formation	GO:0001838	organogenesis	3.069E-02	SOX4,GDNF,SIX1,SEMA4C,SOX9,MTHFD1L,LRP6,SKI,BCL10,PRICKLE1,DLC1,DVL3,PHACTR4,DVL1	14	down
embryonic morphogenesis	GO:0048598	organogenesis	8.275E-03	SEMA4C,IGF2,WNK1,SIX1,CREBBP,SMO,MMP2,LBX2,HMGA2,FBN1,FGFR2,DUSP1,KDM2B,ROCK1,CDC73,MICAL2,LRP2,SMAD2,MYO6,KDM6B,ITGB2,NOTCH1,SOX2,DKK1,PHLDB2,ITGA5,MYO3A,FGF2,KLF4,SKI,WNT7A,TFAP2A,HOXA3,LUZP1,ITGA2,CYP26B1,SALL1,MTHFR,MEF2C,ITGB1,HDAC1,DLL1,PDGFRA,TGFBR2,GATA4,ITGB3,CTNNB1,NANOG,YBX1,SNAI1,BMP7,POU5F1,IL10,BCL10,SOX4,DUSP5,UGDH,SOX11,HOXB3,CHD7,ACVR1,DLC1,MBNL1,AHI1,ZNF281,ECE1,SIX3,TWIST1	68	both
embryonic skeletal system development	GO:0048706	organogenesis	2.201E-02	TWIST1,SIX1,PDGFRA,COL1A1,MTHFD1L,TGFBR1,TGFBR2,HOXA9,CTNNB1,HOXB3,EIF4A3,ALX1,WNT5A,HOXD3,TFAP2A	15	down

endocardial cushion development	GO:0003197	organogenesis	2.736E-02	ROBO1,NOTCH1,RBPJ,HEYL,JAG1,MDM4,TGFBR2,GATA4,SNAI1,BMP7,BMPR1A,ACVR1	12	up
endocardial cushion formation	GO:0003272	organogenesis	1.757E-02	ROBO1,NOTCH1,RBPJ,HEYL,TGFBR2,SNAI1,BMP7,BMPR1A,ACVR1	9	up
endocrine resistance	KEGG:01522	endocrine system	4.920E-04	MAPK1,MAPK14,ESR1,SP1,NOTCH1,MAP2K2,IGF1,CCND1,AKT1,IGF1R,PTK2,NOTCH4,NCOA3,ADCY9,KRAS,NOTCH2,BCL2,CARM1,FOS,MMP2,MDM2,JUN,AKT2,AKT3,CDKN1B,CDKN1A,TP53,E2F3	28	both
endocytosis	KEGG:04144	endocytosis	1.714E-02	RAB10,CHMP3,RNF103-CHMP3,WIPF2,EPN2,DAB2,SNX2,PDGFRA,PARD3,ACAP2,SNX5,RAB11B,IGF1R,TGFBR1,TGFBR2,LDLR,CHMP2B,ARRB2,GRK2,TFRC,WASHC5,EPS15,ARF6,TSG101,AGAP1,CDC42,MDM2,RAB11FIP1,SH3GLB1,SMAD2,SMAD3,WASL,RAB5B,HSPA8,CHMP4B,RHOA,EHD3,RAB7A,GBF1,CHMP1B,PSD4,AGAP9,RAB4A,SH3GL1,KIF5C,ITCH,PSD,EHD1,EPS15L1	49	both
endoderm development	GO:0007492	organogenesis	4.578E-02	MIXL1,DUSP1,EOMES,DUSP5,HMGA2,ZFP36L1,MMP2,DUSP2,MMP15,COL4A2,COL5A2,COL7A1,LAMC1,SOX2,CDC73	15	down
endodermal cell fate specification	GO:0001714	cell proliferation	3.967E-02	SOX2,DKK1,NANOG,POU5F1	4	up
endomembrane system organisation	GO:0010256	cell organisation	1.107E-02	VPS4B,GOLGA8A,SCARB2,TMEM9,CHMP3,VPS51,NUP93,PPP2CA,GOLGA8B,FAM174B,HUWE1,DYNC2H1,EMD,USP8,CXCR4,SQSTM1,WASL,ARL6IP1,STX16,VPS37B,STX6,PTEN,VPS37A,PAFAH1B1,CHMP4B,PI4K2B,STX17,VPS4A,SEC61A1,XKR7,PRKCD,DMPK,SPTBN1,CDK1,SUN1,VPS33B,TBC1D20,CLU,CDC42,TRAM1,RTN4,EPB41L3,SYNGR2,CHMP2B,GORASP2,ALS2,DEGS1,MAPK3,SNX3,LNPK,AR,VPS37D,RAB3GAP2,MYOF,MAP2K1,ANK3,BAG6,UBL4A,STAM2,PRKD1,SURF4,UBXN2B,REEP3,CNEP1R1,TOR1B,GOLGA8J,CCNB1,TRAM2,TMEM33,SUN2,MAPK1,ABCD2,CLCN3,CAMSAP2,SEC16A,RAB18,TMEM170A,TJAP1,TLCD2,LYSMD3,TRDN,TRIM72,LMAN1,RAB10,RAB1A	85	both
endometrial cancer	KEGG:05213	cancer	1.262E-03	TP53,ERBB2,AKT1,BAK1,PIK3CB,APC,RAF1,PIK3CD,EGFR,CDKN1A,CCND1,SOS1,KRAS,SOS2,PIK3R3,PTEN,GRB2,PIK3R1,AKT3,AXIN2,GSK3B,FOXO3,MYC,LEF1,MAPK3,MAP2K1,CTNNB1,CASP9,GADD45A,BAX,TCF7,NRAS,TCF7L2,MAPK1	34	both
endoplasmic reticulum organisation	GO:0007029	cell organisation	3.061E-02	ARL6IP1,SEC61A1,TRAM1,RTN4,LNPK,RAB3GAP2,BAG6,UBL4A,REEP3,TOR1B,TRAM2,TMEM33,SEC16A,RAB18,TMEM170A,TRDN,LMAN1,RAB10	18	up
endoplasmic reticulum tubular network organisation	GO:0071786	cell organisation	5.675E-03	ARL6IP1,RTN4,LNPK,RAB3GAP2,REEP3,TMEM33,RAB18,TMEM170A,RAB10	9	both
endosomal sorting complex required for transport (escrt)	REAC:R-HSA-917729	cellular transport	1.999E-02	VPS4B,CHMP3,VPS37B,VPS37A,CHMP4B,VPS4A,CHMP2B,VPS37D,STAM2,UBB,RPS27A,UBC	12	up
endothelial cell chemotaxis	GO:0035767	cell adhesion and migration	3.618E-02	PLEKHG5,NOTCH1,FGF2,NRP1,VEGFA,KDR,MET,CORO1B,PRKD1,PRKD2,THBS1	11	up
endothelial cell development	GO:0001885	organogenesis	1.996E-02	VCL,TNF,CDH5,ROCK1,ICAM1,S1PR2,VEGFA,PDE4D,RAP2C,RTN4,MET,TJP2,TNFRSF1A,ZDHHC21,F11R,F2RL1	16	up
endothelial cell differentiation	GO:0045446	cell differentiation	2.129E-03	VCL,TNF,CDH5,SMAD4,ROCK1,KDM6B,NOTCH1,ICAM1,NRP1,S1PR2,VEGFA,PDE4D,RBPJ,TMEM100,RAP2C,KDR,RTN4,ZEB1,MET,JAG1,DLL1,TJP2,TNFRSF1A,ZDHHC21,F11R,PDPN,ACVR1,BTG1,F2RL1	29	up
endothelial cell migration	GO:0043542	cell adhesion and migration	9.603E-03	ETS1,AKT1,ANGPT2,TNF,STARD13,CDH5,PLXND1,PIK3CB,PIK3CD,PLEKHG5,ABL1,RHOA,PTGS2,CARD10,ROBO1,NOTCH1,ADAM17,FGF2,KLF4,NRP1,PIK3R3,VEGFA,MECP2,MAP2K3,EFNB2,AMOT,AKT3,KDR,PLPP3,BSG,RHOB,MEF2C,SP1,LGALS8,ITGB1,STAT5A,SCARB1,MET,CORO1B,S100A2,GPI,SIRT1,RRAS,CD40,ITGB3,PLCG1,PIK3CG,HMGB1,GADD45A,EPHA2,PRKD1,S100P,SASH1,EDN1,NUS1,PRKD2,PDGFB,EMP2,THBS1,ADAMTS9	60	up
endothelium development	GO:0003158	organogenesis	2.293E-04	VCL,TNF,STARD13,CDH5,SMAD4,RHOA,ROCK1,KDM6B,NOTCH1,ICAM1,NRP1,S1PR2,VEGFA,PDE4D,RBPJ,TMEM100,RAP2C,KDR,RTN4,BSG,RHOB,ZEB1,MET,JAG1,DLL1,CTNNB1,TJP2,TNFRSF1A,ZDHHC21,F11R,PDPN,ACVR1,BTG1,F2RL1,PRKD2	35	up
energy homeostasis	GO:0097009	homeostasis	3.962E-02	STAT3,PRKAA1,FLCN,FOXO1,DLL1,EIF4G1,BMP8A,CD36,SGIP1	9	up
eph-ephrin mediated repulsion of cells	REAC:R-HSA-3928665	cell adhesion and migration	1.391E-02	MMP2,EPHA7,AP2B1,VAV2,EFNB2,AP2A1,EFNB1,VAV3,ACTG1,CLTB,AP2M1,AP2A2,EPHA5,EPHA2,CLTA,NCSTN,ACTB	17	up
eph-ephrin signalling	REAC:R-HSA-2682334	signalling pathways	5.807E-03	MMP2,EPHA7,RHOA,ROCK1,WASL,AP2B1,ACTR2,VAV2,EFNB2,PAK2,CDC42,MYL9,CFL1,AP2A1,EFNB1,VAV3,ACTG1,CLTB,AP2M1,AP2A2,EPHA5,EPHA2,CLTA,MYH11,NCSTN,ACTB,SDC2,PAK3	28	up
ephrin receptor signalling pathway	GO:0048013	signalling pathways	5.833E-04	MMP2,EPHA7,RHOA,ROCK1,WASL,AP2B1,ACTR2,VAV2,EFNB2,RBPJ,CDC42,CRK,AP2A1,EFNB1,VAV3,ACTG1,SRC,AP2M1,AP2A2,EPHA5,EPHA2,ANKS1A,CDK5R1,NCSTN,ACTB,SDC2,PAK3	27	up
epigenetic regulation of gene expression	REAC:R-HSA-212165	gene expression	3.812E-02	RBBP4,HIST1H2BJ,GTF2H5,MTA3,GTF2H1,EP300,DEK,SIRT1,EED,EZH2,SUZ12,POLR2E,HIST1H2BK,BAZ2A,DNMT3A,DNMT3B,TDG,DDX21,TET3,TET2,JARID2,MTF2,CBX3,POLR1E,CD3EAP,POLR1A,GSK3B	27	down
epithelial cell development	GO:0002064	organogenesis	1.157E-03	VCL,TNF,CDH5,PODXL,ROCK1,ICAM1,CLOCK,S1PR2,VEGFA,PAFAH1B1,CDK6,WNT7A,PDE4D,CCDC88C,RAP2C,GSK3B,RTN4,YAP1,IL6ST,PAX6,MET,JAG1,DLL1,SRC,SLC4A7,TJP2,EPHA2,TNFRSF1A,ZDHHC21,F11R,F2RL1,PDGFB,SIX3	33	up
epithelial cell fate commitment	GO:0072148	organogenesis	1.036E-03	NRP1,RBPJ,DLL1,ESRP1,PDPN,ACVR1	6	up
epithelial cell migration	GO:0010631	cell adhesion and migration	3.634E-02	ETS1,AKT1,ANGPT2,TNF,STARD13,CDH5,PLXND1,PIK3CB,PIK3CD,PLEKHG5,ABL1,RHOA,ROCK1,PTGS2,CARD10,PRKCE,ROBO1,NOTCH1,ADAM17,FGF2,KLF4,NRP1,PIK3R3,PTEN,VEGFA,MECP2,MAP2K3,EFNB2,KANK1,AMOT,AKT3,KDR,PLPP3,RTN4,BSG,RHOB,MEF2C,SP1,LGALS8,ITGB1,STAT5A,SCARB1,MET,CORO1B,SRC,STRAP,S100A2,GPI,SIRT1,RRAS,CD40,ITGB3,PLCG1,PIK3CG,HMGB1,GADD45A,ARF6,EPHA2,KIT,PRKD1,S100P,ZEB2,SASH1,EDN1,MCC,PTPRG,NUS1,PRKD2,PDGFB,EMP2,THBS1,EPB41L4B,ADAMTS9	73	both
epithelial cell proliferation	GO:0050673	cell proliferation	6.385E-03	VDR,RPS6KA1,STAT3,IGF2,ERBB2,AKT1,APLN,MED1,PIK3CB,NME2,NRARP,PIK3CD,ALOX5,EGFR,FGFR2,UHRF1,CDC73,STAT1,SFRP1,BRCA2,IL6,TLR4,ROBO1,NOTCH2,SOX2,ADAM17,FGF2,NRP1,TGFA,VEGFA,CDK6,WNT7A,CASK,AKT3,TGFBR3,LAMC1,KDR,RTN4,YAP1,F3,FBXW7,MEF2C,SP1,STAT5A,MYC,SERPINB1,STRAP,SIRT1,CEBPB,ITGB3,PLCG1,HMGB1,GDF5,EPHA2,PRKD1,SIRT6,WDR77,AREG,AGTR1,NRAS,SOX11,NFIB,TCF7L2,MCC,EREG,PRKD2,PDGFB,B2M,ZNF703,THBS1,MTSS1	71	up
epithelial cell signalling in helicobacter pylori infection	KEGG:05120	viral of bacterial infection	6.736E-03	MAPK14,EGFR,NFKB1,CCL5,CXCL8,ADAM17,CHUK,CDC42,CXCL2,MET,SRC,CASP3,ATP6V1E1,MAP3K14,PLCG1,NOD1,F11R,MAP2K4,ATP6V1C1,ATP6V1B2,ATP6V0E1,ATP6V0D1	22	up
epithelial to mesenchymal transition	GO:0001837	organogenesis	4.660E-03	WNT4,PDCD4,TWIST1,NOTCH1,ZNF703,DAB2,EOMES,FAM83D,COL1A1,EZH2,SOX9,HIF1A,FOXC1,SNAI2,FERMT2,TGFBR1,NOTCH4,TGFBR2,PTEN,HMGA2,WWTR1,LRP6,PHLDB2,TIAM1,SMAD2,SMAD3,DDX5,CTNNB1,SPRED3,HEYL,AKNA,DLG5,ALX1,PDPN,WNT5A,GSK3B	36	both
epithelial to mesenchymal transition involved in endocardial cushion formation	GO:0003198	organogenesis	4.808E-02	NOTCH1,RBPJ,HEYL,TGFBR2,SNAI1,ACVR1	6	up

epithelial tube formation	GO:0072175	organogenesis	2.533E-02	SOX4,GDNF,SIX1,SEMA4C,SOX9,MTHFD1L,LRP6,VEGFA,SKI,BCL10,PRICKLE1,DLC1,DVL3,EGF,PHACTR4,DVL1	16	both
epithelial tube morphogenesis	GO:0060562	organogenesis	2.870E-04	SEMA4C,TNF,STARD13,SIX1,SMO,PODXL,NRARP,PIK3CD,FGFR2,RHOA,KDM2B,MICAL2,LRP2,NOTCH1,FGF2,NRP1,SKI,VEGFA,RBPJ,LUZP1,KDR,SALL1,MTHFR,BSG,RHOB,MEF2C,MYC,MET,DLL1,TGFBR2,GATA4,CTNNB1,BMP7,EPHA2,CSF1R,SIRT6,BCL10,SOX4,SOX11,HOXD11,ACVR1,DLC1,AHI1,PRKD2,COL4A1,MTSS1	46	up
epithelium migration	GO:0090132	cell adhesion and migration	4.059E-02	GLUL,RAB13,PRKX,NR2F2,EMP2,SP1,NOTCH1,DUSP10,BMPR2,ADAM17,HMGB1,PDPK1,PFN2,ADGRA2,SIRT1,SOX9,HIF1A,ROCK2,AKT1,ZEB2,PTK2,CAPN7,PPARG,VASH1,MECP2,PTEN,KIT,PLPP3,ETS1,ARF6,MAP3K3,ITGB1,SPARC,ENPP2,KLF4,AKT3,VEGFA,CYP1B1,MET,RHOA,IL4,AMOT,ROCK1,MAPRE2,GADD45A,KANK2,RREB1,NF1,GIPC1,TBXA2R,ATOH8,LPXN,SRF,EGF,SYNJ2BP,ANGPT4,RRAS,THBS1,WNT5A,ARSB,PFN1	61	both
epstein-barr virus infection	KEGG:05169	viral of bacterial infection	2.846E-09	STAT3,E2F3,NCOR2,TP53,AKT1,TNFAIP3,CCNE1,BCL2,TNF,BAK1,ADRM1,MAPK14,PIK3CB,Fas,CD44,PIK3CD,E2F2,TRAF6,NFKB1,TLR2,FADD,CDKN1A,IRAK1,ISG15,STAT1,IRF7,IL6,CCND1,CCND2,ICAM1,CCNA2,HLA-A,HLA-G,CDKN1B,HLA-C,PIK3R3,CDK4,CCND3,CDK6,BCL2L11,MAP2K3,RBPJ,CHUK,ENTPD1,PIK3R1,AKT3,CCNE2,MAP3K7,CDK2,MDM2,E2F1,MYC,HDAC1,CASP3,CD40,MAP3K14,IFNB1,TRAF3,CASP9,CYCS,GADD45A,TRAF2,BAX,CASP8,APAF1,STAT2,MAP2K4,MAVS,B2M,TAB2	70	both
erbb signalling pathway	KEGG:04012	ERB signalling	7.574E-03	ERBB2,AKT1,EIF4EBP1,PIK3CB,ERBB3,RAF1,PIK3CD,ABL1,EGFR,CDKN1A,ERBB4,SOS1,KRAS,SOS2,CDKN1B,PIK3R3,TGFA,ABL2,RPS6KB1,GRB2,PAK2,CRKL,PIK3R1,AKT3,GSK3B,CRK,STAT5A,MYC,MAPK3,SRC,MAP2K1,PLCG1,AREG,NRAS,MAP2K4,MAPK1,EREG,PAK3	38	both
erbb2 signalling pathway	GO:0038128	ERB signalling	3.618E-02	ERBB2,ERBB3,EGFR,ERBB4,SOS1,HSP90AA1,GRB2,PIK3R1,SRC,EREG,ERBIN	11	up
erk/mapk targets	REAC:R-HSA-198753	MAPK signalling	3.512E-02	RPS6KA1,PPP2CA,DUSP6,MAPK14,RPS6KA3,MEF2C,MAPK3,MAPK1,RPS6KA5	9	up
erythrocyte differentiation	GO:0030218	cell differentiation	1.713E-03	ETS1,STAT3,JAK2,EPO,MED1,MAPK14,MFHAS1,CEBPG,STAT1,MAFB,VEGFA,CDK6,DYRK3,ACVR2A,TGFBR3,FOXO3,TAL1,SPI1,CASP3,KIT,SH2B3,ZBTB7A,HOXA5,RPS14	24	up
erythrocyte homeostasis	GO:0034101	cell proliferation	3.052E-03	ETS1,STAT3,JAK2,EPO,MED1,MAPK14,MFHAS1,CEBPG,STAT1,MAFB,VEGFA,CDK6,DYRK3,ACVR2A,TGFBR3,FOXO3,TAL1,SPI1,CASP3,KIT,SH2B3,ZBTB7A,HOXA5,RPS14	24	up
erythropoietin activates phosphoinositide-3-kinase (pi3k)	REAC:R-HSA-9027276	PI3k signalling	1.059E-02	EPOR,JAK2,EPO,PIK3CB,PIK3CD,PIK3R1,PIK3CG	7	up
erythropoietin activates ras	REAC:R-HSA-9027284	signalling pathways	4.207E-02	EPOR,JAK2,EPO,SOS1,CRKL,NRAS	6	up
esr-mediated signalling	REAC:R-HSA-8939211	signalling pathways	4.957E-05	CBFB,SPHK1,AKT1,BCL2,CREBBP,MED1,IGF1R,MMP2,TNRC6B,EGFR,FOS,CCND1,CXCL12,HSP90AA1,AGO3,TNRC6A,CDKN1B,AGO2,PIK3R3,TGFA,CCNT1,AGO1,GNB1,KANK1,AGO4,CARM1,PIK3R1,AKT3,MYB,POLR2E,GNG12,FOXO3,SP1,MYC,HDAC1,STAG2,YY1,MOV10,NCOA1,MAPK3,HIST1H2AC,SRC,HIST1H2BJ,MMP7,POU2F1,AREG,TLE3,NRAS,GTF2A1,ZDHHC21,CREB1,MAPK1,POLR2D,EREG,ESR1,KPNA2	56	both
establishment of cell polarity	GO:0030010	cell organisation	5.000E-02	RAB10,BRSK1,PARD3,ROCK2,PTK2,RAP1B,CDC42,ITGB1,FSCN1,DYNLT1,GPSM2,RHOA,AMOT,ROCK1,HSP90AB1,GBF1,PATJ,SNX27,NDEL1,LLGL1,GSK3B,NDE1,FAM49B	23	down
establishment of endothelial barrier	GO:0061028	blood brain barrier	9.557E-03	VCL,TNF,CDH5,ROCK1,ICAM1,S1PR2,VEGFA,PDE4D,RAP2C,RTN4,TJP2,TNFRSF1A,ZDHHC21,F11R,F2RL1	15	up
establishment of protein localization to endoplasmic reticulum	GO:0072599	protein localization	1.602E-02	RPL29,RPS12,EDEM1,RPL3,RPS7,RPS3A,RPLP0,RPL35A,RPS28,SRPRB,CHMP4B,SRPRA,SEC61A1,RPL14,RPL10,RPL36,RPS5,RAB3GAP2,RPL37,RPS2,RPL9,SPCS3,RPL23,RPL24,RPS15A,RPL4,RPS27A,RPS14,RAB10	29	up
establishment of protein localization to membrane	GO:0090150	protein localization	4.515E-05	PMAIP1,BMF,TP53,ERBB2,BBC3,BCL2,TIMM10,RPL29,RPS12,RPL3,RPS7,RPS3A,RPLP0,RPL35A,EGFR,RPS28,ITGB2,HSP90AA1,ARL6IP1,RAB34,VPS37B,ZDHHC6,YWHAB,VPS37A,CHMP4B,SRPRA,BCL2L11,SEC61A1,SPTBN1,RPL14,TIMM13,YWHAQ,GGA3,YWHAH,RAB3IP,TRAM1,RPL10,RPL36,RPS5,E2F1,GORASP2,VAMP2,SFN,VPS37D,RAB3GAP2,RPL37,RPS2,ANK3,MYO1C,BAG6,CD24,TP73,UBL4A,BAX,PPP3R1,GDI1,CASP8,MOAP1,TP53BP2,RPL9,ZDHHC21,MFF,TRAM2,RPL23,ZDHHC24,RPL24,PRNP,RPS15A,RPL4,ROMO1,RPS27A,KIF13A,SEC16A,C16orf70,KCNB1,RPS14,RAB31,RAB10	78	up
establishment of protein localization to mitochondrion	GO:0072655	mitochondrial activity	5.000E-02	SAE1,TP63,DNAJC15,TIMM50,TIMM8B,BID,YWHAG,BAG4,PPP1R13B,AKT1,LMAN1,PMAIP1,BCL2,BBC3,FZD5,HUWE1,SH3GLB1,CASP8,TIMM44,PPP3R1,BCL2L11,LEPROT,TP53,TFDP2,YWHAE,YWHAB,UBE2D3,MOAP1	28	both
establishment of protein localization to vacuole	GO:0072666	protein localization	4.704E-02	SCARB2,VPS37B,VPS37A,LAMP2,VPS4A,HSPA8,AP3M1,GGA3,CLU,SMURF1,SNX16,CACNG8,VPS37D,GNPTAB	14	up
establishment of rna localization	GO:0051236	protein localization	1.638E-04	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,SIDT2,POM121C,YTHDC1,ATM,THOC2,RBM15B,TGFBR2,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,CKAP5,YBX1,RAE1,NUP43,RBM27,RAN,POLR2D,SRSF2,NUP54,ARC,SMG1,EIF6,FYTTD1,DDX39A,MRPL18,PABPN1,HNRNPA3	47	both
estrogen signalling pathway	KEGG:04915	signalling pathways	3.052E-02	AKT1,BCL2,PIK3CB,MMP2,RAF1,PIK3CD,EGFR,FOS,SOS1,HSP90AA1,KRAS,SOS2,HSP90B1,PIK3R3,TGFA,GRB2,HSPA8,PRKCD,ITPR1,PIK3R1,AKT3,KRT33B,SP1,NCOA1,MAPK3,SRC,MAP2K1,NRAS,CREB1,GNAQ,MAPK1,ESR1,POMC,PLCB1,KCNJ6	35	both
estrogen-dependent gene expression	REAC:R-HSA-9018519	gene expression	1.169E-02	MYC,NCOA1,ESR1,HIST1H2BJ,AGO3,SP1,YY1,EP300,TNRC6B,AGO4,POLR2D,CCND1,AGO1,POLR2E,HIST1H2BK,NCOA3,STAG1,BCL2,CARM1,FOS,JUN,DDX5,GREB1,KCTD6,SMC3,HSP90AB1,CCNT1,CREBBP,JUND	29	both
estrogen-dependent nuclear events downstream of esr-membrane signalling	REAC:R-HSA-9634638	endocrine system	1.149E-04	AKT1,BCL2,EGFR,FOS,CCND1,CDKN1B,TGFA,AKT3,FOXO3,MAPK3,AREG,CREB1,MAPK1,EREG	14	both
execution phase of apoptosis	GO:0097194	apoptosis	1.591E-05	CDKN2A,TP53,BBC3,KPNB1,IL6,CASP7,DICER1,TAOK1,PAK2,XKR7,KPNA1,CASP3,HMGB1,AIFM1,CIDEA,BAX,CIDEB,DFFA,CASP6,CASP8,BCL2L1,TP53BP2,CIDEC,BLCAP,DLC1,MTRNR2L10,MTRNR2L11,MTRNR2L7,TOP2A,MTRNR2L3	30	up
export of viral ribonucleoproteins from nucleus	REAC:R-HSA-168274	viral of bacterial infection	1.580E-02	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,NUP62,RAE1,NUP43,RAN,NUP54	12	up
extra-nuclear estrogen signalling	REAC:R-HSA-9009391	endocrine system	1.214E-03	SPHK1,AKT1,BCL2,IGF1R,MMP2,EGFR,FOS,CCND1,HSP90AA1,CDKN1B,PIK3R3,TGFA,GNB1,PIK3R1,AKT3,GNG12,FOXO3,MAPK3,SRC,MMP7,AREG,NRAS,ZDHHC21,CREB1,MAPK1,EREG,ESR1	27	both
extrinsic apoptotic signalling pathway	GO:0097191	apoptosis	8.185E-05	PMAIP1,ZMYND11,JAK2,AKT1,TNFAIP3,BCL2,TNF,BAK1,IL6R,SORT1,TNFRSF10B,ERBB3,Fas,MCL1,IFI27,FADD,BCL2A1,SFRP1,BRCA1,ICAM1,FGFR3,PTEN,SMAD3,DDX3X,PAK2,CYLD,RNF41,GABARAP,BCL2L12,GSK3B,RET,ITGA6,PEA15,SRC,CASP3,AR,BIRC6,DIABLO,CASP9,CRADD,TNFRSF10A,TRAF2,BAX,LTBR,FASLG,TNFRSF1A,NOL3,BAG3,BCL10,CD70,CFLAR,CASP8,CD27,MOAP1,BCL2L1,TLR3,TCF7L2,ACVR1,THBS1,HIPK1	60	both
extrinsic apoptotic signalling pathway in absence of ligand	GO:0097192	apoptosis	3.073E-02	GDNF,RET,TERT,CASP3,AKT1,SNAI2,UNC5B,IL1A,BCL2,MCL1,APPL1,IL4,GSK3B,MOAP1	14	both
extrinsic apoptotic signalling pathway via death domain receptors	GO:0008625	apoptosis	2.228E-06	PMAIP1,TNFAIP3,BCL2,TNF,SORT1,TNFRSF10B,Fas,FADD,SFRP1,BRCA1,ICAM1,PTEN,DDX3X,GABARAP,GSK3B,PEA15,DIABLO,CRADD,TNFRSF10A,TRAF2,BAX,FASLG,TNFRSF1A,BAG3,CFLAR,CASP8,MOAP1,BCL2L1,THBS1	29	both
factors involved in megakaryocyte development and platelet production	REAC:R-HSA-983231	organogenesis	1.768E-02	TP53,KLC2,JAK2,ABL1,EHD1,KIF22,KIF2C,KIF5B,WEE1,DOCK11,RCOR1,PRKAR2A,KIF23,MAFK,KIF21A,RACGAP1,KIF3B,MYB,TUBB2A,CDC42,CAPZA2,CDK2,KIF11,HDAC1,VPS45,KLC1,CAPZB,KIF4A,IFNB1,GATA4,MFN2,KIF2A,DOCK3,SH2B3,GATA6,AKAP10,IRF1,CBX5,ACTB,CABLES1	40	up

fat cell differentiation	GO:0045444	cell differentiation	2.124E-02	CEBPA,AKT1,TNF,SIX1,ZNF385A,MED1,HMGA2,ALOX5,PTGS2,SFRP1,IL6,MAFB,WNT1,PPARD,KLF4,SMAD3,FLCN,CARM1,ZBTB16,CREBL2,ASXL1,PIM1,RUNX1T1,YAP1,FOXO1,E2F1,CDS1,TMEM64,SIRT1,CEBPB,INHBB,BMP7,NR4A2,TAF8,ZADH2,CREB1,PER2,CBY1,ZBTB7A,TCF7L2,ZBTB7B,WWTR1,FFAR4	43	both
fc epsilon ri signalling pathway	KEGG:04664	signalling pathways	2.227E-04	PLA2G4F,AKT1,TNF,GAB2,MAPK14,PIK3CB,RAF1,PIK3CD,ALOX5,SOS1,KRAS,SOS2,PIK3R3,VAV2,MAP2K3,GRB2,PIK3R1,AKT3,VAV3,MAPK3,MAP2K1,PLCG1,NRAS,MAP2K4,MAPK1	25	up
fc gamma r-mediated phagocytosis	KEGG:04666	leukocyte activation	1.440E-03	SPHK1,PLA2G4F,AKT1,GAB2,PIK3CB,RAF1,PIK3CD,WASF2,PRKCE,PIK3R3,ACTR3B,ACTR2,RPS6KB1,VAV2,PRKCD,CRKL,PIK3R1,AKT3,CDC42,CRK,PLPP3,CFL1,VAV3,MAPK3,MAP2K1,PLCG1,ARF6,PIP5K1C,CFL2,MAPK1	30	up
ferroptosis	KEGG:04216	homeostasis	1.698E-02	GSS,TP53,PCBP2,ACSL4,ACSL1,ATG5,TFRC,ACSL6,ATG7,CYBB,SLC7A11,SLC39A14,PRNP,SLC39A8	14	up
fgfr1 mutant receptor activation	REAC:R-HSA-1839124	FGFR signalling	3.718E-02	STAT3,GAB2,STAT1,FGF2,BAG4,PIK3R1,STAT5A,ERLIN2,LRRFIP1,FGFR1OP	10	up
fibroblast growth factor receptor signalling pathway	GO:0008543	signalling pathways	2.017E-02	APLN,NPTN,ESRP2,TRIM71,PTBP1,FGFR2,SHCBP1,RAB14,FGFR3,FGF2,SPRED1,GRB2,FGFR4,HNRNPA1,SHOC2,POLR2E,MAPK3,KLB,NCBP2,RBFOX2,ESRP1,DSTYK,MAPK1,POLR2D,PRKD2,FRS2,THBS1	27	up
fibroblast proliferation	GO:0048144	cell proliferation	6.417E-03	SPHK1,TP53,EMD,CDC73,MIF,CDKN1A,SFRP1,WNT1,B4GALT7,SKI,CDK4,CDK6,E2F1,MYC,PDGFRA,CTNNB1,EREG,PDGFB	18	both
fluid shear stress and atherosclerosis	KEGG:05418	diseases	4.490E-04	NCF1,MAPK14,SUMO2,DUSP1,BMPR2,NFE2L2,NFKB1,AKT1,PTK2,MAP2K7,HSP90B1,IL1A,VCAM1,BCL2,FOS,MMP2,JUN,AKT2,AKT3,VEGFA,RHOA,CALML4,CTNNB1,HSP90AB1,ICAM1,TP53,IKBKG,ACTG1,KLF2,BMPR1A	30	both
focal adhesion	KEGG:04510	cell adhesion and migration	3.177E-07	PAK2,THBS2,MAPK1,COL9A2,XIAP,IGF1,PAK5,PDGFRA,PDPK1,COL1A1,CCND1,ROCK2,AKT1,IGF1R,PTK2,CCND3,RELN,PTEN,RAP1B,BCL2,COL1A2,COL4A1,CDC42,ITGB1,COL6A2,PDGFRB,COL4A2,JUN,AKT2,CCND2,ITGA6,AKT3,VEGFA,LAMC2,LAMC1,PPP1CB,PPP1CC,MET,CRKL,RHOA,ROCK1,CTNNB1,PARVB,CRK,ITGA3,EGF,ACTG1,THBS1,GSK3B,ACTN4,PPP1CA,PAK4	52	both
focal adhesion assembly	GO:0048041	cell adhesion and migration	3.595E-02	VCL,ABL1,RHOA,GPM6B,ROCK1,SFRP1,PHLDB2,RCC2,NRP1,PTEN,VEGFA,PTPRJ,KDR,SLC9A1,ACTG1,SRC,CTTN,DLC1,THBS1	19	up
formation of apoptosome	REAC:R-HSA-111458	apoptosis	6.225E-03	XIAP,MAPK3,DIABLO,CASP9,CYCS,APAF1,MAPK1	7	up
formation of primary germ layer	GO:0001704	organogenesis	2.535E-02	MIXL1,DUSP1,BMPR2,EOMES,DUSP5,HMGA2,KDM6B,ITGB1,MMP2,DUSP2,MMP15,COL4A2,KLF4,COL5A2,COL7A1,SMAD2,SOX2,ITGA3,ATOH8,CDC73,FZD7	21	down
foxo signalling pathway	KEGG:04068	FoxO signalling pathway	2.773E-11	MAPK1,MAPK14,PCK1,EP300,MAP2K2,IGF1,HOMER1,PDPK1,FOXO1,CCND1,SIRT1,AKT1,IGF1R,TGFBR1,TGFBR2,ATM,PTEN,KRAS,NLK,SGK1,PRKAB2,MDM2,AKT2,CCND2,AKT3,SMAD3,CDKN1B,STAT3,BCL2L11,SKP2,FOXO3,CCNG2,SOD2,GADD45A,CDKN1A,EGF,SETD7,KLF2,CREBBP	39	both
foxo-mediated transcription	REAC:R-HSA-9614085	FoxO signalling pathway	8.334E-06	PCK1,EP300,YWHAG,FOXO1,SIRT1,AKT1,NR3C1,BBC3,IGFBP1,KLF4,AKT2,AKT3,TXNIP,SMAD2,SMAD3,CDKN1B,BCL2L11,FOXO3,CCNG2,SOD2,GADD45A,CDKN1A,PPARGC1A,YWHAB,CREBBP,ATXN3,CITED2	27	both
foxo-mediated transcription of cell cycle genes	REAC:R-HSA-9617828	FoxO signalling pathway	1.568E-03	FOXO1,KLF4,SMAD2,SMAD3,CDKN1B,FOXO3,CCNG2,GADD45A,CDKN1A	9	both
foxo-mediated transcription of cell death genes	REAC:R-HSA-9614657	FoxO signalling pathway	4.903E-02	BBC3,CREBBP,BCL2L11,FOXO3,FOXO1,FASLG,NFYB	7	up
frs2-mediated activation	REAC:R-HSA-170968	FGFR signalling	2.727E-02	YWHAB,CRKL,MAPK3,MAP2K1,MAPK1,FRS2	6	up
g0 and early g1	REAC:R-HSA-1538133	cell cycle	2.113E-03	CCNE1,LIN52,CCNA2,CDK1,CDC25A,CCNE2,CDK2,E2F1,MYC,HDAC1,E2F5,DYRK1A,TOP2A	13	up
g0 to g1 transition	GO:0045023	cell cycle	3.088E-02	RBBP4,RYBP,EPC1,EED,EZH2,SUZ12,PHC3,CHEK1,PCGF2,CBX3,TFDP2,BMI1,RAD51	13	down
g1 dna damage checkpoint	GO:0044783	cell cycle	2.034E-02	SOX4,ARID3A,EP300,CCND1,ATM,CARM1,BTG2,MDM2,CNOT6,CDKN1B,RFWD3,GADD45A,CDKN1A,TP53,MDM4,RBM38,TFDP2,AURKA	18	both
g1 phase	REAC:R-HSA-69236	cell cycle	1.249E-04	CDKN2A,E2F3,JAK2,PPP2CA,CDKN2D,ABL1,E2F2,CDKN1A,CCND1,CCND2,CDKN1B,CDK4,CCND3,CDK6,E2F1,E2F5,CDKN2C,UBB,RPS27A,UBC	20	up
g1/s dna damage checkpoints	REAC:R-HSA-69615	cell cycle	3.715E-02	CDKN2A,TP53,CCNE1,ZNF385A,PSMB1,CDKN1A,CCNA2,CDKN1B,CHEK1,CDC25A,CCNE2,PSMB5,CDK2,MDM2,ATM,MDM4,UBB,CHEK2,RPS27A,UBC	20	up
g1/s transition	REAC:R-HSA-69206	cell cycle	2.113E-03	AKT1,CCNE1,PPP2CA,PSMB1,LIN52,CDKN1A,CCND1,CCNA2,CDKN1B,CDK4,WEE1,ORC4,CDK1,CDC25A,AKT3,POLE4,CCNE2,PSMB5,CDK2,E2F1,MYC,HDAC1,MCM4,MCM2,MCM7,TYMS,RRM2,E2F5,PRIM1,MCM10,MCM6,MCM3,MCM5,CCNB1,UBB,RPS27A,UBC,ORC1,CABLES1	39	up
g1/s transition of mitotic cell cycle	GO:0000082	cell cycle	5.321E-03	CDKN2A,E2F7,E2F3,TP53,ARID3A,AKT1,CCNE1,RFWD3,ZNF385A,CDKN2D,PHF8,EIF4EBP1,BACH1,EIF4E,BTG2,TRIM71,TNKS1BP1,MUC1,EGFR,CDC73,CDKN1A,CDKN3,CNOT6L,CCND1,CCND2,ADAM17,RBM38,CDKN1B,KLF4,CNOT4,DCUN1D3,PTEN,CDK4,LSM11,CCND3,CDK6,RPS6KB1,WEE1,DDX3X,CDK17,CUL3,CARM1,ORC4,CUL2,CDK1,CDC25A,POLE4,CCNE2,TCF3,PPP2R5C,PPP6C,CACUL1,CDK2,LATS2,MDM2,E2F1,ITGB1,ATM,NASP,MYC,CDC25C,SFN,MDM4,MCM4,MCM2,MCM7,TYMS,RRM2,PRIM1,MCM10,KHDRBS1,MCM6,EIF4G1,CRADD,GADD45A,MCM3,DGKZ,CDKN2C,BAX,MCM5,CNOT2,SOX4,AURKA,BCAT1,CCNB1,CHEK2,CNOT1,CDK2AP2,ACVR1,ORC1,NACC2,PLCB1,CRLF3	93	both
g2 dna damage checkpoint	GO:0031572	cell cycle	1.789E-02	HMGA2,CDKN1A,BRCA1,CHEK1,TAOK1,CDK1,CLSPN,ATM,MRE11,MRNIP,FZR1,FOXN3	12	both
gab1 signalosome	REAC:R-HSA-180292	signalling pathways	4.903E-02	EGFR,TGFA,PAG1,PIK3R1,SRC,AREG,EREG	7	up
gap junction degradation	REAC:R-HSA-190873	cell adhesion and migration	4.207E-02	MYO6,ACTG1,CLTB,AP2M1,CLTA,ACTB	6	up
gastric cancer	KEGG:05226	cancer	4.920E-04	E2F3,FZD4,TP53,ERBB2,FRAT2,AKT1,CCNE1,BCL2,BAK1,PIK3CB,APC,RAF1,PIK3CD,FZD6,SMAD4,EGFR,FGFR2,E2F2,CDKN1A,TGFB1,RARB,SMAD2,CCND1,SOS1,WNT2B,WNT1,KRAS,FZD5,SOS2,FGF2,CDKN1B,PIK3R3,SMAD3,RPS6KB1,WNT7A,GRB2,PIK3R1,AKT3,AXIN2,CCNE2,GSK3B,FZD9,CDK2,ABCB1,E2F1,MYC,MET,LEF1,MAPK3,TGFBR2,MAP2K1,CTNNB1,GADD45A,BAX,TCF7,NRAS,REG4,TCF7L2,MAPK1	59	both
gastrin-creb signalling pathway via pkc and mapk	REAC:R-HSA-881907	MAPK signalling	4.100E-03	RPS6KA1,EGFR,SOS1,CCKBR,RPS6KA3,MAPK3,NRAS,CREB1,MAPK1	9	up
gene and protein expression by jak-stat signalling after interleukin-12 stimulation	REAC:R-HSA-8950505	interleukin signalling	1.052E-02	RPLP0,MIF,PDCD4,PAK2,HNRNPDL,HNRNPA2B1,CDC42,CFL1,SNRPA1,MTAP,AIP,IL10,ARF1,SOD2	14	up

gene silencing by rna	REAC:R-HSA-211000	miRNA/siRNA biogenesis	2.311E-03	NUP93,NUP205,RANBP2,NUP37,PRKRA,TNRC6B,NDC1,HSP90AA1,AGO3,DICER1,TNRC6A,AGO2,TARBP2,AGO1,AGO4,NUP50,POLR2E,POM121C,HIST1H2AC,NUP62,TSN,HIST1H2BJ,RAE1,NUP43,RAN,POLR2D,NUP54,BCDIN3D,PIWIL2,MYBL1,DDX4	31	up
glial cell development	GO:0021782	organogenesis	2.729E-02	TNF,TLR2,IL6,LDLR,DICER1,B4GALT5,PTEN,SKI,CDK6,AGER,EIF2B2,CLU,APP,DLL1,TPPP,TREM2,NSUN5,SOX4,SOX11	19	up
glial cell differentiation	GO:0010001	cell differentiation	3.073E-02	STAT3,TNF,ERBB3,CXCR4,TLR2,IL6,NOTCH1,SOX2,LDLR,DICER1,B4GALT5,PTEN,SKI,CDK6,AGER,CDK1,EIF2B2,CLU,APP,ZNF365,DLL1,TPPP,TNFRSF21,TREM2,NSUN5,SOX4,SOX11,NFIB	28	up
glial cell proliferation	GO:0014009	cell proliferation	3.073E-02	NF2,TNF,IL6,NOTCH1,DICER1,SKI,CLU,SOX4,SOX11	9	up
gliogenesis	GO:0042063	cell proliferation	4.765E-02	NF2,STAT3,TNF,ERBB3,CXCR4,TLR2,LRP2,IL6,NOTCH1,SOX2,LDLR,CSF1,DICER1,B4GALT5,PTEN,SKI,PAFAH1B1,CDK6,AGER,CDK1,CRKL,EIF2B2,CLU,APP,RTN4,ZNF365,CCL3,DLL1,TPPP,TNFRSF21,TREM2,NSUN5,SOX4,SOX11,NFIB	35	up
glioma	KEGG:05214	cancer	4.438E-03	CDKN2A,E2F3,TP53,AKT1,BAK1,IGF1R,PIK3CB,RAF1,PIK3CD,EGFR,E2F2,CDKN1A,CCND1,SOS1,KRAS,SOS2,PIK3R3,TGFA,PTEN,CDK4,CDK6,GRB2,PIK3R1,AKT3,MDM2,E2F1,MAPK3,PDGFRB,PDGFRA,MAP2K1,PLCG1,GADD45A,BAX,NRAS,MAPK1,PDGFB	36	both
glomerulus morphogenesis	GO:0072102	organogenesis	3.967E-02	MEF2C,PDGFRB,PDGFRA,MTSS1	4	up
glycerolipid metabolic process	GO:0046486	lipid metabolism	1.237E-02	PCTP,SEL1L,GPAT4,ARF3,PLA2G4F,MTMR12,IP6K1,PLEKHA8,MTMR3,LYPLA2,DGAT1,PIK3CB,RAB4A,PIGF,PIK3CD,PIP4K2C,MTMR4,CSNK2A1,LDLR,RAB14,SIK1,TMEM246,FGF2,PIK3R3,PLA2G12A,PTEN,PISD,PAFAH1B1,PI4K2B,CPNE1,OCRL,SELENOI,PIK3R1,ABHD2,PLEKHA1,SOCS5,ETNK1,CDS2,PNPLA6,PIP4P1,FBXW7,CDS1,SCARB1,FABP7,MTMR2,PDGFRB,SIRT1,DGAT2L6,SOCS4,PIGT,PLCG1,PIK3CG,GDE1,MTMR9,DGKZ,PLA2G2D,CSF1R,IMPA1,ARF1,CNEP1R1,MTMR10,PIP5K1C,HADHB,LCLAT1,PIGG,FIG4,PIGA,ACP6,SOCS3,MOGAT1,SMG1,PDGFB,ABHD12,AGPAT5,SOCS7,STARD7,PLCB1,DGKB,CRLS1,DGKI,SREBF1	81	up
glycerophospholipid metabolic process	GO:0006650	lipid metabolism	1.268E-02	PCTP,GPAT4,ARF3,PLA2G4F,MTMR12,IP6K1,PLEKHA8,MTMR3,PIK3CB,RAB4A,PIGF,PIK3CD,PIP4K2C,MTMR4,CSNK2A1,LDLR,RAB14,TMEM246,FGF2,PIK3R3,PLA2G12A,PTEN,PISD,PAFAH1B1,PI4K2B,CPNE1,OCRL,SELENOI,PIK3R1,PLEKHA1,SOCS5,ETNK1,CDS2,PNPLA6,PIP4P1,CDS1,SCARB1,MTMR2,PDGFRB,SOCS4,PIGT,PLCG1,PIK3CG,GDE1,MTMR9,DGKZ,PLA2G2D,CSF1R,IMPA1,ARF1,MTMR10,PIP5K1C,HADHB,LCLAT1,PIGG,FIG4,PIGA,ACP6,SOCS3,SMG1,PDGFB,ABHD12,AGPAT5,SOCS7,STARD7,PLCB1,DGKB,CRLS1	68	up
golgi vesicle transport	GO:0048193	cellular transport	1.857E-02	SEC24A,ARF3,KLC2,VPS51,SORT1,COPZ1,KIF22,BGLAP,COPA,MCFD2,RAB14,GAS1,RAB34,KIF2C,PPP6R1,TGFA,RAB1B,NAPG,STX17,MYO5A,COPB1,DCTN5,CUL3,KIF23,TBC1D14,ARCN1,RACGAP1,SPTBN1,PPP6R3,KIF3B,GOSR1,DYNLL2,GGA3,TBC1D20,RAB3IP,PPP6C,HYOU1,CAPZA2,PLPP3,AP2A1,KIF11,VAMP2,SNX12,SNAP23,SNX3,KLC1,CAPZB,KIF4A,SPTAN1,ANK3,SAR1A,PRKD1,SURF4,CYTH3,AREG,KIF2A,INSIG1,CNIH1,EXOC5,DYNC1LI2,ERGIC2,GOLGA3,MYO1B,IER3IP1,SEC23B,KDELR1,KIF13A,SEC16A,C16orf70,RAB6A,RABIF,RAB31,LMAN1,RAB10,RAB1A,ACTR1A	76	up
golgi-to-er retrograde transport	REAC:R-HSA-8856688	cellular transport	1.599E-02	ARF3,KLC2,COPZ1,KIF22,COPA,KIF2C,RAB1B,NAPG,PAFAH1B1,KIF5B,COPB1,GALNT1,DCTN5,KIF23,ARCN1,KIF21A,RACGAP1,KIF3B,PAFAH1B2,DYNLL2,TUBB2A,CAPZA2,KIF11,KLC1,CAPZB,KIF4A,RAB3GAP2,SURF4,KIF2A,ARF1,DYNC1LI2,KDELR1,RAB18,RAB6A,RAB1A,ACTR1A	36	up
grb2 events in egfr signalling	REAC:R-HSA-179812	EGFR signalling	2.727E-02	EGFR,SOS1,TGFA,AREG,NRAS,EREG	6	up
growth hormone receptor signalling	REAC:R-HSA-982772	endocrine system	4.467E-02	STAT3,JAK2,STAT1,IRS1,ADAM17,STAT5A,MAPK3,MAPK1,SOCS3	9	up
growth hormone synthesis, secretion and action	KEGG:04935	endocrine system	1.561E-04	STAT3,JAK2,AKT1,CREBBP,MAPK14,PIK3CB,RAF1,PIK3CD,FOS,STAT1,SOS1,IRS1,KRAS,SOS2,PIK3R3,MAP2K3,GRB2,ITPR1,CRKL,PIK3R1,AKT3,GSK3B,CRK,STAT5A,MAPK3,MAP2K1,MAP3K1,PLCG1,NRAS,CREB1,MAP2K4,GNAQ,MAPK1,SSTR2,SOCS3,GHSR,SSTR1,PLCB1	38	up
hcmv infection	REAC:R-HSA-9609646	viral of bacterial infection	4.207E-02	NCOR2,CHMP3,HNRNPK,NUP93,NUP205,RANBP2,NUP37,EGFR,NDC1,NFKB1,VPS37B,VPS37A,CHMP4B,VPS4A,NUP50,DYNLL2,TUBB2A,TBL1XR1,POM121C,ITGB1,CHMP2B,HIST1H2AC,VPS37D,NUP62,HIST1H2BJ,HIST1H2AH,RAE1,NUP43,DYNC1LI2,CREB1,NUP54	31	up
hcmv late events	REAC:R-HSA-9610379	viral of bacterial infection	2.604E-02	CHMP3,HNRNPK,NUP93,NUP205,RANBP2,NUP37,NDC1,VPS37B,VPS37A,CHMP4B,VPS4A,NUP50,POM121C,CHMP2B,HIST1H2AC,VPS37D,NUP62,HIST1H2BJ,HIST1H2AH,RAE1,NUP43,NUP54	22	up
heart development	GO:0007507	organogenesis	1.982E-05	WDR11,BCOR,NEBL,DUSP6,APLN,REST,SMO,ERBB3,SMAD4,NTRK3,EGFR,FBN1,GLI1,FGFR2,ROCK1,MICAL2,CDKN1A,ERBB4,LRP2,KDM6B,ROBO1,NOTCH2,NOTCH1,DKK1,SIK1,FGF2,CDKN1B,NRP1,PTEN,PDCD4,VEGFA,SPRED1,EFNB2,ELN,RBPJ,INSR,HEYL,FKBP1A,TGFBR3,SMAD7,SALL1,PIM1,ZDHHC16,MEF2C,ITGB1,JAG1,DLL1,TPM1,MDM4,PDGFRB,PDGFRA,TGFBR2,DSP,GATA4,CTNNB1,PKP2,TP73,SNAI1,BMP7,POU5F1,TNFRSF1A,CASP8,SOX4,ACTC1,S1PR1,BMPR1A,GATA6,SOX11,DAND5,CBY1,CHD7,EDN1,ACVR1,DLC1,RBM20,LEFTY1,MYH11,AHI1,ECE1,PDGFB,HAS2,FRS2,TAB2,TWIST1,VGLL4,ADAMTS9	86	up
heart morphogenesis	GO:0003007	organogenesis	7.686E-04	SMO,SMAD4,FGFR2,MICAL2,LRP2,ROBO1,NOTCH2,NOTCH1,DKK1,NRP1,PDCD4,VEGFA,ELN,RBPJ,INSR,HEYL,FKBP1A,TGFBR3,SMAD7,PIM1,MEF2C,JAG1,DLL1,TPM1,MDM4,TGFBR2,DSP,GATA4,CTNNB1,PKP2,SNAI1,BMP7,POU5F1,SOX4,ACTC1,S1PR1,BMPR1A,GATA6,SOX11,CHD7,ACVR1,DLC1,LEFTY1,AHI1,HAS2	45	up
heart valve development	GO:0003170	organogenesis	1.139E-03	SOX4,TWIST1,NOTCH1,BMPR2,SOX9,ROCK2,SNAI2,TGFBR2,NOTCH2,ZFPM1,ROCK1,MDM4,HEYL,BMPR1A	14	both
heart valve morphogenesis	GO:0003179	organogenesis	8.703E-04	SOX4,TWIST1,NOTCH1,BMPR2,SOX9,ROCK2,SNAI2,TGFBR2,NOTCH2,ZFPM1,ROCK1,MDM4,HEYL,BMPR1A	14	both
hemostasis	GO:0007599	diseases	9.382E-04	VCL,JAK2,PABPC4,PIK3CB,RAF1,EHD1,CD40LG,IL6,PRKCE,TLR4,PLAUR,VAV2,ALOX12,DOCK11,RCOR1,PRKAR2A,GNB1,MAFK,PRKCD,ENTPD1,ITPR1,PIK3R1,ITGA2,CDC42,STXBP3,CAPZA2,F3,MYL9,HDAC1,VAV3,HNF4A,ACTG1,VPS45,MAPK3,SRC,PDGFRA,CAPZB,GPI,METAP1,CD40,IFNB1,GATA4,ITGB3,MFN2,AXL,PIK3CG,SAA1,DGKZ,GGCX,SH2B3,GATA6,F11R,PDPN,AKAP10,GNAQ,MAPK1,EDN1,IRF1,ENPP4,TRPC3,F2RL1,CD36,UBASH3B,PDGFB,CBX5,CSRP1,CYP4F11,ACTB,THBS1,DGKB,DGKI,LMAN1	72	up
hepatitis b	KEGG:05161	viral of bacterial infection	4.438E-03	MYC,MAPK1,MAPK14,DDX3X,TRAF3,EP300,MAP2K2,NFATC2,BID,CASP3,NFKB1,AKT1,MAP2K7,TGFBR1,TGFBR2,KRAS,BCL2,FOS,CCNA2,JUN,AKT2,CREB5,AKT3,CASP8,MAP3K1,SMAD3,STAT3,CDKN1A,IRAK4,TP53,IKBKG,BIRC5,STAT2,CYCS,YWHAB,CREBBP,E2F3	37	both
hepatitis c	KEGG:05160	viral of bacterial infection	1.257E-02	STAT3,E2F3,TP53,AKT1,PPP2CA,TNF,BAK1,PIK3CB,Fas,RAF1,PIK3CD,EGFR,E2F2,TRAF6,NFKB1,FADD,CDKN1A,STAT1,IRF7,MX2,RSAD2,IFIT1,CCND1,SOS1,LDLR,KRAS,SOS2,PIK3R3,YWHAB,CDK4,CDK6,GRB2,CHUK,PIK3R1,AKT3,YWHAQ,YWHAH,GSK3B,CDK2,E2F1,SCARB1,MYC,MAPK3,CASP3,MAP2K1,IFNB1,TRAF3,CTNNB1,CASP9,CYCS,TRAF2,BAX,FASLG,TNFRSF1A,PPARA,CFLAR,CASP8,APAF1,NRAS,STAT2,TLR3,MAVS,MAPK1,SOCS3	64	both
hepatocellular carcinoma	KEGG:05225	cancer	6.977E-12	CDKN2A,SMARCD2,E2F3,IGF2,FZD4,TP53,FRAT2,AKT1,BAK1,IGF1R,PIK3CB,APC,RAF1,PIK3CD,FZD6,SMAD4,EGFR,E2F2,CDKN1A,TGFB1,SMAD2,CCND1,SOS1,WNT2B,WNT1,KRAS,FZD5,SOS2,PIK3R3,TGFA,PTEN,CDK4,CDK6,SMAD3,RPS6KB1,WNT7A,GRB2,PIK3R1,AKT3,AXIN2,GSK3B,FZD9,SMARCD1,E2F1,MYC,MET,ACTG1,LEF1,MAPK3,SMARCC2,TGFBR2,MAP2K1,PLCG1,CTNNB1,SMARCA4,SMARCC1,TXNRD1,GADD45A,BAX,BCL2L1,TCF7,NRAS,ARID1B,TCF7L2,MAPK1,ARID1A,ACTB	67	both
herpes simplex virus 1 infection	KEGG:05168	viral of bacterial infection	1.391E-04	ZNF442,ZNF200,ZNF573,ZNF419,ZNF440,ZFP14,ZNF793,ZNF429,TAPBP,ZFP82,ZNF708,ZNF154,TRAF3,ZNF285,ZNF25,ZNF554,POU2F2,ZNF226,ZNF699,ZNF845,BID,ZNF519,CASP3,EIF4EBP1,NFKB1,AKT1,ZNF607,ZNF426,ZNF780B,ZNF846,ZFP69B,ZNF556,ZNF829,ZNF415,ZNF23,ZNF253,ZNF83,ZNF597,ZNF439,ZNF136,ZNF791,ZNF268,BCL2,ZNF669,ZNF616,ZNF667,ZNF107,ZNF850,ZNF45,AKT2,AKT3,ZNF286A,CASP8,ZNF566,PPP1CB,PPP1CC,SRSF7,ZNF619,B2M,ZNF701,ZNF324B,SOCS3,IRAK4,IFNGR2,ZNF589,ZNF783,TP53,ZNF641,IKBKG,ZNF43,ZNF81,ZNF557,ZNF587,ZNF584,ZNF665,ZNF124,EIF2AK2,ZNF101,ZNF674,ZNF766,ZNF790,ZNF33A,ZNF460,ZNF99,ZNF583,STAT2,ZNF891,ZNF623,CYCS,C3,ZNF805,ZNF749,NXF1,ZNF490,ZNF714,ZNF486,ZNF431,SRSF4,PPP1CA,HCFC1	100	down

hif-1 signalling pathway	KEGG:04066	signalling pathways	6.024E-03	STAT3,ERBB2,MKNK2,AKT1,ANGPT2,EPO,BCL2,EIF4EBP1,CREBBP,IL6R,IGF1R,PIK3CB,PFKM,EIF4E,PIK3CD,EGFR,HK2,NFKB1,CDKN1A,IL6,TLR4,CDKN1B,PIK3R3,VEGFA,RPS6KB1,CUL2,INSR,PIK3R1,AKT3,MAPK3,LDHA,MAP2K1,TFRC,PLCG1,LTBR,CYBB,MAPK1,EDN1,EGLN3	39	both
hippo signalling	GO:0035329	signalling pathways	4.667E-04	NF2,MAPK14,YWHAB,MAP2K3,AMOT,AMOTL1,YAP1,LATS2,CASP3,TJP2,SOX11,DLG5,MOB3B,WWTR1,MOB1B,STK4,LIMD1,VGLL4	18	up
hippo signalling pathway	KEGG:04390	signalling pathways	6.086E-06	NF2,BMPR1B,FZD4,BBC3,PPP2CA,APC,FZD6,SMAD4,PPP1CA,PARD6B,TGFB1,SMAD2,ITGB2,CCND1,CCND2,SOX2,WNT2B,WNT1,FZD5,YWHAB,CCND3,SMAD3,WNT7A,BTRC,BIRC5,AMOT,NKD1,AXIN2,SMAD7,YWHAQ,YWHAH,GSK3B,FZD9,YAP1,LATS2,MYC,ACTG1,LEF1,BIRC3,TGFBR2,CTNNB1,TP73,BMP7,GDF5,AREG,PPP1CC,TCF7,BIRC2,TP53BP2,BMPR1A,BMP8A,DLG5,TCF7L2,WWTR1,MOB1B,ACTB,LIMD1	57	both
histone deacetylation	GO:0016575	epigenetic mechanism	4.573E-02	SIRT7,REST,AKAP8,MTA2,VEGFA,BAZ2A,RCOR1,ELK4,TBL1XR1,HDAC1,SIRT1,PER1,PRKD1,SIRT6,PER2,ZBTB7B,PRKD2,BRMS1L	18	up
histone h3 deacetylation	GO:0070932	epigenetic mechanism	2.731E-02	SIRT7,ELK4,HDAC1,SIRT1,PER1,SIRT6,PER2	7	up
histone h3-k9 modification	GO:0061647	epigenetic mechanism	3.844E-02	SUV39H1,SMAD4,BRCA1,JARID2,DNMT1,SETDB1,CHEK1,MYB,RIF1,SIRT1	10	up
histone methylation	GO:0016571	epigenetic mechanism	1.403E-02	EHMT1,BCOR,SUV39H1,SUPT6H,SIRT7,CREBBP,TET2,KMT2D,SMAD4,BRCA1,JARID2,DNMT1,SETDB1,TET3,OGT,ASH1L,PHF19,CARM1,PAGR1,PRDM4,MYB,SETD1B,RIF1,MTHFR,SIRT1,SETD3,CTNNB1,TET1	28	up
histone modification	GO:0016570	epigenetic mechanism	4.381E-05	KMT2A,WDR82,RYBP,EPC1,TWIST1,FMR1,PRKCD,MTA3,ATRX,RIF1,DTX3L,EP300,KAT6B,RPS6KA5,MCRS1,MEAF6,SIRT1,EZH2,KDM5C,INCENP,KDM5A,KMT2E,PER2,ELK4,ATXN7,SUV39H2,NAA50,HMGA2,CARM1,TBL1XR1,RCOR1,BAZ2A,MORF4L1,KDM6B,DNMT3B,DOT1L,KDM5B,PER1,NAA40,KMT5C,MORF4L2,CCNA2,HUWE1,REST,TET3,TET2,VEGFA,PRDM4,CHEK1,BCOR,PCGF2,LMNA,JARID2,DR1,MTF2,CTNNB1,PPARGC1A,HASPIN,CDC73,USP22,MSL2,BMI1,RNF40,KDM2A,CREBBP,UBE2B,BRPF3,ZBTB7B,KMT2B,HCFC1	70	both
histone monoubiquitination	GO:0010390	ubiquitination	4.733E-02	BCOR,RYBP,UHRF1,KDM2B,CDC73,RNF168,RNF40,RAG1,TRIM37,DTX3L	10	up
histone phosphorylation	GO:0016572	phosphorylation	2.045E-03	JAK2,AURKB,HMGA2,AKAP8,CCNA2,RPS6KA4,PRKCD,CDK2,MAPK3,INCENP,RPS6KA5,TWIST1	12	up
hiv infection	REAC:R-HSA-162906	viral of bacterial infection	7.352E-03	VPS4B,CHMP3,NUP93,NUP205,RANBP2,NUP37,NPM1,TAF15,PSMB1,HMGA1,NDC1,KPNB1,CXCR4,FURIN,VPS37B,VPS37A,AP2B1,SUPT16H,CHMP4B,CCNT1,BTRC,PAK2,SSRP1,VPS4A,TAF13,CCNT2,NUP50,POLR2E,RNMT,KPNA1,PSMB5,POM121C,RANGAP1,CHMP2B,AP2A1,NELFCD,SUPT5H,FEN1,VPS37D,NUP62,AP2M1,AP2A2,NCBP2,RAE1,ARF1,ELOA,GTF2A1,NUP43,GTF2E1,UBB,RPS27A,UBC,RAN,POLR2D,NUP54,B2M,ELL	57	up
hiv life cycle	REAC:R-HSA-162587	viral of bacterial infection	4.565E-04	VPS4B,CHMP3,NUP93,NUP205,RANBP2,NUP37,TAF15,HMGA1,NDC1,CXCR4,FURIN,VPS37B,VPS37A,SUPT16H,CHMP4B,CCNT1,SSRP1,VPS4A,TAF13,CCNT2,NUP50,POLR2E,RNMT,KPNA1,POM121C,RANGAP1,CHMP2B,NELFCD,SUPT5H,FEN1,VPS37D,NUP62,NCBP2,RAE1,ELOA,GTF2A1,NUP43,GTF2E1,UBB,RPS27A,UBC,RAN,POLR2D,NUP54,ELL	45	up
homeostasis of number of cells	GO:0048872	cancer	2.056E-05	ETS1,PMAIP1,STAT3,JAK2,AKT1,TNFAIP3,EPO,MED1,MAPK14,PIK3CB,UBAP2L,Fas,PIK3CD,MFHAS1,CEBPG,FADD,STAT1,IL6,NOTCH1,MAFB,ADAM17,VEGFA,CDK6,DOCK11,DYRK3,ACVR2A,TGFBR3,FOXO3,MEF2C,TAL1,SPI1,CASP3,HMGB1,KIT,BCL10,SH2B3,ZBTB7A,HOXA5,RPS14	39	both
homotypic cell-cell adhesion	GO:0034109	cell adhesion and migration	6.803E-04	VCL,PIK3CB,CCL5,PLAUR,ALOX12,PRKCD,STXBP3,PLPP3,MYL9,ACTG1,PDGFRA,METAP1,DSP,ITGB3,ANK3,PIK3CG,TJP2,PKP2,SH2B3,F11R,PDPN,UBASH3B,CSRP1,ACTB,ZNF703	25	up
hormone-mediated signalling pathway	GO:0009755	signalling pathways	4.765E-02	CBFB,NCOR2,MED1,STRN3,KMT2D,SFRP1,RARB,BRCA1,CLOCK,PPARD,CARM1,PAGR1,ABHD2,HEYL,YWHAH,YAP1,LATS2,HDAC1,SRC,SIRT1,AR,PER1,SMARCA4,BMP7,PPARA,CNOT2,RBFOX2,TMF1,PMEPA1,CNOT1,ZBTB7A,THRA,ESR1,GHSR,ARID1A	35	up
human cytomegalovirus infection	KEGG:05163	viral of bacterial infection	5.672E-03	MYC,CDK6,MAPK1,MAPK14,IL10RB,GNAQ,TAPBP,SP1,MAP2K2,NFATC2,BID,PDGFRA,CCND1,CASP3,IL10RA,EIF4EBP1,NFKB1,ROCK2,AKT1,PTK2,GNAI2,ADCY9,KRAS,GNB4,MDM2,AKT2,CREB5,AKT3,VEGFA,CASP8,STAT3,PPP3R1,ITPR1,B2M,CRKL,RHOA,CALML4,ROCK1,CTNNB1,CDKN1A,CRK,TP53,IKBKG,GNAI3,CYCS,GSK3B,E2F3	47	both
human immunodeficiency virus 1 infection	KEGG:05170	viral of bacterial infection	4.672E-06	PAK2,WEE1,AP1S1,MAPK1,MAPK14,GNAQ,TAPBP,MAP2K2,APOBEC3C,NFATC2,PAK5,BID,CASP3,NFKB1,AKT1,PTK2,GNAI2,MAP2K7,ATM,CUL5,KRAS,BCL2,GNB4,FOS,JUN,AKT2,AKT3,CASP8,CHEK1,PPP3R1,ITPR1,B2M,CRKL,CALML4,CD3D,IRAK4,CRK,IKBKG,AP1S3,CD4,APOBEC3F,GNAI3,CYCS,PAK4	44	both
human papillomavirus infection	KEGG:05165	viral of bacterial infection	1.182E-04	WNT4,CDK6,THBS2,MAPK1,APC,NOTCH1,COL9A2,TRAF3,EP300,MAP2K2,PARD3,COL1A1,FOXO1,TERT,CCND1,CASP3,EIF4EBP1,NFKB1,AKT1,PTK2,CCND3,RELN,NOTCH4,ATM,PTEN,KRAS,PPP2R5E,CSNK1A1,NOTCH2,MPP5,COL1A2,COL4A1,CDC42,ITGB1,COL6A2,PDGFRB,MDM2,CCNA2,COL4A2,FZD5,FZD4,AKT2,CCND2,CREB5,ITGA6,AKT3,VEGFA,LAMC2,LAMC1,CASP8,CDKN1B,CTNNB1,CDKN1A,HES2,ITGA3,TP53,IKBKG,DVL3,PATJ,EGF,HEYL,EIF2AK2,ATP6V0D2,FZD7,STAT2,LLGL1,THBS1,WNT5A,GSK3B,CREBBP,PKM,HES7,DVL1	73	both
human t-cell leukemia virus 1 infection	KEGG:05166	viral of bacterial infection	1.968E-04	MYC,CRTC3,MAPK1,XIAP,EP300,MAP2K2,NFATC2,TERT,CCND1,NFKB1,AKT1,CCND3,FOSL1,RAN,TGFBR1,TGFBR2,ATM,PTEN,ADCY9,KRAS,ELK4,ETS1,IL2,MAP3K3,CDC23,FOS,CCNA2,JUN,AKT2,CCND2,CREB5,AKT3,MAP3K1,SMAD2,SMAD3,CHEK1,CANX,PPP3R1,B2M,CD3D,CDKN1A,CDC27,ICAM1,TP53,XPO1,IKBKG,ESPL1,SRF,CD4,TNFRSF13C,CREBBP,E2F3	52	both
i-κb kinase/nf-κb signalling	GO:0007249	Nfκ	3.997E-02	TRIM27,TIAF1,ESR1,VAPA,TNIP3,RORA,TRAF3,NUP62,TRIM13,PDPK1,TRIM38,CANT1,SIRT1,ROCK2,AKT1,RHOC,ZMYND11,UBE2V1,IRAK1BP1,ZFAND6,FKBP1A,TFRC,MAP3K3,REL,RIOK3,PER1,MAPKBP1,DDX21,CASP8,NKIRAS2,TNFRSF10B,TRIM59,BCL10,TNIP2,RHOA,PELI1,ROCK1,TRAF1,IRAK4,IKBKG,CD4,PYCARD,CC2D1A,IRAK2,NLRC3,WNT5A,PRDX4,ZC3HAV1,CARD8,SHISA5	50	both
ikk complex recruitment mediated by rip1	REAC:R-HSA-937041	Nfκ	3.832E-03	TRAF6,TLR4,UBE2D3,UBE2V1,CHUK,BIRC3,BIRC2,UBB,RPS27A,UBC,UBE2D2	11	up
il-17 signalling pathway	KEGG:04657	interleukin signalling	4.341E-04	S100A8,TNFAIP3,TNF,MAPK14,MMP13,FOS,TRAF6,NFKB1,FADD,PTGS2,IL6,CXCL8,ELAVL1,HSP90AA1,HSP90B1,CHUK,SRSF1,TAB3,GSK3B,MAP3K7,CXCL2,MAPK3,CASP3,CEBPB,ANAPC5,TRAF3,FOSL1,TRAF2,CASP8,MAPK1,TAB2	31	up
immune response to tumor cell	GO:0002418	cellular response to external stimuli	1.552E-02	FBXO38,HSPD1,HLA-A,CD274,HMGB1,ADAM15,CD226,PVR	8	up
import into nucleus	GO:0051170	cellular transport	3.016E-02	STAT3,E2F3,AKT1,NUP93,RANBP2,TNPO3,SNRPB,KPNB1,KPNA4,SMAD3,RAB23,PRKCD,HNRNPA1,PIK3R1,NUP50,KPNA1,KPNA3,POM121C,ECT2,TNPO1,GEMIN5,PPP1R10,NUP62,CSE1L,BAG3,RANBP6,GEMIN2,RPL23,SNRPD1,MAVS,RAN,NUP54,IPO7,KPNA2,TNPO2	35	both
in utero embryonic development	GO:0001701	organogenesis	2.533E-02	E2F7,IGF2,FGFR2,VEGFA,FLCN,RBPJ,ITGB1,NASP,MFN2,FUT8,BMP7,POU5F1,CASP8,CHD7,MBNL1,TET1,PDGFB	17	up
infection with mycobacterium tuberculosis	REAC:R-HSA-9635486	viral of bacterial infection	4.503E-02	KPNB1,TLR2,VPS33B,KPNA1,MAPK3,UBB,MAPK1,RPS27A,UBC,B2M	10	up
inflammatory cell apoptotic process	GO:0006925	apoptosis	1.881E-02	CDKN2A,PIK3CB,PIK3CD,IRF7,IL6,MEF2C,SIRT1	7	up
influenza a	KEGG:05164	viral of bacterial infection	1.265E-02	JAK2,AKT1,TNF,BAK1,CREBBP,TNFRSF10B,VDAC1,PIK3CB,Fas,RAF1,PIK3CD,NFKB1,FADD,STAT1,IRF7,MX2,IL6,RSAD2,CCL5,CXCL8,TLR4,ICAM1,PIK3R3,CDK4,CCND3,CDK6,CHUK,PIK3R1,AKT3,KPNA1,NLRP3,ACTG1,MAPK3,CASP3,HNRNPUL1,MAP2K1,IFNB1,TRAF3,NUP98,CASP1,CASP9,CYCS,TNFRSF10A,RAE1,BAX,FASLG,TNFRSF1A,CASP8,APAF1,STAT2,TLR3,MAVS,MAPK1,SOCS3,PABPN1,ACTB,KPNA2	57	both

influenza infection	REAC:R-HSA-168255	viral of bacterial infection	4.319E-04	NUP93,RPL29,RPS12,RPL3,NUP205,RANBP2,NUP37,RPS7,RPS3A,RPLP0,RPL35A,NDC1,RPS28,KPNB1,ISG15,HSP90AA1,KPNA4,RPL14,NUP50,POLR2E,CANX,RPL10,RPL36,KPNA1,KPNA3,POM121C,RPS5,NUP62,RPL37,RPS2,RAE1,RPL9,NUP43,CLTA,RPL23,RPL24,GRSF1,RPS15A,RPL4,RPS27A,RAN,POLR2D,NUP54,RPS14,PABPN1,KPNA2	46	up
influenza viral rna transcription and replication	REAC:R-HSA-168273	viral of bacterial infection	1.292E-02	NUP93,RPL29,RPS12,RPL3,NUP205,RANBP2,NUP37,RPS7,RPS3A,RPLP0,RPL35A,NDC1,RPS28,HSP90AA1,RPL14,NUP50,POLR2E,RPL10,RPL36,POM121C,RPS5,NUP62,RPL37,RPS2,RAE1,RPL9,NUP43,RPL23,RPL24,GRSF1,RPS15A,RPL4,RPS27A,POLR2D,NUP54,RPS14	36	up
inhibition of cysteine-type endopeptidase activity involved in apoptotic process	GO:1990001	endopeptidase activity	4.660E-03	XIAP,BCL2L12,BIRC3,NOL3,BIRC2	5	up
inla-mediated entry of listeria monocytogenes into host cells	REAC:R-HSA-8876493	viral of bacterial infection	4.467E-02	SRC,CTNNB1,UBB,RPS27A,UBC	5	up
inositol lipid-mediated signalling	GO:0048017	lipid metabolism	2.929E-04	EPOR,ERBB2,JAK2,AKT1,EPO,TNF,GAB2,IGF1R,PIK3CB,ERBB3,PIK3CD,NTRK3,EGFR,PIP4K2C,RHOA,ENTPD5,CCL5,IRS1,FGF2,PTEN,VEGFA,RPS6KB1,OGT,INSR,PIK3R1,PLEKHA1,PPP2R5C,KDR,HAX1,MAZ,MAPK3,SRC,PDGFRB,PDGFRA,KCNH1,SIRT1,PIK3CG,BECN1,CSF1R,KIT,PIP5K1C,MAPK1,EDN1,F2RL1,PDGFB,PLCB1,TWIST1	47	up
insulin receptor signalling pathway	GO:0008286	endocrine system	1.403E-02	IGF2,AKT1,SIK2,IGF1R,APC,SOS1,IRS1,PIK3R3,RPS6KB1,OGT,NUCKS1,GRB2,KANK1,PRKCD,INSR,PIK3R1,GSK3B,FOXO3,FOXO1,SIRT1,ATP6V1E1,SLC39A14,ATP6V1C1,ATP6V1B2,GRB10,ATP6V0E1,ZBTB7B,ATP6V0D1,SNX5	29	up
insulin resistance	KEGG:04931	endocrine system	9.550E-03	RPS6KA1,STAT3,AKT1,TNF,PRKAG1,PIK3CB,PIK3CD,PPP1CA,NFKB1,IL6,PRKCE,IRS1,PIK3R3,PTEN,RPS6KB1,OGT,PRKAA1,PRKCD,INSR,PIK3R1,AKT3,GSK3B,MLXIP,RPS6KA3,FOXO1,SLC2A4,GFPT1,PYGB,TNFRSF1A,PPP1CC,PPARA,GFPT2,PPP1R3D,CREB1,G6PC,SOCS3,CD36,SREBF1	38	both
insulin signalling pathway	KEGG:04910	endocrine system	8.747E-05	MKNK2,AKT1,EIF4EBP1,PRKAG1,PIK3CB,EIF4E,EXOC7,RAF1,PIK3CD,PPP1CA,HK2,SOS1,IRS1,KRAS,SOS2,PIK3R3,RPS6KB1,PHKA1,PRKAA1,FASN,PRKAR2A,GRB2,FLOT2,CRKL,INSR,PIK3R1,AKT3,GSK3B,CRK,TRIP10,FOXO1,SLC2A4,MAPK3,SOCS4,MAP2K1,PYGB,PPP1CC,NRAS,PPP1R3D,G6PC,MAPK1,SOCS3,SREBF1	43	up
integrin-mediated signalling pathway	GO:0007229	signalling pathways	4.577E-02	NME2,ABL1,CD40LG,ISG15,ITGBL1,ITGB2,RCC2,ITGA5,NRP1,ITGB8,CUL3,ITGA2,CDC42,PLPP3,ITGB1,ITGA11,SRC,ITGB3,PRKD1,ADAM15,ERBIN,EMP2	22	up
interactions of rev with host cellular proteins	REAC:R-HSA-177243	protein metabolism	2.235E-03	NUP93,NUP205,RANBP2,NUP37,NPM1,NDC1,KPNB1,NUP50,POM121C,RANGAP1,NUP62,RAE1,NUP43,RAN,NUP54	15	up
interactions of vpr with host cellular proteins	REAC:R-HSA-176033	protein metabolism	1.625E-02	NUP93,NUP205,RANBP2,NUP37,HMGA1,NDC1,NUP50,KPNA1,POM121C,NUP62,RAE1,NUP43,NUP54	13	up
interferon signalling	REAC:R-HSA-913531	interferon signalling	2.402E-03	IRF4,JAK2,NUP93,NUP205,RANBP2,NUP37,EIF4E,CD44,NDC1,KPNB1,TRIM22,IFI27,IFIT3,ISG15,IFITM3,IFITM1,STAT1,IRF7,MX2,OASL,RSAD2,IFIT1,ICAM1,HLA-A,KPNA4,HLA-G,HLA-C,TRIM35,ARIH1,PRKCD,NUP50,KPNA1,KPNA3,POM121C,MAPK3,NUP62,IFNB1,PLCG1,EIF4G1,RAE1,NUP43,STAT2,UBB,IRF1,RPS27A,UBC,NUP54,SOCS3,UBA7,B2M,KPNA2,PPM1B	52	up
interferon-α production	GO:0032607	interferon signalling	2.358E-02	HSPD1,STAT1,IRF7,TLR4,DDX3X,CHUK,RIPK2,IL10,TLR3,MAVS	10	up
interferon-β production	GO:0032608	interferon signalling	3.400E-02	TLR2,IRF7,TLR4,DDX3X,REL,POLR3G,YY1,TRAF3,RIPK2,TIRAP,TLR3,MAVS,IRF1,PPM1B	14	up
interleukin-10 production	GO:0032613	interleukin signalling	2.772E-02	IRF4,STAT3,HSPD1,CD40LG,TLR2,ISG15,IL6,TLR4,IL23R,CD274,VSIR,AGER,DLL1,HMGB1,TNFRSF21,F2RL1	16	up
interleukin-10 signalling	REAC:R-HSA-6783783	interleukin signalling	1.395E-02	STAT3,TNF,LIF,PTGS2,CD80,IL6,CCL5,CXCL8,ICAM1,CSF1,CCL4,CXCL2,CCL3,CCL22,TNFRSF1A,IL10	16	up
interleukin-12 family signalling	REAC:R-HSA-447115	interleukin signalling	4.099E-03	STAT3,JAK2,RPLP0,MIF,STAT1,IL23R,PDCD4,PAK2,HNRNPDL,HNRNPA2B1,CDC42,CANX,IL6ST,CFL1,SNRPA1,MTAP,AIP,IL10,ARF1,SOD2	20	up
interleukin-12 production	GO:0032615	interleukin signalling	1.680E-02	MAPK14,HSPD1,CD40LG,TLR2,TLR4,IL23R,HLA-G,AGER,CD40,HMGB1,RIPK2,IL10,TIRAP,TLR3,PLCB1,THBS1	16	up
interleukin-12 signalling	REAC:R-HSA-9020591	interleukin signalling	2.951E-02	JAK2,RPLP0,MIF,PDCD4,PAK2,HNRNPDL,HNRNPA2B1,CDC42,CFL1,SNRPA1,MTAP,AIP,IL10,ARF1,SOD2	15	up
interleukin-12-mediated signalling pathway	GO:0035722	interleukin signalling	8.998E-03	JAK2,RPLP0,MIF,PDCD4,PAK2,HNRNPDL,HNRNPA2B1,CDC42,CFL1,SNRPA1,MTAP,AIP,IL10,ARF1,SOD2,PLCB1	16	up
interleukin-15 signalling	REAC:R-HSA-8983432	interleukin signalling	2.644E-02	STAT3,GAB2,SOS1,SOS2,GRB2,STAT5A,IL15	7	up
interleukin-17 signalling	REAC:R-HSA-448424	interleukin signalling	1.219E-05	RPS6KA1,PPP2CA,DUSP6,MAPK14,FOS,IRAK2,TRAF6,NFKB1,IRAK1,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,TAB3,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	30	up
interleukin-2 family signalling	REAC:R-HSA-451927	interleukin signalling	4.997E-02	STAT3,JAK2,GAB2,PIK3CB,PIK3CD,STAT1,SOS1,SOS2,PIK3R3,GRB2,PIK3R1,STAT5A,IL21R,IL15	14	up
interleukin-4 and interleukin-13 signalling	REAC:R-HSA-6785807	interleukin signalling	4.247E-04	MYC,TWIST1,RORA,VIM,FOXO1,CCND1,LCN2,HIF1A,AKT1,MMP3,HSP90B1,CCL22,IL1A,VCAM1,BCL2,COL1A2,MCL1,FOS,ITGB1,MMP2,FSCN1,VEGFA,SOCS5,STAT3,SOX2,HSPA8,FOXO3,IL4,SOCS3,CDKN1A,ICAM1,TP53,BIRC5	33	both
interleukin-6 family signalling	REAC:R-HSA-6783589	interleukin signalling	2.275E-02	LIFR,STAT3,JAK2,IL6R,LIF,STAT1,IL6,IL6ST,OSMR,SOCS3	10	up
interleukin-6 signalling	REAC:R-HSA-1059683	interleukin signalling	6.225E-03	STAT3,JAK2,IL6R,STAT1,IL6,IL6ST,SOCS3	7	up
interleukin-6-mediated signalling pathway	GO:0070102	interleukin signalling	2.233E-02	STAT3,CEBPA,JAK2,IL6R,SMAD4,STAT1,IL6,YAP1,IL6ST,SPI1,SRC,SOCS3	12	up
interleukin-8 production	GO:0032637	interleukin signalling	4.391E-02	STAT3,BCL3,TNF,IL6R,CD244,TLR2,FADD,IL6,TLR4,KLF4,F3,ANXA4,AFAP1L2,HMGB1,NOD1,IL10,BCL10,LILRA2,TIRAP,OTUD7B,TLR3,MAVS,F2RL1,PRKD2,RAB1A	25	up
intra-golgi and retrograde golgi-to-er traffic	REAC:R-HSA-6811442	protein metabolism	8.165E-03	ARF3,KLC2,VPS51,GOLGA1,COPZ1,KIF22,RHOBTB3,MAN1C1,COPA,STX16,KIF2C,STX6,RAB1B,NAPG,PAFAH1B1,KIF5B,COPB1,GALNT1,DCTN5,KIF23,ARCN1,KIF21A,RACGAP1,KIF3B,GOSR1,PAFAH1B2,DYNLL2,TUBB2A,CAPZA2,KIF11,CYTH1,VPS45,KLC1,CAPZB,PLIN3,KIF4A,RAB3GAP2,RGP1,SURF4,CYTH3,KIF2A,ARF1,DYNC1LI2,TMF1,CYTH2,IGF2R,KDELR1,RAB18,RAB6A,NAA30,RAB1A,ACTR1A	52	up
intracellular receptor signalling pathway	GO:0030522	signalling pathways	2.319E-05	CBFB,VDR,STAT3,NCOR2,XIAP,TNFAIP3,MED1,STRN3,KMT2D,CYP24A1,IRAK2,TRAF6,IRAK1,SFRP1,RARB,IRF7,BRCA1,CLOCK,UBE2V1,CARM1,PAGR1,ZCCHC3,CYLD,TAB3,HEYL,USP15,YWHAH,CYP26B1,ASXL1,MAP3K7,PIM1,YAP1,HDAC1,BIRC3,SRC,SIRT1,AR,PUM2,PER1,SMARCA4,RIPK2,NOD1,CASP8,BIRC2,CNOT2,RBFOX2,TMF1,PMEPA1,UBB,CNOT1,ZBTB7A,DCBLD2,RNF125,RPS27A,UBC,THRA,ERBIN,ESR1,ARID1A,TAB2	60	both

intracellular signalling by second messengers	REAC:R-HSA-9006925	signalling pathways	1.214E-03	TP53,XIAP,ERBB2,AKT1,PPP2CA,REST,PIK3CB,PSMB1,PIK3CD,TNRC6B,EGFR,PIP4K2C,CSNK2A1,TRAF6,CDKN1A,IRAK1,CD80,MTA2,PRKCE,AGO3,IRS1,FGF2,TNRC6A,CDKN1B,AGO2,PIK3R3,TGFA,PTEN,RCOR1,PRKAR2A,AGO1,CBX2,AGO4,CHUK,PRKCD,CBX4,GATAD2A,ITPR1,FGFR4,INSR,PIK3R1,PHC3,AKT3,PHLPP2,PPP2R5C,CBX6,GSK3B,PSMB5,FOXO3,FOXO1,MDM2,MET,HDAC1,MOV10,MAPK3,SRC,PDGFRB,PDGFRA,KLB,RRAGD,RRAGA,PLCG1,CASP9,RICTOR,SNAI1,KIT,AREG,CREB1,GATAD2B,PIP5K1C,SLC38A9,UBB,USP13,MAPK1,RPS27A,UBC,OTUD3,EREG,ESR1,PDGFB,AKT1S1,FRK,FRS2,KPNA2,PHLPP1	85	both
intracellular steroid hormone receptor signalling pathway	GO:0030518	signalling pathways	2.017E-02	CBFB,NCOR2,MED1,STRN3,KMT2D,SFRP1,BRCA1,CLOCK,CARM1,PAGR1,HEYL,YWHAH,YAP1,HDAC1,SRC,SIRT1,AR,PER1,SMARCA4,CNOT2,RBFOX2,TMF1,PMEPA1,CNOT1,ZBTB7A,ESR1,ARID1A	27	up
intracellular transport of virus	GO:0075733	viral of bacterial infection	1.162E-04	NUP93,NUP205,RANBP2,NUP37,NDC1,KPNB1,VPS37B,VPS37A,NUP50,KPNA1,POM121C,VPS37D,NUP62,NUP98,RAE1,NUP43,UBB,RPS27A,UBC,RAN,NUP54,KPNA2	22	both
intrinsic apoptotic signalling pathway	GO:0097193	apoptosis	2.049E-10	PMAIP1,BMF,BCL3,TP53,S100A8,BBC3,AKT1,EPO,BCL2,ZNF385A,CDKN2D,BAK1,RPS7,TNFRSF10B,PIK3CB,CD44,MCL1,DYRK2,ABL1,MUC1,MIF,CDKN1A,BCL2A1,BRCA1,BCLAF1,CXCL12,PLAUR,TMEM109,ZNF622,BCL2L11,DDX3X,CHAC1,CUL3,DNAJA1,PRKCD,CUL2,ITPR1,CYLD,CLU,PPP2R5C,HYOU1,DNAJC10,FBXW7,MDM2,E2F1,ATM,SFN,SRC,SIRT1,CEBPB,MAGEA3,DIABLO,BNIP3,CASP9,BAG6,CD24,TP73,AIFM1,TRAF2,SNAI1,BECN1,BAX,EPHA2,NOL3,CIDEB,MOAP1,BCL2L1,APAF1,TP53BP2,USP28,AEN,DDIT4,UBB,CHEK2,JMY,NACC2,SOD2,HIPK1	78	up
intrinsic apoptotic signalling pathway by p53 class mediator	GO:0072332	apoptosis	8.944E-05	PMAIP1,BCL3,TP53,BCL2,ZNF385A,RPS7,CD44,DYRK2,MUC1,MIF,TMEM109,PPP2R5C,MDM2,SIRT1,BAG6,TP73,TP53BP2,USP28,AEN,DDIT4,UBB,JMY,HIPK1	23	up
intrinsic apoptotic signalling pathway in response to dna damage	GO:0008630	apoptosis	3.912E-10	BCL3,TP53,BCL2,ZNF385A,CDKN2D,BAK1,CD44,MCL1,DYRK2,ABL1,MUC1,MIF,BCL2A1,BRCA1,CXCL12,TMEM109,BCL2L11,CLU,PPP2R5C,E2F1,ATM,SFN,SIRT1,CASP9,BAG6,TP73,SNAI1,BAX,EPHA2,CIDEB,MOAP1,BCL2L1,USP28,AEN,DDIT4,CHEK2,NACC2,HIPK1	38	up
intrinsic apoptotic signalling pathway in response to dna damage by p53 class mediator	GO:0042771	apoptosis	6.041E-05	BCL3,TP53,BCL2,ZNF385A,CD44,DYRK2,MUC1,MIF,TMEM109,PPP2R5C,SIRT1,BAG6,TP73,USP28,AEN,DDIT4,HIPK1	17	up
intrinsic apoptotic signalling pathway in response to endoplasmic reticulum stress	GO:0070059	apoptosis	1.680E-02	PMAIP1,BBC3,BCL2,BAK1,TNFRSF10B,BCL2L11,CHAC1,ITPR1,DNAJC10,CEBPB,MAGEA3,BAG6,AIFM1,TRAF2,BAX,BCL2L1	16	up
intrinsic apoptotic signalling pathway in response to hypoxia	GO:1990144	apoptosis	3.967E-02	PIK3CB,HYOU1,BNIP3,NOL3	4	up
intrinsic pathway for apoptosis	REAC:R-HSA-109606	apoptosis	8.819E-11	MAPK1,TP63,XIAP,BID,YWHAG,CASP3,PPP1R13B,AKT1,PMAIP1,BCL2,BBC3,AKT2,AKT3,CASP8,STAT3,PPP3R1,BCL2L11,TP53,CYCS,TFDP2,YWHAE,YWHAB,CARD8	23	both
irak1 recruits ikk complex	REAC:R-HSA-937039	signalling pathways	2.644E-02	TRAF6,IRAK1,UBE2V1,CHUK,UBB,RPS27A,UBC	7	up
irak1 recruits ikk complex upon tlr7/8 or 9 stimulation	REAC:R-HSA-975144	TLR signalling	2.644E-02	TRAF6,IRAK1,UBE2V1,CHUK,UBB,RPS27A,UBC	7	up
irak2 mediated activation of tak1 complex	REAC:R-HSA-937042	signalling pathways	3.898E-04	IRAK2,TRAF6,TAB3,MAP3K7,UBB,RPS27A,UBC,TAB2	8	up
irak2 mediated activation of tak1 complex upon tlr7/8 or 9 stimulation	REAC:R-HSA-975163	TLR signalling	2.428E-03	IRAK2,TRAF6,TLR4,TAB3,MAP3K7,UBB,RPS27A,UBC,TAB2	9	up
ire1-mediated unfolded protein response	GO:0036498	protein metabolism	1.335E-02	BBC3,EXTL3,EDEM1,BAK1,HDGF,SRPRB,SRPRA,BCL2L11,HYOU1,PDIA6,GFPT1,TATDN2,BAX,BFAR,FICD,DNAJB9,TMEM33,ATP6V0D1,TPP1,KLHDC3	20	up
isg15 antiviral mechanism	REAC:R-HSA-1169408	viral of bacterial infection	1.219E-05	NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,KPNB1,ISG15,STAT1,MX2,IFIT1,KPNA4,ARIH1,NUP50,KPNA1,KPNA3,POM121C,MAPK3,NUP62,PLCG1,EIF4G1,RAE1,NUP43,UBB,RPS27A,UBC,NUP54,UBA7,KPNA2,PPM1B	30	up
jak-stat signalling pathway	KEGG:04630	signalling pathways	8.928E-05	LIFR,STAT3,EPOR,JAK2,AKT1,EPO,BCL2,CREBBP,IL6R,PIK3CB,PIAS3,LIF,RAF1,PIK3CD,MCL1,EGFR,CDKN1A,STAT1,IL6,CCND1,CCND2,SOS1,IL23R,SOS2,PIK3R3,CCND3,GRB2,PIK3R1,AKT3,SOCS5,PIM1,IL6ST,STAT5A,MYC,PDGFRB,PDGFRA,IFNLR1,SOCS4,IFNB1,STAM2,IL10,BCL2L1,OSMR,STAT2,SOCS3,PDGFB,SOCS7,IL21R,IL15	49	up
jnk (c-jun kinases) phosphorylation and activation mediated by activated human tak1	REAC:R-HSA-450321	phosphorylation	1.959E-04	IRAK2,TRAF6,IRAK1,UBE2V1,TAB3,MAP3K7,RIPK2,NOD1,MAP2K4,UBB,RPS27A,UBC,TAB2	13	up
jnk cascade	GO:0007254	signalling pathways	4.017E-05	MAP3K2,ZMYND11,MAP3K11,IGF1R,RASGRP1,MFHAS1,EGFR,CD40LG,IRAK2,TRAF6,IRAK1,MAP3K9,PDCD4,TAOK1,PAFAH1B1,UBE2V1,WNT7A,ZNF622,DNAJA1,AGER,CRKL,CYLD,TAB3,MINK1,APP,MAP4K2,MAP3K7,RASSF2,SEMA3A,RAP2A,TRAF3,PER1,HMGB1,GADD45A,TRAF2,RIPK2,NOD1,LTBR,CD27,TIRAP,MAP2K4,UBB,FKTN,RPS27A,UBC,F2RL1,PLCB1,TAB2,PHLPP1	49	up
kaposi sarcoma-associated herpesvirus infection	KEGG:05167	viral of bacterial infection	2.299E-14	MYC,MICB,CDK6,MAPK1,MAPK14,BECN1,CCR4,TRAF3,EP300,MAP2K2,NFATC2,BID,PIK3C3,CCND1,CASP3,HIF1A,NFKB1,AKT1,MAP2K7,KRAS,GNB4,FOS,JUN,AKT2,AKT3,VEGFA,CASP8,STAT3,PPP3R1,ITPR1,CALML4,CTNNB1,CDKN1A,ICAM1,TP53,IKBKG,EIF2AK2,MICA,STAT2,CYCS,C3,GSK3B,CREBBP,E2F3	44	both
kidney development	GO:0001822	organogenesis	3.554E-02	ANGPT2,SIX1,ENPEP,IL6R,SMO,PODXL,LIF,FGFR2,STAT1,FGF2,VEGFA,TFAP2A,FLCN,SEC61A1,ZBTB16,RET,SALL1,MEF2C,MYC,JAG1,DLL1,PDGFRB,PDGFRA,CTNNB1,BAG6,CD24,BMP7,AGTR1,SOX4,HOXD11,AHI1,PDGFB,HAS2,MTSS1	34	up
l1cam interactions	REAC:R-HSA-373760	cell adhesion and migration	1.369E-03	RPS6KA1,LYPLA2,EGFR,CSNK2A1,NUMB,L1CAM,ITGA5,NRP1,ALCAM,RPS6KA4,AP2B1,VAV2,HSPA8,SPTBN1,ITGA2,LAMC1,TUBB2A,RPS6KA3,ITGB1,AP2A1,ACTG1,MAPK3,KIF4A,AP2M1,SPTAN1,MAP2K1,AP2A2,ITGB3,ANK3,CD24,GAP43,CLTA,MAPK1,DPYSL2,RPS6KA5,ACTB,ITGA1	37	up
lamellipodium assembly	GO:0030032	cytoskeleton	3.408E-02	VCL,WASF2,ABLIM1,WNT1,ACTR2,PIK3R1,NCKAP1,CDC42,TWF1,ITGB1,CAPZB,EPHA2,KIT,S1PR1,FSCN1,SPATA13,AKIRIN1	17	up
lamellipodium organisation	GO:0097581	cell organisation	3.381E-03	VCL,CD44,WASF2,ABLIM1,WNT1,ACTR2,KANK1,PIK3R1,NCKAP1,CDC42,TWF1,ITGB1,CORO1B,SRC,CAPZB,EPHA2,KIT,CTTN,S1PR1,PDPN,FSCN1,SPATA13,AKIRIN1	23	up
late endosomal microautophagy	REAC:R-HSA-9615710	autophagy	1.625E-02	CHMP3,VPS37B,VPS37A,CHMP4B,HSPA8,CFTR,CHMP2B,PLIN3,VPS37D,UBB,RPS27A,UBC,PCNT	13	up
late phase of hiv life cycle	REAC:R-HSA-162599	viral of bacterial infection	9.340E-04	VPS4B,CHMP3,NUP93,NUP205,RANBP2,NUP37,TAF15,NDC1,FURIN,VPS37B,VPS37A,SUPT16H,CHMP4B,CCNT1,SSRP1,VPS4A,TAF13,CCNT2,NUP50,POLR2E,RNMT,POM121C,RANGAP1,CHMP2B,NELFCD,SUPT5H,VPS37D,NUP62,NCBP2,RAE1,ELOA,GTF2A1,NUP43,GTF2E1,UBB,RPS27A,UBC,RAN,POLR2D,NUP54,ELL	41	up
legionellosis	KEGG:05134	viral of bacterial infection	2.654E-06	BCL2L13,EEF1A1,TNF,HBS1L,HSPD1,NFKB1,TLR2,IL6,ITGB2,CXCL8,TLR4,CASP7,RAB1B,HSPA8,CXCL2,CASP3,NAIP,BNIP3,CASP1,CASP9,CYCS,SAR1A,CASP8,APAF1,ARF1,RAB1A	26	up
leishmaniasis	KEGG:05140	viral of bacterial infection	2.339E-02	JAK2,EEF1A1,TNF,MAPK14,FOS,TRAF6,NFKB1,TLR2,IRAK1,PTGS2,STAT1,TGFB1,ITGB2,TLR4,MAP3K7,ITGB1,MAPK3,IL10,CYBB,MAPK1,TAB2	21	up
leukocyte adhesion to arterial endothelial cell	GO:0061757	cell adhesion and migration	1.166E-02	TNF,ALOX5,KLF4,ZDHHC21,SLC39A8	5	up

leukocyte adhesion to vascular endothelial cell	GO:0061756	cell adhesion and migration	4.182E-02	ETS1,TNF,ALOX5,RHOA,ROCK1,TRAF6,NFAT5,IRAK1,IL6,ITGB2,CXCL12,KLF4,ITGB1,ZDHHC21,SLC39A8	15	up
leukocyte apoptotic process	GO:0071887	apoptosis	2.637E-04	CDKN2A,TP53,BBC3,AKT1,AURKB,PIK3CB,Fas,PIK3CD,FADD,IRF7,IL6,CCL5,CXCL12,ADAM17,CD274,PDCD1,MEF2C,SIRT1,AXL,TNFRSF21,BAX,FASLG,IL10,BCL10,FNIP1	25	up
leukocyte cell-cell adhesion	GO:0007159	cell adhesion and migration	3.345E-06	ETS1,CDKN2A,SLC7A1,CBFB,IGF2,S100A8,AKT1,TNF,WNK1,CD44,ALOX5,HSPD1,RHOA,CD40LG,ROCK1,TRAF6,NFAT5,FADD,IRAK1,GRAP2,CD80,BTN2A2,IL6,CCL5,ITGB2,CXCL12,ICAM1,IL23R,HLA-A,HLA-G,CD274,KLF4,VSIR,PDCD1,TNFSF9,PAG1,GRB2,PAK2,FLOT2,AGER,PIK3R1,MYB,SMAD7,CDC42,SOCS5,IL6ST,NLRP3,ITGB1,LEF1,ZAP70,SRC,TGFBR2,CEBPB,TFRC,IFNB1,NT5E,HMGB1,CD24,BMP7,TNFRSF21,PLA2G2D,IL10,CD70,PPARA,SOX4,LAX1,ZDHHC21,F11R,TNFRSF13C,NKAP,DLG5,PRNP,CERCAM,IRF1,ZBTB7B,RHOH,SLC39A8,HAS2,SDC4,PAK3,IL15	81	up
leukocyte differentiation	GO:0002521	cell differentiation	1.259E-08	CDKN2A,CBFB,IRF4,STAT3,CEBPA,IKZF3,TNF,GAB2,MAPK14,PRDM1,LIF,PIK3CD,FES,CEBPG,ABL1,FBN1,PARP1,TRAF6,TLR2,FADD,CD80,BGLAP,LFNG,SFRP1,IRF7,LBR,IL6,RSAD2,TLR4,NOTCH2,IL23R,CSF1,MAFB,HLA-G,ADAM17,SH3PXD2A,KLF6,VEGFA,PAFAH1B1,CDK6,VSIR,PTPRJ,DOCK11,TNFSF9,AGER,CBFA2T3,MYB,SMAD7,APP,CDC42,TCF3,POU2AF1,SOCS5,OSCAR,HAX1,FBXW7,NLRP3,ITGB1,TAL1,CCL3,TOX,ATM,MYC,DLL1,TPD52,LEF1,ZAP70,SRC,SIRT1,TGFBR2,CEBPB,RRAS,IFNB1,AXL,HMGB1,EPHA2,CSF1R,KIT,TREM2,IL10,ADGRG3,CASP8,CD27,TCF7,SOX4,FNIP1,DNAJB9,TLR3,NKAP,RAG1,ZBTB7A,CHD7,IRF1,ZBTB7B,CCR6,F2RL1,RHOH,UBASH3B,SIGLEC15,ATP7A,IL15	101	up
leukocyte homeostasis	GO:0001776	leukocyte activation	3.466E-03	PMAIP1,AKT1,TNFAIP3,PIK3CB,Fas,PIK3CD,FADD,IL6,ADAM17,DOCK11,MEF2C,HMGB1,BCL10,SH2B3	14	up
leukocyte proliferation	GO:0070661	cell proliferation	1.022E-03	CDKN2A,CD320,SLC7A1,IGF2,IKZF3,TNFAIP3,BCL2,RASGRP1,HSPD1,CD40LG,MIF,FADD,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,CSF1,HLA-G,CD274,VSIR,TNFSF9,AGER,CLU,TCF3,CD180,IL6ST,MEF2C,ATM,VAV3,MAPK3,TGFBR2,CEBPB,CD40,TFRC,IFNB1,PIK3CG,HMGB1,CD24,TNFRSF21,PLA2G2D,CSF1R,KIT,IL10,CD70,TIRAP,TNFRSF13C,SOX11,DLG5,PRNP,MAPK1,IRF1,ZBTB7B,F2RL1,SDC4,IL15	57	up
limb development	GO:0060173	organogenesis	6.521E-03	BMPR1B,CREBBP,FGFR2,DKK1,SKI,WNT7A,TFAP2A,CYP26B1,SALL1,ZNRF3,HDAC1,ITGA6,LNPK,CTNNB1,SOX4,SOX11,CHD7,SMOC1,MBNL1,KREMEN1,ECE1,TWIST1	22	up
limb morphogenesis	GO:0035108	organogenesis	3.073E-02	BMPR1B,CREBBP,FGFR2,SKI,WNT7A,TFAP2A,CYP26B1,SALL1,HDAC1,CTNNB1,SOX4,SOX11,MBNL1,ECE1,TWIST1	15	up
lipid phosphorylation	GO:0046834	lipid metabolism	3.073E-02	IP6K1,PIK3CB,PIK3CD,PIK3R3,PI4K2B,PIK3R1,SOCS5,SOCS4,PIK3CG,DGKZ,SOCS3,SMG1,SOCS7,DGKB,DGKI	15	up
lipopolysaccharide-mediated signalling pathway	GO:0031663	signalling pathways	4.419E-02	TNFAIP3,TNF,IRAK1,CCL5,PRKCE,TLR4,CD180,CCL3,MTDH,BCL10,LILRA2,SASH1,CD36	13	up
longevity regulating pathway	KEGG:04211	senescence	1.151E-02	EHMT1,TP53,AKT1,EIF4EBP1,PRKAG1,IGF1R,PIK3CB,EIF4E,PIK3CD,NFKB1,IRS1,KRAS,PIK3R3,SESN3,RPS6KB1,PRKAA1,INSR,PIK3R1,AKT3,FOXO3,FOXO1,SIRT1,ATG5,SESN2,BAX,NRAS,CREB1,AKT1S1,SOD2,SESN1	30	both
longevity regulating pathway - multiple species	KEGG:04213	senescence	3.424E-04	AKT1,PRKAG1,IGF1R,PIK3CB,PIK3CD,IRS1,KRAS,PIK3R3,RPS6KB1,PRKAA1,HSPA8,INSR,PIK3R1,AKT3,FOXO3,FOXO1,HDAC1,SIRT1,ATG5,NRAS,EIF4EBP2,AKT1S1,SOD2	23	up
low-density lipoprotein receptor particle metabolic process	GO:0032799	metabolic process	1.881E-02	FURIN,AP2B1,AP2A1,AP2M1,AP2A2,MYLIP,CLTA	7	up
lymphocyte apoptotic process	GO:0070227	apoptosis	1.489E-02	TP53,BBC3,AKT1,AURKB,Fas,FADD,CCL5,CD274,PDCD1,TNFRSF21,BAX,FASLG,IL10,BCL10,FNIP1	15	up
lymphocyte differentiation	GO:0030098	cell differentiation	2.779E-03	CDKN2A,CBFB,IRF4,STAT3,IKZF3,PRDM1,PIK3CD,CEBPG,ABL1,FADD,CD80,LFNG,SFRP1,IL6,RSAD2,NOTCH2,IL23R,HLA-G,ADAM17,KLF6,VSIR,PTPRJ,DOCK11,TNFSF9,MYB,SMAD7,TCF3,POU2AF1,SOCS5,NLRP3,ITGB1,TOX,ATM,DLL1,TPD52,LEF1,ZAP70,TGFBR2,IFNB1,AXL,HMGB1,KIT,IL10,ADGRG3,CD27,TCF7,SOX4,FNIP1,DNAJB9,NKAP,RAG1,ZBTB7A,CHD7,IRF1,ZBTB7B,CCR6,RHOH,ATP7A	58	up
lymphocyte proliferation	GO:0046651	cell proliferation	6.513E-03	CDKN2A,CD320,SLC7A1,IGF2,IKZF3,BCL2,RASGRP1,HSPD1,CD40LG,MIF,FADD,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,HLA-G,CD274,VSIR,TNFSF9,AGER,TCF3,CD180,IL6ST,MEF2C,ATM,VAV3,TGFBR2,CEBPB,CD40,TFRC,IFNB1,PIK3CG,HMGB1,CD24,TNFRSF21,PLA2G2D,IL10,CD70,TIRAP,TNFRSF13C,SOX11,DLG5,PRNP,IRF1,ZBTB7B,SDC4,IL15	49	up
macroautophagy	REAC:R-HSA-1632852	autophagy	3.267E-06	VPS4B,TP53INP1,CHMP3,AKT1,ZFYVE1,MTMR3,PRKAG1,VDAC1,HUWE1,EXOC7,YOD1,PIP4K2C,CSNK2A1,SQSTM1,ATG9A,PACS2,VPS37B,ATG14,RAB1B,SESN3,VPS37A,RUBCN,CHMP4B,GABARAPL1,STX17,LAMP2,RAB23,PRKAA1,VPS4A,TBC1D14,WIPI2,GABARAP,PAFAH1B2,DYNLL2,C6orf106,KDR,SMURF1,SPTLC1,MAP3K7,LGALS8,CHMP2B,SUPT5H,SRC,CASP3,SIRT1,VPS37D,ATP6V1E1,RAB3GAP2,LARP1,ATG5,UBQLN2,RRAGD,RRAGA,MFN2,ATG4B,BNIP3,STAM2,RALB,BECN1,SESN2,TOMM40,ATG7,BAG3,CAPN1,UBXN2B,CDK5R1,WDR81,ATP6V1C1,SLC38A9,ATP6V1B2,ATP6V0E1,QSOX1,ATP6V0D1,SNX5,SMG1,SESN1,RAB1A	77	both
macroautophagy	REAC:R-HSA-1632852	autophagy	3.267E-06	VPS4B,TP53INP1,CHMP3,AKT1,ZFYVE1,MTMR3,PRKAG1,VDAC1,HUWE1,EXOC7,YOD1,PIP4K2C,CSNK2A1,SQSTM1,ATG9A,PACS2,VPS37B,ATG14,RAB1B,SESN3,VPS37A,RUBCN,CHMP4B,GABARAPL1,STX17,LAMP2,RAB23,PRKAA1,VPS4A,TBC1D14,WIPI2,GABARAP,PAFAH1B2,DYNLL2,C6orf106,KDR,SMURF1,SPTLC1,MAP3K7,LGALS8,CHMP2B,SUPT5H,SRC,CASP3,SIRT1,VPS37D,ATP6V1E1,RAB3GAP2,LARP1,ATG5,UBQLN2,RRAGD,RRAGA,MFN2,ATG4B,BNIP3,STAM2,RALB,BECN1,SESN2,TOMM40,ATG7,BAG3,CAPN1,UBXN2B,CDK5R1,WDR81,ATP6V1C1,SLC38A9,ATP6V1B2,ATP6V0E1,QSOX1,ATP6V0D1,SNX5,SMG1,SESN1,RAB1A	77	both
macroautophagy	GO:0016236	autophagy	3.267E-06	VPS4B,TP53INP1,CHMP3,AKT1,ZFYVE1,MTMR3,PRKAG1,VDAC1,HUWE1,EXOC7,YOD1,PIP4K2C,CSNK2A1,SQSTM1,ATG9A,PACS2,VPS37B,ATG14,RAB1B,SESN3,VPS37A,RUBCN,CHMP4B,GABARAPL1,STX17,LAMP2,RAB23,PRKAA1,VPS4A,TBC1D14,WIPI2,GABARAP,PAFAH1B2,DYNLL2,C6orf106,KDR,SMURF1,SPTLC1,MAP3K7,LGALS8,CHMP2B,SUPT5H,SRC,CASP3,SIRT1,VPS37D,ATP6V1E1,RAB3GAP2,LARP1,ATG5,UBQLN2,RRAGD,RRAGA,MFN2,ATG4B,BNIP3,STAM2,RALB,BECN1,SESN2,TOMM40,ATG7,BAG3,CAPN1,UBXN2B,CDK5R1,WDR81,ATP6V1C1,SLC38A9,ATP6V1B2,ATP6V0E1,QSOX1,ATP6V0D1,SNX5,SMG1,SESN1,RAB1A	77	both
macroautophagy	GO:0016236	autophagy	3.267E-06	VPS4B,TP53INP1,CHMP3,AKT1,ZFYVE1,MTMR3,PRKAG1,VDAC1,HUWE1,EXOC7,YOD1,PIP4K2C,CSNK2A1,SQSTM1,ATG9A,PACS2,VPS37B,ATG14,RAB1B,SESN3,VPS37A,RUBCN,CHMP4B,GABARAPL1,STX17,LAMP2,RAB23,PRKAA1,VPS4A,TBC1D14,WIPI2,GABARAP,PAFAH1B2,DYNLL2,C6orf106,KDR,SMURF1,SPTLC1,MAP3K7,LGALS8,CHMP2B,SUPT5H,SRC,CASP3,SIRT1,VPS37D,ATP6V1E1,RAB3GAP2,LARP1,ATG5,UBQLN2,RRAGD,RRAGA,MFN2,ATG4B,BNIP3,STAM2,RALB,BECN1,SESN2,TOMM40,ATG7,BAG3,CAPN1,UBXN2B,CDK5R1,WDR81,ATP6V1C1,SLC38A9,ATP6V1B2,ATP6V0E1,QSOX1,ATP6V0D1,SNX5,SMG1,SESN1,RAB1A	77	both
macromolecule deacylation	GO:0098732	protein metabolism	1.797E-02	SIRT7,LYPLA2,REST,AKAP8,MTA2,VEGFA,SPRED1,BAZ2A,PRKAA1,RCOR1,ELK4,SIRT4,TBL1XR1,HDAC1,SIRT1,TPPP,PER1,PRKD1,SIRT6,PER2,ZBTB7B,DYRK1A,PRKD2,BRMS1L,LYPLAL1	25	up
macrophage differentiation	GO:0030225	cell differentiation	1.383E-02	LIF,PARP1,TLR2,FADD,CSF1,VEGFA,APP,CDC42,SIRT1,CSF1R,CASP8,IL15	12	up
maintenance of blood-brain barrier	GO:0035633	blood brain barrier	1.789E-02	VCL,CDH5,CLDN12,IL6,VEGFA,WNK3,LAMC1,ITGB1,ACTG1,TJP2,F11R,ACTB	12	up
maintenance of cell number	GO:0098727	cell proliferation	1.423E-03	STAT3,LIN28A,REST,SMAD4,HMGA2,CDC73,SMAD2,NOTCH2,ELAVL1,NOTCH1,SOX2,FGF2,KLF4,SKI,POLR2E,SALL1,MYC,JAG1,DLL1,CTNNB1,NANOG,POU5F1,KIT,CNOT2,CNOT1,POLR2D,TET1,PIWIL2	28	both

malaria	KEGG:05144	viral of bacterial infection	3.536E-02	TNF,CD40LG,TLR2,TGFB1,IL6,ITGB2,CXCL8,TLR4,ICAM1,MET,CD40,IL10,CD36,THBS1,SDC2	15	up
mammary gland epithelium development	GO:0061180	organogenesis	3.844E-02	JAK2,AKT1,FGFR2,ERBB4,BRCA2,ROBO1,RTN4,EPHA2,CSF1R,ZNF703	10	up
map3k8 (tpl2)-dependent mapk1/3 activation	REAC:R-HSA-5684264	MAPK signalling	1.599E-02	NFKB1,BTRC,CHUK,MAP2K1,MAP2K4,UBB,RPS27A,UBC	8	up
mapk family signalling cascades	REAC:R-HSA-5683057	MAPK signalling	3.680E-03	VCL,ERBB2,JAK2,PPP2CA,DUSP6,IL6R,MAP3K11,RASAL2,PSMB1,RAF1,RASGRP1,TNRC6B,EGFR,DUSP1,IL6,SOS1,AGO3,IRS1,FGF2,TNRC6A,AGO2,TGFA,YWHAB,CCND3,SPRED1,AGO1,PAK2,CUL3,AGO4,SPTBN1,CDK1,FGFR4,CDC42,PPP2R5C,RET,PSMB5,FOXO3,ARTN,FOXO1,MYC,MET,ACTG1,PEA15,MOV10,MAPK3,SRC,PDGFRB,PDGFRA,KLB,SPTAN1,MAP2K1,SEPT7,ITGB3,KIT,AREG,GFRA3,DUSP5,NRAS,MAPKAPK5,RAG1,UBB,MAPK1,RPS27A,UBC,EREG,PDGFB,FRS2,ACTB,PAK3	69	up
mapk signalling pathway	KEGG:04010	MAPK signalling	3.362E-05	MYC,DUSP9,PAK2,MAPK1,MAPK14,CACNG1,MAP3K13,DUSP1,DUSP10,MAP2K2,IGF1,RPS6KA5,TAOK3,MAP3K2,PDGFRA,TAOK1,RPS6KA6,CASP3,MAP3K11,NFKB1,AKT1,IGF1R,FGF19,MAP2K7,TGFBR1,TGFBR2,KIT,KRAS,DUSP5,ELK4,ARRB2,IL1A,RAP1B,RPS6KA3,NLK,MAP3K3,EREG,CDC42,FOS,DUSP2,PDGFRB,JUN,AKT2,AKT3,VEGFA,STMN1,MAP3K1,PPP3R1,HSPA8,MET,CRKL,GADD45A,IRAK4,CRK,CACNA1A,NF1,MAP3K8,TP53,IKBKG,PLA2G4A,SRF,EGF,CACNG8,MAPKAPK5,ANGPT4,RRAS,TAOK2,MKNK2,JUND	69	both
mapk targets/ nuclear events mediated by map kinases	REAC:R-HSA-450282	MAPK signalling	1.999E-02	RPS6KA1,PPP2CA,DUSP6,MAPK14,FOS,MAPKAPK2,RPS6KA3,MEF2C,MAPK3,CREB1,MAPK1,RPS6KA5	12	up
mapk3 (erk1) activation	REAC:R-HSA-110056	MAPK signalling	9.795E-03	JAK2,IL6R,IL6,CDK1,MAPK3,MAP2K1	6	up
maternal process involved in female pregnancy	GO:0060135	endocrine system	1.881E-02	VDR,STOX2,SPP1,PPARD,APOL2,TCF23,GHSR	7	up
measles	KEGG:05162	viral of bacterial infection	1.405E-08	STAT3,TP53,BBC3,AKT1,TNFAIP3,CCNE1,BCL2,BAK1,PIK3CB,Fas,PIK3CD,CSNK2A1,FOS,TRAF6,NFKB1,TLR2,FADD,IRAK1,STAT1,IRF7,MX2,IL6,CCND1,TLR4,CCND2,CDKN1B,PIK3R3,CDK4,CCND3,CDK6,CHUK,HSPA8,PIK3R1,AKT3,CCNE2,GSK3B,MAP3K7,CDK2,STAT5A,CASP3,IFNB1,TRAF3,CASP9,CYCS,TP73,BAX,FASLG,CASP8,BCL2L1,APAF1,STAT2,MAVS,TAB2	53	both
mecp2 regulates neuronal receptors and channels	REAC:R-HSA-9022699	neuronal architecture	1.599E-02	GRIN2A,GPRIN1,SLC2A3,MET,HDAC1,CREB1,PTPN4,TRPC3	8	up
melanoma	KEGG:05218	cancer	4.920E-04	CDK6,MAPK1,CDH1,MAP2K2,IGF1,PDGFRA,CCND1,AKT1,IGF1R,FGF19,PTEN,KRAS,PDGFRB,MDM2,AKT2,AKT3,MITF,MET,GADD45A,CDKN1A,TP53,EGF,E2F3	23	both
mesenchymal cell differentiation	GO:0048762	cell differentiation	1.158E-02	WNT4,SEMA6B,PDCD4,SEMA6A,TWIST1,GDNF,SEMA3E,NOTCH1,ZNF703,DAB2,EOMES,FAM83D,COL1A1,SEMA4C,EZH2,SOX9,HIF1A,FOXC1,SNAI2,CDH2,FERMT2,TGFBR1,NOTCH4,TGFBR2,PTEN,PHOX2B,HMGA2,WWTR1,LRP6,PHLDB2,TIAM1,SMAD2,SMAD3,SEMA7A,DDX5,CTNNB1,SPRED3,SEMA4G,HEYL,AKNA,DLG5,ALX1,PHACTR4,PDPN,WNT5A,GSK3B	46	both
mesenchymal cell proliferation	GO:0010463	cell proliferation	4.279E-02	MYC,NFIB,SOX9,TGFBR2,CTNNBIP1,VEGFA,LMNA,WNT5A	8	down
mesenchyme development	GO:0060485	organogenesis	5.004E-05	SEMA4C,SEMA4B,PPP2CA,SIX1,SMO,SMAD4,HMGA2,FGFR2,ERBB4,STAT1,SFRP1,SMAD2,IL6,ROBO1,NOTCH1,PHLDB2,NRP1,PTEN,PDCD4,SMAD3,SPRED1,NOLC1,RBPJ,HEYL,TGFBR3,AXIN2,SMAD7,GSK3B,MEF2C,SEMA3A,MYC,JAG1,VASN,MDM4,LEF1,STRAP,TGFBR2,GATA4,CTNNB1,TCOF1,SNAI1,BMP7,ACTC1,BMPR1A,PDPN,SOX11,DAND5,DLG5,TCF7L2,ACVR1,BNC2,WWTR1,HAS2,ZNF703,TWIST1,ACTA1	56	both
met promotes cell motility	REAC:R-HSA-8875878	signalling pathways	4.124E-02	COL1A1,PTK2,RAP1B,COL1A2,COL3A1,ITGB1,COL5A2,LAMC2,LAMC1,MET,CRKL,CRK,ITGA3	13	down
met receptor recycling	REAC:R-HSA-8875656	signalling pathways	9.795E-03	RAB4A,CRKL,GGA3,CRK,MET,ARF6	6	up
metabolism of non-coding rna	REAC:R-HSA-194441	miRNA/siRNA biogenesis	1.391E-02	NUP93,NUP205,RANBP2,NUP37,SNRPB,NDC1,NUP50,POM121C,GEMIN5,NUP62,NCBP2,RAE1,WDR77,NUP43,GEMIN2,SNRPD1,NUP54	17	up
microrna (mirna) biogenesis	REAC:R-HSA-203927	miRNA/siRNA biogenesis	5.440E-03	PRKRA,AGO3,DICER1,AGO2,TARBP2,AGO1,AGO4,POLR2E,RAN,POLR2D,BCDIN3D	11	up
micrornas in cancer	KEGG:05206	cancer	2.050E-07	MYC,SOX4,CDK6,RASSF1,PDCD4,MAPK1,TP63,APC,NOTCH1,BMPR2,ABCB1,EP300,MAP2K2,RPS6KA5,VIM,PDGFRA,IGF2BP1,CCND1,CASP3,SIRT1,EZH2,NFKB1,ZEB2,SLC45A3,NOTCH4,ATM,PTEN,KRAS,NOTCH2,CCNG1,BCL2,HMGA2,DDIT4,SLC7A1,MCL1,DNMT3A,DNMT3B,DICER1,PDGFRB,FSCN1,MDM2,CCND2,VEGFA,STMN1,CDKN1B,STAT3,KIF23,BCL2L11,CYP1B1,MET,CRKL,RHOA,ROCK1,CDKN1A,CRK,TP53,MDM4,THBS1,BMI1,CREBBP,PAK4,E2F3	62	both
microtubule anchoring at microtubule organizing center	GO:0072393	cell organisation	4.578E-02	HOOK3,PCM1,NIN,KIF3A,GSK3B,BICD2	6	down
microtubule cytoskeleton organisation involved in mitosis	GO:1902850	cell organisation	2.112E-02	KIF3B,CEP126,DCTN6,XIAP,NUP62,RAN,MECP2,STAG1,CHMP2B,ITGB1,DYNLT1,STMN1,GPSM2,RMDN1,KIF23,KIF11,CHMP4B,CCSAP,SMC3,RHOA,DYNC1H1,ESPL1,CHMP1B,BIRC5,SPAST,NDEL1,NDE1,CEP97,WDR62,AURKA	30	down
mirna loading onto risc involved in gene silencing by mirna	GO:0035280	miRNA/siRNA biogenesis	1.036E-03	AGO3,DICER1,AGO2,TARBP2,AGO1,AGO4	6	up
mirna metabolic process	GO:0010586	miRNA/siRNA biogenesis	5.938E-03	LIN28A,LIN28B,KHSRP,TRIM71,PRKRA,NFKB1,DICER1,AGO2,TARBP2,AGO1,RAN,BCDIN3D	12	up
mitochondrial outer membrane permeabilization	GO:0097345	mitochondrial activity	7.312E-04	PMAIP1,BMF,TP53,BBC3,BCL2,BAK1,YWHAB,BCL2L11,YWHAQ,YWHAH,GSK3B,FZD9,E2F1,SFN,BNIP3,TP73,BAX,PPP3R1,CASP8,MOAP1,TP53BP2	21	both
mitochondrial outer membrane permeabilization involved in programmed cell death	GO:1902686	mitochondrial activity	2.123E-03	PMAIP1,BMF,TP53,BBC3,BCL2,BAK1,YWHAB,BCL2L11,YWHAQ,YWHAH,GSK3B,FZD9,E2F1,SFN,BNIP3,TP73,BAX,PPP3R1,CASP8,MOAP1,TP53BP2	21	both
mitochondrial transport	GO:0006839	mitochondrial activity	5.685E-03	PMAIP1,STAT3,BMF,TP53,BBC3,BCL2,TIMM23,TIMM10,SLC25A1,BAK1,VDAC1,HUWE1,HSPD1,ARIH2,HSP90AA1,UBE2D3,FZD5,YWHAB,BCL2L11,BAG4,SLC25A12,TIMM13,SMDT1,YWHAQ,YWHAH,GSK3B,FZD9,SLC25A22,SLC25A29,HAX1,FBXW7,E2F1,SFN,CPT2,MFN2,BNIP3,TP73,AIFM1,TOMM40,BAX,AIP,PPP3R1,CASP8,MOAP1,BCL2L1,TP53BP2,SLC25A36,LETM1,MFF,SLC25A32,MID1IP1,ROMO1,TIMM50,SLC39A8,SLC25A16,MRPL18,TOMM40L,SREBF1,LMAN1	59	up
mitochondrion disassembly	GO:0061726	mitochondrial activity	3.519E-02	VDAC1,HUWE1,HK2,SQSTM1,ATG9A,FZD5,ATG14,GABARAPL1,WIPI2,GABARAP,HAX1,FBXW7,ATG5,MFN2,BNIP3,BECN1,ATG7,SREBF1	18	up
mitophagy - animal	KEGG:04137	cell cycle	2.889E-04	TP53,BCL2L13,USP8,CSNK2A1,SQSTM1,ATG9A,KRAS,GABARAPL1,GABARAP,USP15,FOXO3,RRAS2,SP1,E2F1,SRC,RRAS,ATG5,MFN2,BNIP3,BECN1,BCL2L1,NRAS,UBB,RPS27A,UBC	25	up

mitotic anaphase	REAC:R-HSA-68882	cell cycle	3.715E-02	PDS5A,CHMP3,AURKB,NUP93,PPP2CA,NUP205,RANBP2,NUP37,PSMB1,EMD,ANAPC16,CENPP,NDC1,KPNB1,LBR,NSL1,RCC2,KIF2C,TAOK1,PAFAH1B1,CHMP4B,VPS4A,BIRC5,CDK1,CDC27,DYNLL2,TUBB2A,PPP2R5C,PSMB5,RANGAP1,CHMP2B,STAG2,ERCC6L,CDC20,TNPO1,NUP62,ANAPC5,CKAP5,KIF2A,CDC23,PPP1CC,NUP43,CCNB1,INCENP,DYNC1LI2,UBB,RPS27A,UBC,CLIP1,RAN,NUP54,DSN1,SKA2	53	up
mitotic cytokinesis	GO:0000281	cell cycle	3.427E-02	VPS4B,CHMP3,APC,USP8,RHOA,ROCK1,CEP55,CHMP4B,VPS4A,KIF23,RACGAP1,SPTBN1,STMN1,RHOB,CHMP2B,ECT2,KIF4A,NUP62,SON,ANK3,INCENP,TRIM36	22	both
mitotic dna damage checkpoint	GO:0044773	cell cycle	3.753E-04	E2F7,TP53,ARID3A,RFWD3,ZNF385A,BTG2,TNKS1BP1,HMGA2,MUC1,CDKN1A,CNOT6L,CCND1,RBM38,CDKN1B,CNOT4,TAOK1,CARM1,CDK1,PPP2R5C,CLSPN,CDK2,MDM2,E2F1,ATM,MRE11,CDC25C,MRNIP,SFN,MDM4,FOXN3,PPP1R10,CRADD,GADD45A,DGKZ,BAX,CNOT2,SOX4,AURKA,CCNB1,CHEK2,CNOT1	41	both
mitotic dna integrity checkpoint	GO:0044774	cell cycle	1.235E-03	E2F7,TP53,ARID3A,RFWD3,ZNF385A,BTG2,TNKS1BP1,HMGA2,MUC1,CDKN1A,CNOT6L,CCND1,RBM38,CDKN1B,CNOT4,TAOK1,CARM1,CDK1,PPP2R5C,CLSPN,CDK2,MDM2,E2F1,ATM,MRE11,CDC25C,MRNIP,SFN,MDM4,FOXN3,PPP1R10,CRADD,GADD45A,DGKZ,BAX,CNOT2,SOX4,AURKA,CCNB1,CHEK2,CNOT1,ORC1,TOP2A	43	both
mitotic dna replication	GO:1902969	cell cycle	7.119E-03	BRCA2,MCMDC2,MCM4,MCM2,MCM6,MCM3,CHEK2	7	up
mitotic g1 phase and g1/s transition	REAC:R-HSA-453279	cell cycle	4.954E-06	CDKN2A,E2F3,JAK2,AKT1,CCNE1,PPP2CA,CDKN2D,PSMB1,ABL1,E2F2,LIN52,CDKN1A,CCND1,CCND2,CCNA2,CDKN1B,CDK4,CCND3,CDK6,WEE1,ORC4,CDK1,CDC25A,AKT3,POLE4,CCNE2,PSMB5,CDK2,E2F1,MYC,HDAC1,MCM4,MCM2,MCM7,TYMS,RRM2,E2F5,PRIM1,MCM10,MCM6,MCM3,CDKN2C,MCM5,CCNB1,UBB,RPS27A,UBC,ORC1,DYRK1A,CABLES1,TOP2A	51	up
mitotic g1/s transition checkpoint	GO:0044819	cell cycle	2.034E-02	E2F7,TP53,ARID3A,RFWD3,ZNF385A,BTG2,TNKS1BP1,MUC1,CDKN1A,CNOT6L,CCND1,RBM38,CDKN1B,CNOT4,CARM1,CDK1,PPP2R5C,CDK2,MDM2,E2F1,ATM,CDC25C,SFN,MDM4,CRADD,GADD45A,DGKZ,BAX,CNOT2,SOX4,AURKA,CCNB1,CHEK2,CNOT1	34	both
mitotic g2/m transition checkpoint	GO:0044818	cell cycle	3.314E-03	BRSK1,TAOK3,TAOK1,ATM,TOPBP1,HMGA2,DONSON,CDKN1A,MRNIP,MRE11,HUS1,TAOK2	12	both
mitotic metaphase and anaphase	REAC:R-HSA-2555396	cell cycle	4.007E-02	PDS5A,CHMP3,AURKB,NUP93,PPP2CA,NUP205,RANBP2,NUP37,PSMB1,EMD,ANAPC16,CENPP,NDC1,KPNB1,LBR,NSL1,RCC2,KIF2C,TAOK1,PAFAH1B1,CHMP4B,VPS4A,BIRC5,CDK1,CDC27,DYNLL2,TUBB2A,PPP2R5C,PSMB5,RANGAP1,CHMP2B,STAG2,ERCC6L,CDC20,TNPO1,NUP62,ANAPC5,CKAP5,KIF2A,CDC23,PPP1CC,NUP43,CCNB1,INCENP,DYNC1LI2,UBB,RPS27A,UBC,CLIP1,RAN,NUP54,DSN1,SKA2	53	up
mitotic nuclear division	GO:0140014	cell cycle	2.092E-03	VPS4B,IGF2,PDS5A,XIAP,AURKB,PPP2CA,SIRT7,APC,EMD,SMC2,KPNB1,RHOA,DUSP1,KIF22,NSL1,TACC3,KIF2C,TGFA,CHEK1,AURKAIP1,CHMP4B,CUL3,VPS4A,KIF23,BIRC5,RACGAP1,KIF3B,CDK1,INSR,CDC27,CHMP2B,ATM,UBE2S,KIF11,STAG2,CDC25C,CDC20,PDGFRB,IK,KIF4A,NUP62,ANAPC5,NCAPG,POGZ,MKI67,BECN1,BMP7,KIF2A,CDC23,UBXN2B,REEP3,CNEP1R1,AURKA,CCNB1,NCAPG2,NCAPD2,CHEK2,EDN1,RAN,EREG,NAA50,DSN1,PDGFB,PHF13	64	both
mitotic prophase	REAC:R-HSA-68875	cell cycle	3.305E-02	NUP93,PPP2CA,NUP205,RANBP2,NUP37,EMD,SMC2,SET,NDC1,RAB1B,CDK1,NUP50,POM121C,GORASP2,HIST1H2AC,NUP62,HIST1H2BJ,RAE1,CNEP1R1,NUP43,CCNB1,NCAPG2,MASTL,MAPK1,NUP54,ARPP19,RAB1A	27	up
mitotic spindle checkpoint	REAC:R-HSA-69618	cell cycle	3.184E-02	AURKB,PPP2CA,RANBP2,NUP37,ANAPC16,CENPP,NSL1,RCC2,KIF2C,TAOK1,PAFAH1B1,BIRC5,CDC27,DYNLL2,PPP2R5C,RANGAP1,ERCC6L,CDC20,ANAPC5,CKAP5,KIF2A,CDC23,PPP1CC,NUP43,INCENP,DYNC1LI2,CLIP1,DSN1,SKA2	29	up
mitotic spindle organisation	GO:0007052	cell organisation	4.600E-02	VPS4B,XIAP,AURKB,KPNB1,RHOA,TACC3,CHMP4B,MECP2,KIF23,BIRC5,RACGAP1,KIF3B,STMN1,CHMP2B,KIF11,STAG2,KIF4A,NUP62,CKAP5,MAP4,RAE1,KIF2A,AURKA,CCNB1,CHEK2,SUN2,RAN,PCNT	28	both
mitral valve morphogenesis	GO:0003183	organogenesis	4.060E-02	SOX4,NOTCH1,BMPR2,ZFPM1,BMPR1A	5	down
modulation by host of symbiont process	GO:0051851	viral of bacterial infection	4.497E-02	REST,HMGA2,IFI27,CCL5,CCL4,CCNT1,NUCKS1,TBC1D20,SP1,CCL3,CFL1,HDAC1,RRP1B,LEF1,SMARCA4,SUGT1,IGF2R	17	up
modulation by mtb of host immune system	REAC:R-HSA-9637628	adaptive immune system	1.500E-02	TLR2,UBB,RPS27A,UBC,B2M	5	up
modulation by symbiont of host cellular process	GO:0044068	leukocyte activation	4.693E-03	KPNB1,KPNA4,KPNA1,KPNA3,ATG5,ATG7,CASP8,BCL2L1,PABPN1,KPNA2	10	up
modulation by symbiont of host process	GO:0044003	viral of bacterial infection	2.233E-02	KPNB1,KPNA4,INSR,KPNA1,KPNA3,ATG5,RRAGA,ATG7,CASP8,BCL2L1,PABPN1,KPNA2	12	up
modulation by virus of host cellular process	GO:0019054	viral of bacterial infection	1.156E-03	KPNB1,KPNA4,KPNA1,KPNA3,ATG7,CASP8,BCL2L1,PABPN1,KPNA2	9	up
modulation by virus of host process	GO:0019048	viral of bacterial infection	7.628E-03	KPNB1,KPNA4,INSR,KPNA1,KPNA3,RRAGA,ATG7,CASP8,BCL2L1,PABPN1,KPNA2	11	up
modulation of age-related behavioral decline	GO:0090647	diseases	3.859E-02	DKK1,AGER,APP,PRNP,B2M	5	up
modulation of process of other organism	GO:0035821	signalling pathways	9.611E-03	REST,HMGA2,KPNB1,IFI27,SLPI,CCL5,KPNA4,CCL4,CCNT1,NUCKS1,INSR,TBC1D20,KPNA1,KPNA3,SP1,CCL3,CFL1,HDAC1,RRP1B,LEF1,ATG5,RRAGA,SMARCA4,ATG7,SUGT1,CASP8,BCL2L1,IGF2R,F2RL1,PABPN1,KPNA2	31	up
modulation of process of other organism involved in symbiotic interaction	GO:0051817	signalling pathways	8.910E-04	REST,HMGA2,KPNB1,IFI27,CCL5,KPNA4,CCL4,CCNT1,NUCKS1,INSR,TBC1D20,KPNA1,KPNA3,SP1,CCL3,CFL1,HDAC1,RRP1B,LEF1,ATG5,RRAGA,SMARCA4,ATG7,SUGT1,CASP8,BCL2L1,IGF2R,PABPN1,KPNA2	29	up
mononuclear cell differentiation	GO:1903131	cell differentiation	8.727E-04	CDKN2A,CBFB,IRF4,STAT3,IKZF3,PRDM1,PIK3CD,FES,CEBPG,ABL1,FADD,CD80,LFNG,SFRP1,IRF7,IL6,RSAD2,NOTCH2,IL23R,CSF1,HLA-G,ADAM17,KLF6,VEGFA,CDK6,VSIR,PTPRJ,DOCK11,TNFSF9,AGER,MYB,SMAD7,TCF3,POU2AF1,SOCS5,NLRP3,ITGB1,TOX,ATM,MYC,DLL1,TPD52,LEF1,ZAP70,TGFBR2,IFNB1,AXL,HMGB1,CSF1R,KIT,TREM2,IL10,ADGRG3,CD27,TCF7,SOX4,FNIP1,DNAJB9,NKAP,RAG1,ZBTB7A,CHD7,IRF1,ZBTB7B,CCR6,F2RL1,RHOH,ATP7A	68	up
mononuclear cell migration	GO:0071674	cell adhesion and migration	4.808E-02	AKT1,TNF,WNK1,IL6R,PIK3CD,ALOX5,CXCR4,RHOA,DUSP1,FADD,IL6,CCL5,S100A12,CXCL12,WASL,CSF1,ADAM17,CCL4,AGER,APP,RET,CCL3,MAPK3,ZAP70,CCL22,PIK3CG,SAA1,HMGB1,CSF1R,S1PR1,F11R,MAPK1,CCR6,PDGFB,PLCB1,AKIRIN1,THBS1	37	up
mononuclear cell proliferation	GO:0032943	cell proliferation	5.173E-03	CDKN2A,CD320,SLC7A1,IGF2,IKZF3,BCL2,RASGRP1,HSPD1,CD40LG,MIF,FADD,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,CSF1,HLA-G,CD274,VSIR,TNFSF9,AGER,TCF3,CD180,IL6ST,MEF2C,ATM,VAV3,TGFBR2,CEBPB,CD40,TFRC,IFNB1,PIK3CG,HMGB1,CD24,TNFRSF21,PLA2G2D,IL10,CD70,TIRAP,TNFRSF13C,SOX11,DLG5,PRNP,IRF1,ZBTB7B,SDC4,IL15	50	up
morphogenesis of an epithelial sheet	GO:0002011	organogenesis	3.400E-02	CD44,RHOA,NOTCH1,PHLDB2,ITGA5,CD151,ADAM17,PTEN,WNT7A,ARHGAP12,BMP7,PDPN,SOX11,PLET1	14	both
morphogenesis of an epithelium	GO:0002009	organogenesis	1.081E-04	VCL,SEMA4C,FZD4,TNF,STARD13,SIX1,SMO,PODXL,PSMB1,LIF,NRARP,CD44,PIK3CD,FZD6,LBX2,FGFR2,RHOA,KDM2B,MICAL2,LRP2,STAT1,NOTCH1,DKK1,PHLDB2,WNT1,ITGA5,CD151,ADAM17,FZD5,FGF2,NRP1,PTEN,SKI,AP2B1,VEGFA,PAFAH1B1,WNT7A,ARHGAP12,TFAP2A,RBPJ,LUZP1,PRICKLE2,NKD1,CDC42,KDR,SMURF1,SALL1,MTHFR,PSMB5,BSG,RHOB,MEF2C,MYC,AP2A1,MET,DLL1,ACTG1,TGFBR2,AP2M1,AP2A2,GATA4,CTNNB1,BMP7,EPHA2,CSF1R,SIRT6,BCL10,SOX4,PDPN,SOX11,HOXD11,ACVR1,DLC1,AHI1,PRKD2,PLET1,ACTB,COL4A1,MTSS1,RAB10,ATP7A	81	up

morphogenesis of embryonic epithelium	GO:0016331	organogenesis	2.167E-02	SOX4,GDNF,SIX1,SEMA4C,SOX9,MTHFD1L,LRP6,SKI,BCL10,PRICKLE1,DLC1,DVL3,PHACTR4,WNT5A,TFAP2A,DVL1	16	down
mrna 3'-end processing	GO:0031124	transcription and translation	3.170E-02	DHX38,PABPC1,CASC3,CDC73,LSM11,CPSF7,CCNT1,RPRD1B,RNPS1,SRSF1,RPRD2,CPEB3,POLDIP3,APP,SSU72,SUPT5H,THOC2,RNF40,NCBP2,GRSF1,POLR2D,SRSF2,MTPAP,DDX39A,PABPN1,PAPOLA	26	up
mrna processing	GO:0006397	transcription and translation	4.166E-02	SPEN,DHX38,PABPC1,SUPT6H,HNRNPK,LSM4,CASC3,FUS,THRAP3,PCBP2,REST,NPM1,SRRM2,FXR1,KHSRP,PTBP1,LUC7L3,SNRPB,CDC73,PPWD1,ELAVL1,RBM23,RALY,LSM11,PPIL1,SRPK1,AURKAIP1,CPSF7,CCNT1,SNRPB2,RPRD1B,RNPS1,SRSF1,HSPA8,PLRG1,RPRD2,CPEB3,HNRNPA1,U2SURP,POLDIP3,POLR2E,HNRNPA2B1,APP,RNMT,EFTUD2,YTHDC1,SSU72,NOVA2,SUPT5H,SNRPA1,THOC2,RBM15B,GEMIN5,STRAP,CHERP,SF3B3,IK,RNF40,HNRNPUL1,KHDRBS1,SON,NCBP2,CDC5L,NUP98,YBX1,WBP11,NOL3,WDR77,RBFOX2,GEMIN2,SNRPD1,SMU1,GRSF1,ZBTB7A,QKI,PRPF38A,PRPF4,MBNL1,MBNL3,POLR2D,SF3A1,SRSF2,MTPAP,DDX39A,SNRNP48,PABPN1,ELAVL2,RBM3,COIL,PAPOLA,HNRNPC,SF1,HNRNPA3	93	both
mrna splicing	REAC:R-HSA-72172	transcription and translation	4.503E-02	DHX38,HNRNPK,LSM4,CASC3,FUS,PCBP2,SRRM2,PTBP1,SNRPB,PPWD1,ELAVL1,PPIL1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PLRG1,HNRNPA1,U2SURP,POLR2E,HNRNPA2B1,EFTUD2,SNRPA1,CHERP,SF3B3,HNRNPUL1,NCBP2,CDC5L,YBX1,WBP11,SNRPD1,PRPF38A,PRPF4,POLR2D,SF3A1,SRSF2,SNRNP48,PABPN1,ELAVL2,PAPOLA,HNRNPC,SF1,HNRNPA3	44	up
mrna splicing - major pathway	REAC:R-HSA-72163	transcription and translation	3.715E-02	DHX38,HNRNPK,LSM4,CASC3,FUS,PCBP2,SRRM2,PTBP1,SNRPB,PPWD1,ELAVL1,PPIL1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PLRG1,HNRNPA1,U2SURP,POLR2E,HNRNPA2B1,EFTUD2,SNRPA1,CHERP,SF3B3,HNRNPUL1,NCBP2,CDC5L,YBX1,WBP11,SNRPD1,PRPF38A,PRPF4,POLR2D,SF3A1,SRSF2,PABPN1,ELAVL2,PAPOLA,HNRNPC,SF1,HNRNPA3	43	up
mrna splicing, via spliceosome	GO:0000398	transcription and translation	4.995E-03	SPEN,DHX38,PABPC1,HNRNPK,LSM4,CASC3,FUS,THRAP3,PCBP2,REST,NPM1,SRRM2,FXR1,PTBP1,LUC7L3,SNRPB,PPWD1,ELAVL1,RBM23,RALY,PPIL1,SRPK1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PLRG1,HNRNPA1,U2SURP,POLR2E,HNRNPA2B1,EFTUD2,YTHDC1,NOVA2,SNRPA1,RBM15B,GEMIN5,STRAP,CHERP,SF3B3,IK,HNRNPUL1,KHDRBS1,SON,NCBP2,CDC5L,NUP98,YBX1,WBP11,NOL3,WDR77,RBFOX2,GEMIN2,SNRPD1,SMU1,ZBTB7A,QKI,PRPF38A,PRPF4,MBNL1,MBNL3,POLR2D,SF3A1,SRSF2,DDX39A,SNRNP48,PABPN1,ELAVL2,RBM3,COIL,PAPOLA,HNRNPC,SF1,HNRNPA3	75	up
mrna transport	GO:0051028	cellular transport	2.531E-03	DHX38,SUPT6H,CASC3,NUP93,NUP205,RANBP2,NUP37,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,NUP50,POLDIP3,HNRNPA2B1,POM121C,YTHDC1,THOC2,RBM15B,NUP62,NCBP2,NUP98,RAE1,NUP43,POLR2D,SRSF2,NUP54,ARC,SMG1,FYTTD1,DDX39A,PABPN1,HNRNPA3	33	up
mrna-containing ribonucleoprotein complex export from nucleus	GO:0071427	protein metabolism	4.398E-03	DHX38,SUPT6H,CASC3,NUP93,NUP205,RANBP2,NUP37,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,NUP50,POLDIP3,HNRNPA2B1,POM121C,YTHDC1,THOC2,RBM15B,NUP62,NCBP2,NUP98,RAE1,NUP43,POLR2D,SRSF2,NUP54,SMG1,FYTTD1,DDX39A,PABPN1	31	up
mtor signalling pathway	KEGG:04150	signalling pathways	5.125E-04	WNT4,MAPK1,FNIP2,LPIN1,RRAGC,MAP2K2,IGF1,SLC38A9,PDPK1,RPS6KA6,SLC7A5,EIF4EBP1,AKT1,IGF1R,CASTOR2,PTEN,KRAS,TBC1D7,RPS6KA3,DDIT4,ULK1,SGK1,LRP6,FZD5,FZD4,AKT2,AKT3,CAB39,CLIP1,RRAGD,SKP2,RHOA,DVL3,FZD7,WNT5A,GSK3B,LPIN2,EIF4E,DVL1	39	both
mtor signalling	REAC:R-HSA-165159	signalling pathways	4.390E-03	AKT1,EIF4EBP1,PRKAG1,EIF4E,STRADB,YWHAB,RPS6KB1,PRKAA1,PPM1A,CAB39,RRAGD,RRAGA,EIF4G1,SLC38A9,AKT1S1,EEF2K	16	up
mtorc1-mediated signalling	REAC:R-HSA-166208	signalling pathways	1.671E-02	EIF4EBP1,EIF4E,YWHAB,RPS6KB1,RRAGD,RRAGA,EIF4G1,SLC38A9,AKT1S1,EEF2K	10	up
multi-organism localization	GO:1902579	protein localization	2.119E-04	NUP93,NUP205,RANBP2,NUP37,NDC1,KPNB1,IFIT1,VPS37B,VPS37A,NUP50,KPNA1,POM121C,VPS37D,TPCN2,NUP62,NUP98,RAE1,NUP43,UBB,RPS27A,UBC,RAN,NUP54,KPNA2	24	both
multi-organism transport	GO:0044766	cellular transport	7.423E-03	NUP93,NUP205,RANBP2,NUP37,NDC1,KPNB1,IFIT1,VPS37B,VPS37A,NUP50,KPNA1,POM121C,VPS37D,TPCN2,NUP62,NUP98,RAE1,NUP43,UBB,RPS27A,UBC,RAN,NUP54,KPNA2	24	both
multicellular organismal homeostasis	GO:0048871	cell proliferation	5.075E-03	VCL,IRF4,EHMT1,STAT3,PCTP,JAK2,PTGES,IP6K1,TNFAIP3,CNGB1,TNF,CDH5,NRDC,SCNN1A,IGF1R,APC,CLDN12,DRAM2,CXCR4,PTGS2,SPP1,BGLAP,DECR1,IL6,KDM6B,TLR4,NOTCH1,LNPEP,ADAM17,VEGFA,CHMP4B,OGT,ALOX12,PRKAA1,PRKAR2A,WNK3,FLCN,RBPJ,RAB11FIP2,LAMC1,BSG,STMN1,FOXO1,ITGB1,CFTR,NOVA2,TRPV2,MET,DLL1,SFN,ACTG1,SRC,STRAP,CPT2,CEBPB,ACSL1,FH,ITGB3,MFN2,EIF4G1,TJP2,CIDEA,CSF1R,SIRT6,TLE3,S1PR1,F11R,PER2,RAB3D,BMP8A,GRB10,ZBTB7B,THRA,TPP1,CD36,UBASH3B,SGIP1,SLC39A8,HAS2,SIGLEC15,B2M,ACTB,ADAMTS5,IL15,FFAR4	85	up
muscle cell differentiation	GO:0042692	cell differentiation	2.055E-02	SEMA4C,MYEF2,NEBL,IGF2,SUPT6H,SIX1,SORT1,MAPK14,PTBP1,SMAD4,LBX2,ABL1,EHD1,FGFR2,NOS1,KDM6B,NOTCH1,DNMT1,DKK1,SIK1,SKI,PDCD4,VEGFA,EFNB2,DMPK,CCNT2,KLHL40,CDC42,TCF3,MEF2C,ITGB1,TPM1,CDON,PDGFRB,PDGFRA,KCNH1,MYOF,CTNNB1,TMOD3,KIT,BNIP2,CFLAR,TMOD2,ACTC1,GATA6,CBY1,EDN1,ACVR1,EREG,MYH11,TCF23,PDGFB,FRS2,CSRP1,SOD2,ACTA1	56	up
muscle cell proliferation	GO:0033002	cell proliferation	1.133E-03	STAT3,AKT1,TNFAIP3,APLN,TNF,SIX1,IL6R,MMP2,GLI1,FGFR2,CDKN1A,ERBB4,STAT1,IL6,CCL5,NOTCH1,DNMT1,FGF2,CDKN1B,IGFBP5,PTEN,PDCD4,ELN,RBPJ,TGFBR3,PIM1,MEF2C,TPM1,PDGFRB,MFN2,CTNNB1,TP73,IL10,CFLAR,BMPR1A,TCF7L2,EDN1,EREG,PDGFB,SOD2,AKIRIN1,THBS1,VGLL4	43	up
muscle organ morphogenesis	GO:0048644	organogenesis	2.607E-02	SMAD4,FGFR2,LRP2,MYLK,NOTCH1,RBPJ,FKBP1A,TGFBR3,SMAD7,TPM1,DSP,PKP2,ACTC1,S1PR1,BMPR1A	15	up
muscle structure development	GO:0061061	organogenesis	3.667E-03	SEMA4C,MYEF2,NEBL,IGF2,SUPT6H,SIX1,REST,SORT1,MAPK14,FXR1,EMD,PTBP1,SMAD4,LBX2,ABL1,EHD1,FGFR2,MSC,LRP2,NOS1,MYLK,KDM6B,NOTCH1,DNMT1,DKK1,SIK1,SKI,PDCD4,VEGFA,MKX,EFNB2,FLOT2,RBPJ,DMPK,NKD1,CCNT2,FKBP1A,TGFBR3,SMAD7,KLHL40,CDC42,TCF3,MEF2C,ZBTB18,ITGB1,JAG1,DLL1,ITGA11,TPM1,CDON,PDGFRB,PDGFRA,KCNH1,DSP,MYOF,CTNNB1,PKP2,TMOD3,KIT,BNIP2,CFLAR,TMOD2,ACTC1,S1PR1,BMPR1A,GATA6,EID2B,CBY1,TCF7L2,EDN1,FKTN,MTPN,ACVR1,MBNL1,BTG1,EREG,MYH11,TCF23,PDGFB,FRS2,CSRP1,SOD2,PLCB1,TRIM72,AKIRIN1,ACTA1	86	up
muscle tissue development	GO:0060537	organogenesis	6.335E-03	NEBL,SIX1,SMO,SMAD4,GLI1,FGFR2,MSC,ERBB4,LRP2,MYLK,KDM6B,NOTCH1,DKK1,SIK1,FGF2,SKI,VEGFA,EFNB2,RBPJ,FKBP1A,TGFBR3,SMAD7,KLHL40,PIM1,MEF2C,ZBTB18,ITGB1,DLL1,TPM1,PDGFRB,PDGFRA,DSP,PKP2,TP73,BMP7,CFLAR,ACTC1,S1PR1,BMPR1A,CBY1,EDN1,MTPN,ACVR1,MYH11,FRS2,CSRP1,AKIRIN1,VGLL4,ADAMTS9,ACTA1	50	up
muscle tissue morphogenesis	GO:0060415	organogenesis	2.607E-02	SMAD4,FGFR2,LRP2,MYLK,NOTCH1,RBPJ,FKBP1A,TGFBR3,SMAD7,TPM1,DSP,PKP2,ACTC1,S1PR1,BMPR1A	15	up
myd88 cascade initiated on plasma membrane	REAC:R-HSA-975871	MyD88 signalling	2.590E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	37	up
myd88 dependent cascade initiated on endosome	REAC:R-HSA-975155	MyD88 signalling	2.590E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,IRF7,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	39	up
myd88-dependent toll-like receptor signalling pathway	GO:0002755	MyD88 signalling	2.321E-05	HSPD1,IRAK2,TRAF6,TLR2,IRAK1,IRF7,TLR4,TAB3,MAP3K7,MAP3K1,TIRAP,UBB,IRF1,RPS27A,UBC,CD36,TAB2	17	up
myd88-independent tlr4 cascade	REAC:R-HSA-166166	MyD88 signalling	2.098E-10	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,FADD,IRAK1,IRF7,TLR4,S100A12,UBE2D3,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,BIRC3,MAPK3,MAP2K1,TRAF3,SAA1,HMGB1,RIPK2,NOD1,CASP8,BIRC2,TANK,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,UBE2D2,TAB2	46	up
myd88-independent toll-like receptor signalling pathway	GO:0002756	MyD88 signalling	1.167E-06	FADD,IRF7,PRKCE,TLR4,UBE2D3,CHUK,RAB11FIP2,BIRC3,CD40,TRAF3,CASP8,BIRC2,TLR3,TANK,UBB,RPS27A,UBC,UBE2D2,TNIP3	19	up
myelin maintenance	GO:0043217	neuronal architecture	3.339E-02	CXCR4,PTEN,CLU,EPB41L3,DEGS1,ABCD2	6	up
myeloid cell apoptotic process	GO:0033028	apoptosis	8.466E-03	CDKN2A,EPO,PIK3CB,PIK3CD,IRF7,IL6,ADAM17,MEF2C,SIRT1	9	up

myeloid cell development	GO:0061515	organogenesis	1.642E-03	ZNF385A,MED1,FBN1,TLR2,NOTCH2,PAFAH1B1,APP,FBXW7,SRC,KIT,SH2B3,ZBTB7A,SIGLEC15	13	up
myeloid cell differentiation	GO:0030099	cell differentiation	7.978E-09	ETS1,CBFB,STAT3,CEBPA,JAK2,EPO,TNF,ZNF385A,CREBBP,MED1,TET2,GAB2,MAPK14,KMT2D,LIF,PIK3CD,FES,MFHAS1,CEBPG,TNRC6B,FBN1,PARP1,TRAF6,TLR2,CDC73,FADD,BGLAP,STAT1,IRF7,LBR,TLR4,NOTCH2,IL23R,CSF1,AGO3,MAFB,SH3PXD2A,TNRC6A,CNOT4,VEGFA,PAFAH1B1,CDK6,AGO1,AGO4,DYRK3,CBFA2T3,ZBTB16,ACVR2A,TGFBR3,APP,CDC42,OSCAR,FOXO3,HAX1,FBXW7,MEF2C,MYL9,TAL1,CCL3,MYC,HDAC1,LEF1,MOV10,SPI1,SRC,CASP3,SIRT1,TGFBR2,CEBPB,CASP9,HOXB8,EPHA2,CSF1R,KIT,TREM2,CASP8,SH2B3,TIRAP,TLR3,ZBTB7A,HOXA5,F2RL1,UBASH3B,RPS14,EIF6,SIGLEC15,THBS1,IL15	88	up
myeloid cell homeostasis	GO:0002262	cell proliferation	3.227E-04	ETS1,STAT3,JAK2,EPO,MED1,MAPK14,PIK3CB,PIK3CD,MFHAS1,CEBPG,STAT1,IL6,MAFB,ADAM17,VEGFA,CDK6,DYRK3,ACVR2A,TGFBR3,FOXO3,TAL1,SPI1,CASP3,HMGB1,KIT,SH2B3,ZBTB7A,HOXA5,RPS14	29	up
myeloid leukocyte differentiation	GO:0002573	cell differentiation	5.013E-07	CEBPA,TNF,GAB2,MAPK14,LIF,PIK3CD,FES,FBN1,PARP1,TRAF6,TLR2,FADD,BGLAP,IRF7,LBR,TLR4,NOTCH2,IL23R,CSF1,MAFB,SH3PXD2A,VEGFA,PAFAH1B1,CDK6,CBFA2T3,APP,CDC42,OSCAR,HAX1,FBXW7,TAL1,CCL3,MYC,LEF1,SRC,SIRT1,TGFBR2,CEBPB,EPHA2,CSF1R,KIT,TREM2,CASP8,TLR3,F2RL1,UBASH3B,SIGLEC15,IL15	48	up
n-glycan trimming in the er and calnexin/calreticulin cycle	REAC:R-HSA-532668	protein metabolism	2.080E-02	SEL1L,EDEM1,GANAB,MAN1B1,EDEM3,MLEC,RAD23B,CANX,UBB,RPS27A,UBC,PRKCSH,DERL2	13	up
natural killer cell chemotaxis	GO:0035747	cell adhesion and migration	3.859E-02	PIK3CD,CCL5,CCL4,CCL3,PIK3CG	5	up
natural killer cell mediated cytotoxicity	KEGG:04650	leukocyte activation	6.479E-03	TNF,ICAM2,TNFRSF10B,PIK3CB,Fas,RAF1,PIK3CD,CD244,ITGB2,SOS1,ICAM1,HLA-A,KRAS,HLA-G,SOS2,HLA-C,PIK3R3,VAV2,GRB2,PIK3R1,VAV3,MAPK3,ZAP70,CASP3,ULBP2,MAP2K1,IFNB1,PLCG1,TNFRSF10A,PPP3R1,FASLG,NRAS,MAPK1,KLRD1	34	up
ncrna export from nucleus	GO:0097064	cellular transport	2.628E-03	NUP93,NUP205,RANBP2,NUP37,NPM1,NDC1,NUP50,POM121C,NUP62,NCBP2,NUP98,RAE1,NUP43,RAN,NUP54	15	up
necroptosis	KEGG:04217	apoptosis	4.435E-04	VPS4B,STAT3,XIAP,PLA2G4F,JAK2,CHMP3,TNFAIP3,BCL2,TNF,TNFRSF10B,VDAC1,Fas,PARP1,FADD,STAT1,SQSTM1,TLR4,FAF1,HSP90AA1,CHMP4B,VPS4A,CYLD,NLRP3,STAT5A,CHMP2B,BIRC3,HIST1H2AC,IFNB1,PYGB,HIST1H2AH,CASP1,HMGB1,AIFM1,TNFRSF10A,TRAF2,RBCK1,BAX,FASLG,TNFRSF1A,CAPN1,CYBB,CFLAR,CASP8,BIRC2,STAT2,TLR3	46	up
necroptotic process	GO:0070266	apoptosis	3.102E-02	TNF,Fas,FADD,TLR4,CYLD,FZD9,BIRC3,FASLG,CFLAR,CASP8,BIRC2,TLR3,IPMK	13	up
necroptotic signalling pathway	GO:0097527	signalling pathways	2.287E-02	TNF,Fas,FADD,FASLG,TLR3	5	up
nef mediated cd4 down-regulation	REAC:R-HSA-167590	signalling pathways	4.467E-02	AP2B1,AP2A1,AP2M1,AP2A2,ARF1	5	up
negative feedback regulation of mapk pathway	REAC:R-HSA-5674499	MAPK signalling	4.447E-02	RAF1,MAPK3,MAP2K1,MAPK1	4	up
negative regulation by host of viral transcription	GO:0043922	viral of bacterial infection	1.881E-02	REST,HMGA2,CCL5,CCL4,NUCKS1,CCL3,HDAC1	7	up
negative regulation of binding	GO:0051100	cell adhesion and migration	1.915E-02	JAK2,AKT1,AURKB,NES,SMO,HMGA2,PPP1CA,ROCK1,CDKN1A,SLPI,IFIT1,DKK1,CPNE1,PRKCD,C6orf106,GSK3B,E2F1,BAG2,LEF1,RALB,BAX,IL10,ADNP,AURKA,ADAM15,PER2,SOX11,HABP4,ERCC4,PDGFB,B2M,ACTB	32	up
negative regulation of cyclin-dependent protein kinase activity	GO:1904030	protein kinase activity	1.221E-02	APC,NR2F2,CEBPA,PTEN,LATS2,IPO5,CDKN1B,IPO7,CDKN1A,HEXIM1	10	down
negative regulation of cysteine-type endopeptidase activity	GO:2000117	endopeptidase activity	2.228E-06	RPS6KA1,XIAP,AKT1,TNF,CDKN2D,CD44,RAF1,CSNK2A1,PLAUR,ARL6IP1,KLF4,VEGFA,DDX3X,PAK2,BIRC5,BCL2L12,RPS6KA3,SFN,BIRC3,SRC,MAGEA3,NAIP,DNAJB6,USP47,NOL3,BIRC2,FNIP1,DHCR24,THBS1	29	up
negative regulation of endopeptidase activity	GO:0010951	endopeptidase activity	3.427E-02	RPS6KA1,XIAP,AKT1,TNF,CDKN2D,CD44,RAF1,CSNK2A1,SERPINA4,PLAUR,ARL6IP1,KLF4,VEGFA,DDX3X,RECK,PAK2,BIRC5,BCL2L12,RPS6KA3,SFN,BIRC3,SERPINB1,SRC,MAGEA3,NAIP,DNAJB6,USP47,NOL3,BIRC2,FNIP1,DHCR24,THBS1	32	up
negative regulation of fgfr4 signalling	REAC:R-HSA-5654733	FGFR signalling	4.503E-02	PPP2CA,FGF2,FGFR4,MAPK3,KLB,UBB,MAPK1,RPS27A,UBC,FRS2	10	up
negative regulation of hydrolase activity	GO:0051346	protein metabolism	1.211E-02	RPS6KA1,TP53,XIAP,PPP1R37,AKT1,ZFYVE1,TNF,WNK1,CDKN2D,SORT1,CSRNP2,CD44,RAF1,ABL1,CSNK2A1,ROCK1,NOS1,PPP1R11,IFIT1,SERPINA4,PLAUR,ARL6IP1,RCC2,KLF4,ARL2,VEGFA,SPRED1,DDX3X,RECK,PAK2,SH3BP4,BIRC5,CPEB2,GNAT1,FKBP1A,BCL2L12,GSK3B,RPS6KA3,RRP1B,SFN,BIRC3,SERPINB1,SRC,SIRT1,RBM26,MAGEA3,NAIP,DNAJB6,USP47,FKBP1B,NOL3,DFFA,FICD,BIRC2,FNIP1,WDR81,F11R,SLC39A14,PXK,MASTL,TERF2,DHCR24,THBS1,ELL	64	up
negative regulation of mapk pathway	REAC:R-HSA-5675221	MAPK signalling	2.106E-02	PPP2CA,DUSP6,RAF1,DUSP1,YWHAB,PPP2R5C,MAPK3,MAP2K1,DUSP5,NRAS,UBB,MAPK1,RPS27A,UBC	14	up
negative regulation of protein binding	GO:0032091	protein metabolism	3.238E-02	AKT1,AURKB,NES,PPP1CA,ROCK1,CDKN1A,SLPI,IFIT1,DKK1,PRKCD,GSK3B,BAG2,LEF1,RALB,BAX,IL10,ADNP,AURKA,ADAM15,PDGFB,B2M,ACTB	22	up
negative regulation of protein serine/threonine kinase activity	GO:0071901	protein kinase activity	5.690E-03	DUSP9,PRKAR2A,PDCD4,LAX1,APC,PRKCD,NR2F2,DUSP1,DUSP10,SH2B3,SPRY4,HEG1,GPS1,SIRT1,CEBPA,AKT1,PTEN,DUSP5,LATS2,IPO5,DUSP2,LRP6,PRKAR1A,CDKN1B,IPO7,GADD45A,NF1,SPRED3,HEXIM1,PYCARD	30	down
negative regulation of the pi3k/akt network	REAC:R-HSA-199418	PI3k signalling	2.680E-05	ERBB2,AKT1,PPP2CA,PIK3CB,PIK3CD,EGFR,PIP4K2C,TRAF6,IRAK1,CD80,IRS1,FGF2,PIK3R3,TGFA,PTEN,FGFR4,INSR,PIK3R1,AKT3,PHLPP2,PPP2R5C,MET,MAPK3,SRC,PDGFRB,PDGFRA,KLB,KIT,AREG,PIP5K1C,MAPK1,EREG,ESR1,PDGFB,FRS2,PHLPP1	36	up
negative regulation of transferase activity	GO:0051348	protein metabolism	2.254E-03	DUSP9,PRKAR2A,EPHB2,TRIM27,PAK2,PDCD4,LAX1,APC,GNAQ,PRKCD,NR2F2,DUSP1,DUSP10,DTX3L,SH2B3,FGFR1OP,SPRY4,MCRS1,PDPK1,HEG1,YWHAG,GPS1,SIRT1,CEBPA,AKT1,IGF1R,PTEN,DUSP5,LATS2,IPO5,GSKIP,TSG101,SMCR8,WWTR1,DUSP2,LRP6,SOCS5,PRKAR1A,CDKN1B,SH3BP5,IPO7,GADD45A,CDKN1A,NF1,SPRED3,TP53,HEXIM1,PYCARD,WNK1,PTK6,GSK3B,DVL1,DBNDD1	53	both
negative regulators of ddx58/ifih1 signalling	REAC:R-HSA-936440	signalling pathways	2.235E-03	TNFAIP3,PCBP2,ISG15,UBE2D3,CYLD,ATG5,TRAF3,NLRC5,UBB,MAVS,RNF125,RPS27A,UBC,UBE2D2,UBA7	15	up
nep/ns2 interacts with the cellular export machinery	REAC:R-HSA-168333	cellular transport	1.197E-02	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,NUP62,RAE1,NUP43,RAN,NUP54	12	up
nephron development	GO:0072006	organogenesis	5.893E-03	ANGPT2,SIX1,ENPEP,IL6R,SMO,PODXL,LIF,STAT1,FGF2,VEGFA,SEC61A1,RET,SALL1,MEF2C,MYC,JAG1,DLL1,PDGFRB,PDGFRA,CTNNB1,CD24,BMP7,HOXD11,AHI1,PDGFB,MTSS1	26	up
nephron tubule epithelial cell differentiation	GO:0072160	cell differentiation	3.339E-02	LIF,STAT1,MEF2C,CTNNB1,CD24,MTSS1	6	up
neurodegenerative diseases	REAC:R-HSA-8863678	AD	8.874E-03	PRDX2,BCL2L11,CDC25A,APP,FOXO3,CDC25C,FASLG,CAPN1,CDK5R1,SOD2	10	up

neuron apoptotic process	GO:0051402	apoptosis	6.713E-03	BBC3,BCL2,TNF,SIX1,ERBB3,Fas,MCL1,EPHA7,SET,KDM2B,Bace1,TFAP2A,APP,LANCL1,FZD9,FOXO3,FBXW7,MEF2C,CCL3,DIABLO,CTNNB1,NAIP,BNIP3,AIFM1,TNFRSF21,BAX,ADNP,CPEB4,CDK5R1,PRNP,FOXQ1,EGLN3,KCNB1,AKT1S1,SOD2	35	up
neuron death	GO:0070997	apoptosis	1.105E-04	STAT3,BBC3,AKT1,BCL2,TNF,SIX1,REST,ERBB3,Fas,MCL1,EPHA7,SET,FOS,KDM2B,CCL5,ITGB2,TLR4,CSF1,DKK1,CHMP4B,Bace1,SNCG,TFAP2A,EFNB2,CLU,APP,LANCL1,GSK3B,FZD9,FOXO3,FBXW7,MEF2C,RRAS2,CCL3,DIABLO,CTNNB1,NAIP,EIF4G1,BNIP3,AIFM1,TRAF2,TNFRSF21,BAX,IL10,ADNP,CPEB4,CDK5R1,DDIT4,GPR75,UBB,PRNP,FOXQ1,EGLN3,KCNB1,AKT1S1,DHCR24,SOD2	57	up
neuron projection arborization	GO:0140058	neuronal architecture	3.024E-02	NTNG2,MAP3K13,NTNG1,FZD4,ROCK1,DVL3,WNT5A,TAOK2,DVL1	9	down
neuron projection morphogenesis	GO:0048812	organogenesis	1.027E-02	SEMA4C,BTBD3,ZSWIM6,SEMA4B,FZD4,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,PIK3CD,ABL1,EPHA7,FGFR2,CXCR4,RHOA,LAMC2,ROCK1,LRP2,PARD6B,ACTBL2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,HSP90AA1,WASL,NPTX1,DICER1,B4GALT5,NRP1,ALCAM,PTEN,VEGFA,TAOK1,PAFAH1B1,KIF5B,WNT7A,PTPRD,CPNE1,GRB2,EFNB2,PAK2,SLC9A6,SPTBN1,PIK3R1,NCKAP1,MINK1,ARHGDIA,YWHAH,APP,CDC42,GSK3B,SMURF1,RET,RTN4,BSG,EPB41L3,ARTN,CAPRIN1,ZNF365,ITGB1,SEMA3A,CFL1,EFNB1,ALS2,MOV10,MAPK3,SRC,SPTAN1,SYT1,RAP2A,PLCG1,ANK3,CTNNB1,EPHA5,LLPH,BMP7,MAP1B,EPHA2,GDI1,GFRA3,CTTN,ADNP,GAP43,CDK5R1,PLXNA3,NFIB,UBB,GRB10,MAPK1,CAPRIN2,RPS6KA5,RHOH,ARC,ENAH,UNC5C,FRS2,ACTB,RAB10,SDC2,PAK3,ATP7A,EMB	107	both
neuron projection organisation	GO:0106027	cell organisation	2.127E-02	IGF1R,WASL,PTEN,PAFAH1B1,WNT7A,INSR,APP,CDC42,GSK3B,CAPRIN1,ZNF365,CFL1,MTMR2,ARF1,CDK5R1,PRNP,ABCD2,CAPRIN2,ARC,PAK3	20	up
neurotrophin signalling pathway	KEGG:04722	signalling pathways	9.590E-09	MAPK1,MAPK14,PRKCD,MAP2K2,RPS6KA5,SH2B3,PDPK1,RPS6KA6,NFKB1,AKT1,MAP2K7,KRAS,SORT1,RAP1B,BCL2,RPS6KA3,MAP3K3,CDC42,JUN,AKT2,AKT3,MAP3K1,PRDM4,FRS2,FOXO3,CRKL,RHOA,CALML4,IRAK4,CRK,TP53,ARHGDIA,IRAK2,YWHAE,GSK3B	35	both
neutrophil activation	GO:0042119	leukocyte activation	6.182E-04	VCL,ACLY,PKM,S100A8,EEF1A1,DGAT1,MAPK14,HUWE1,PSMB1,NME2,CD44,LTA4H,NEU1,ALOX5,KPNB1,RHOA,ARL8A,ROCK1,NFKB1,TLR2,MIF,METTL7A,SLPI,PTGES2,CCL5,ITGB2,CXCL8,S100A12,PA2G4,PLAUR,HSP90AA1,RAB14,MLEC,HLA-C,SLC2A3,ACTR2,LAMP2,PTPRJ,COPB1,CPNE1,TMC6,DDX3X,CREG1,HSPA8,PRKCD,TUBB,CAND1,PAFAH1B2,B4GALT1,CAB39,RAP2C,STXBP3,ALDH3B1,DIAPH1,OSCAR,SNAP23,DEGS1,SERPINB1,GPI,GYG1,APEH,UBR4,DSP,SPTAN1,AP2A2,PYGB,PDXK,IMPDH1,TOM1,HMGB1,ATG7,TSPAN14,S100P,SURF4,CAPN1,IMPDH2,CYBB,ADGRG3,DNAJC5,APAF1,C1orf35,LILRA2,NRAS,RAB3D,GM2A,RAB5B,TMEM30A,ARSA,MAPK1,IGF2R,QSOX1,ENPP4,SIGLEC9,F2RL1,C6orf120,RAB18,DSN1,CD36,PTPRB,NCSTN,RAB6A,FRK,EEF2,B2M,RAB31,RAB10,IL15	107	up
neutrophil activation involved in immune response	GO:0002283	leukocyte activation	1.419E-03	VCL,ACLY,PKM,S100A8,EEF1A1,DGAT1,MAPK14,HUWE1,PSMB1,NME2,CD44,LTA4H,NEU1,ALOX5,KPNB1,RHOA,ARL8A,ROCK1,NFKB1,TLR2,MIF,METTL7A,SLPI,PTGES2,ITGB2,S100A12,PA2G4,PLAUR,HSP90AA1,RAB14,MLEC,HLA-C,SLC2A3,ACTR2,LAMP2,PTPRJ,COPB1,CPNE1,TMC6,DDX3X,CREG1,HSPA8,PRKCD,TUBB,CAND1,PAFAH1B2,B4GALT1,CAB39,RAP2C,STXBP3,ALDH3B1,DIAPH1,OSCAR,SNAP23,DEGS1,SERPINB1,GPI,GYG1,APEH,UBR4,DSP,SPTAN1,AP2A2,PYGB,PDXK,IMPDH1,TOM1,HMGB1,ATG7,TSPAN14,S100P,SURF4,CAPN1,IMPDH2,CYBB,ADGRG3,DNAJC5,APAF1,C1orf35,LILRA2,NRAS,RAB3D,GM2A,RAB5B,TMEM30A,ARSA,MAPK1,IGF2R,QSOX1,ENPP4,SIGLEC9,C6orf120,RAB18,DSN1,CD36,PTPRB,NCSTN,RAB6A,FRK,EEF2,B2M,RAB31,RAB10	103	up
neutrophil degranulation	REAC:R-HSA-6798695	leukocyte activation	3.279E-02	VCL,ACLY,PKM,S100A8,EEF1A1,DGAT1,MAPK14,HUWE1,PSMB1,NME2,CD44,LTA4H,NEU1,ALOX5,KPNB1,RHOA,ARL8A,ROCK1,NFKB1,TLR2,MIF,METTL7A,SLPI,PTGES2,ITGB2,S100A12,PA2G4,PLAUR,HSP90AA1,RAB14,MLEC,HLA-C,SLC2A3,ACTR2,LAMP2,PTPRJ,COPB1,CPNE1,TMC6,DDX3X,CREG1,HSPA8,PRKCD,TUBB,CAND1,PAFAH1B2,B4GALT1,CAB39,RAP2C,ALDH3B1,DIAPH1,OSCAR,SNAP23,DEGS1,SERPINB1,GPI,GYG1,APEH,UBR4,DSP,SPTAN1,AP2A2,PYGB,PDXK,IMPDH1,TOM1,HMGB1,ATG7,TSPAN14,S100P,SURF4,CAPN1,IMPDH2,CYBB,ADGRG3,DNAJC5,APAF1,C1orf35,NRAS,RAB3D,GM2A,RAB5B,TMEM30A,ARSA,MAPK1,IGF2R,QSOX1,ENPP4,SIGLEC9,C6orf120,RAB18,DSN1,CD36,PTPRB,NCSTN,RAB6A,FRK,EEF2,B2M,RAB31,RAB10	101	up
neutrophil homeostasis	GO:0001780	leukocyte activation	3.859E-02	PIK3CB,PIK3CD,IL6,HMGB1,SH2B3	5	up
neutrophil mediated immunity	GO:0002446	leukocyte activation	7.504E-04	VCL,ACLY,PKM,S100A8,EEF1A1,IL6R,DGAT1,MAPK14,HUWE1,PSMB1,NME2,CD44,LTA4H,NEU1,ALOX5,KPNB1,RHOA,ARL8A,ROCK1,NFKB1,TLR2,MIF,METTL7A,SLPI,PTGES2,IL6,ITGB2,S100A12,PA2G4,PLAUR,HSP90AA1,RAB14,MLEC,ADAM17,HLA-C,SLC2A3,ACTR2,LAMP2,PTPRJ,COPB1,CPNE1,TMC6,DDX3X,CREG1,HSPA8,PRKCD,TUBB,CAND1,PAFAH1B2,B4GALT1,CAB39,RAP2C,STXBP3,ALDH3B1,DIAPH1,OSCAR,SNAP23,DEGS1,SERPINB1,GPI,GYG1,APEH,UBR4,DSP,SPTAN1,AP2A2,PYGB,PDXK,IMPDH1,TOM1,HMGB1,ATG7,TSPAN14,S100P,SURF4,CAPN1,IMPDH2,CYBB,ADGRG3,DNAJC5,APAF1,C1orf35,NRAS,RAB3D,GM2A,RAB5B,TMEM30A,ARSA,MAPK1,IGF2R,QSOX1,ENPP4,SIGLEC9,F2RL1,C6orf120,RAB18,DSN1,CD36,PTPRB,NCSTN,RAB6A,FRK,EEF2,B2M,RAB31,RAB10	106	up
nf-κ b signalling pathway	KEGG:04064	Nfκ	4.497E-08	XIAP,TNFAIP3,BCL2,TNF,PARP1,CSNK2A1,CD40LG,TRAF6,NFKB1,IRAK1,PTGS2,BCL2A1,CARD10,CXCL8,TLR4,CXCL12,ICAM1,CCL4,CHUK,CYLD,TAB3,MAP3K7,CXCL2,ATM,BIRC3,ZAP70,CD40,MAP3K14,PLCG1,TRAF3,GADD45A,TRAF2,LTBR,TNFRSF1A,LTA,BCL10,CFLAR,BCL2L1,BIRC2,TIRAP,TNFRSF13C,TAB2	42	up
nf-kb is activated and signals survival	REAC:R-HSA-209560	Nfκ	1.704E-02	TRAF6,NFKB1,IRAK1,SQSTM1,UBB,RPS27A,UBC	7	up
nik/nf-κb signalling	GO:0038061	Nfκ	1.134E-03	SPHK1,BCL3,AKT1,TNF,TNFRSF10B,PSMB1,EGFR,RHOA,COPS8,TRAF6,TLR2,NFAT5,IRAK1,CARD10,TLR4,DICER1,PDCD4,CPNE1,AGO1,DDX3X,PPM1A,BTRC,CHUK,AGER,CYLD,REL,APP,MAP3K7,PSMB5,NLRP3,BIRC3,MAP3K14,HMGB1,TNFRSF10A,TRAF2,BMP7,NOD1,ADGRG3,CD27,BIRC2,TIRAP,TLR3,SASH1,PPM1B	44	up
nitric-oxide synthase biosynthetic process	GO:0051767	oxygen levels	2.731E-02	JAK2,TLR2,STAT1,TLR4,KDR,NAMPT,EDN1	7	up
nk t cell differentiation	GO:0001865	cell differentiation	3.967E-02	PRDM1,TOX,TGFBR2,ZBTB7B	4	up
nod-like receptor signalling pathway	KEGG:04621	signalling pathways	2.220E-05	XIAP,TNFAIP3,BCL2,TNF,DHX33,MAPK14,VDAC1,RHOA,TRAF6,NFKB1,FADD,STAT1,IRF7,IL6,CCL5,CXCL8,TLR4,HSP90AA1,TXNIP,GABARAPL1,CHUK,PRKCD,ITPR1,TAB3,GABARAP,MAP3K7,NLRP3,CXCL2,NAMPT,TRPV2,BIRC3,MAPK3,ATG5,IFNB1,MFN2,TRAF3,NAIP,CASP1,TRAF2,RBCK1,RIPK2,NOD1,SUGT1,CYBB,CASP8,BCL2L1,BIRC2,CARD6,STAT2,TANK,MAVS,MAPK1,ERBIN,PLCB1,TAB2	55	up
nod1/2 signalling pathway	REAC:R-HSA-168638	signalling pathways	9.755E-07	TNFAIP3,MAPK14,IRAK2,TRAF6,IRAK1,UBE2V1,CHUK,CYLD,TAB3,MAP3K7,BIRC3,CASP1,CASP9,RIPK2,NOD1,CASP8,BIRC2,UBB,RPS27A,UBC,TAB2	21	up
non-alcoholic fatty liver disease	KEGG:04932	diseases	3.197E-03	CEBPA,AKT1,COX7C,SDHB,TNF,IL6R,PRKAG1,MAP3K11,PIK3CB,Fas,PIK3CD,FOS,COX2,NFKB1,TGFB1,IL6,CXCL8,CASP7,IRS1,PIK3R3,PRKAA1,BCL2L11,INSR,PIK3R1,AKT3,CDC42,GSK3B,MLXIP,CASP3,CYCS,TRAF2,BAX,FASLG,TNFRSF1A,PPARA,CASP8,UQCRFS1,UQCRB,SOCS3,CYP2E1,SREBF1	41	up
non-canonical wnt signalling pathway	GO:0035567	Wnt signalling	1.195E-02	FZD4,PSMB1,FZD6,LBX2,TNRC6B,RHOA,SFRP1,AGO3,DKK1,WNT1,FZD5,TNRC6A,AGO2,AP2B1,WNT7A,AGO1,GNB1,CCDC88C,AGO4,PRICKLE2,NKD1,CDC42,SMURF1,MAP3K7,ZNRF3,PSMB5,AP2A1,LEF1,MOV10,AP2M1,AP2A2,CTNNB1,PPP3R1,TCF7L2,PLCB1	35	up
non-small cell lung cancer	KEGG:05223	cancer	6.024E-03	CDKN2A,STAT3,E2F3,TP53,ERBB2,AKT1,BAK1,PIK3CB,RAF1,PIK3CD,EGFR,E2F2,CDKN1A,RARB,CCND1,SOS1,KRAS,SOS2,PIK3R3,TGFA,CDK4,CDK6,KIF5B,RASSF5,GRB2,PIK3R1,AKT3,RET,FOXO3,E2F1,STAT5A,MET,MAPK3,MAP2K1,PLCG1,CASP9,GADD45A,BAX,NRAS,MAPK1,STK4	41	both
nonsense mediated decay (nmd) enhanced by the exon junction complex (ejc)	REAC:R-HSA-975957	transcription and translation	4.447E-02	PABPC1,CASC3,PPP2CA,RPL29,RPS12,RPL3,RPS7,RPS3A,RPLP0,RPL35A,ETF1,RPS28,PNRC2,RNPS1,RPL14,RPL10,RPL36,RPS5,RPL37,RPS2,NCBP2,EIF4G1,RPL9,RPL23,RPL24,RPS15A,RPL4,RPS27A,RPS14,SMG1	30	up
nonsense-mediated decay (nmd)	REAC:R-HSA-927802	transcription and translation	4.447E-02	PABPC1,CASC3,PPP2CA,RPL29,RPS12,RPL3,RPS7,RPS3A,RPLP0,RPL35A,ETF1,RPS28,PNRC2,RNPS1,RPL14,RPL10,RPL36,RPS5,RPL37,RPS2,NCBP2,EIF4G1,RPL9,RPL23,RPL24,RPS15A,RPL4,RPS27A,RPS14,SMG1	30	up
notch signalling involved in heart development	GO:0061314	NOTCH signalling	2.184E-02	NOTCH2,NOTCH1,RBPJ,HEYL,JAG1,SNAI1	6	up

notch signalling pathway	KEGG:04330	NOTCH signalling	4.584E-02	MYC,TP63,SORBS2,NOTCH1,DTX3L,EPN2,EP300,ADAM17,POFUT1,TSPAN14,YAP1,AKT1,SNAI2,NOTCH4,NOTCH2,STAT3,CD46,TRAF7,TSPAN15,EGF,HEYL,SYNJ2BP,ITCH,LLGL1,CREBBP,NCSTN,HOXD3,PRAG1	28	both
notch signalling pathway	GO:0007219	NOTCH signalling	4.584E-02	MYC,TP63,SORBS2,NOTCH1,DTX3L,EPN2,EP300,ADAM17,POFUT1,TSPAN14,YAP1,AKT1,SNAI2,NOTCH4,NOTCH2,STAT3,CD46,TRAF7,TSPAN15,EGF,HEYL,SYNJ2BP,ITCH,LLGL1,CREBBP,NCSTN,HOXD3,PRAG1	28	both
notch3 activation and transmission of signal to the nucleus	REAC:R-HSA-9013507	NOTCH signalling	2.863E-02	EGFR,TACC3,MIB1,JAG1,DLL1,YBX1,UBB,RPS27A,UBC,NCSTN	10	up
ns1 mediated effects on host pathways	REAC:R-HSA-168276	signalling pathways	2.415E-04	NUP93,NUP205,RANBP2,NUP37,NDC1,KPNB1,ISG15,KPNA4,NUP50,KPNA1,KPNA3,POM121C,NUP62,RAE1,NUP43,NUP54,PABPN1,KPNA2	18	up
nuclear chromosome segregation	GO:0098813	cell cycle	1.254E-02	VPS4B,PDS5A,AURKB,SIRT7,APC,SMC2,KPNB1,DUSP1,HORMAD2,KIF22,FANCM,NSL1,TACC3,RCC2,KIF2C,CHMP4B,CUL3,VPS4A,KIF23,RACGAP1,CDC27,AXIN2,CDC42,FBXW7,CHMP2B,ECT2,ATM,STAG2,MRE11,CDC20,FEN1,MCMBP,IK,KIF4A,NUP62,ANAPC5,NCAPG,CTNNB1,POGZ,BAG6,BECN1,CDC23,CCNB1,SLX4,INCENP,NCAPG2,NCAPD2,RAN,NAA50,DSN1,ERCC4,PHF13,TOP2A	53	up
nuclear division	GO:0000280	cell cycle	1.141E-02	VPS4B,IGF2,PDS5A,XIAP,AURKB,PPP2CA,SIRT7,APC,EMD,SMC2,KPNB1,RHOA,DUSP1,HORMAD2,KIF22,FANCM,NSL1,TACC3,KIF2C,TGFA,CHEK1,AURKAIP1,CHMP4B,BCL2L11,CUL3,VPS4A,KIF23,BIRC5,RACGAP1,KIF3B,CDK1,INSR,CDC27,CYP26B1,CHMP2B,ATM,UBE2S,KIF11,STAG2,MRE11,CDC25C,CDC20,PDGFRB,IK,KIF4A,NUP62,ANAPC5,NCAPG,POGZ,MKI67,RAD51,BAG6,BECN1,BMP7,KIF2A,CDC23,UBXN2B,REEP3,CNEP1R1,AURKA,CCNB1,SLX4,INCENP,NCAPG2,NCAPD2,CHEK2,ZNF711,EDN1,RAN,EREG,NAA50,DSN1,ERCC4,MYBL1,DDX4,PDGFB,KLHDC3,PLCB1,PHF13,TOP2A	80	up
nuclear dna replication	GO:0033260	cell cycle	3.266E-02	BRCA2,MCMDC2,POLE4,POLD1,MCM4,MCM2,MCM7,FEN1,PRIM1,MCM6,MCM3,MCM5,NUGGC,CHEK2,RFC2,TERF2	16	up
nuclear envelope (ne) reassembly	REAC:R-HSA-2995410	cell organisation	2.698E-02	CHMP3,NUP93,PPP2CA,NUP205,NUP37,EMD,NDC1,KPNB1,LBR,CHMP4B,VPS4A,CDK1,TUBB2A,RANGAP1,CHMP2B,TNPO1,NUP62,NUP43,CCNB1,RAN,NUP54	21	up
nuclear envelope breakdown	REAC:R-HSA-2980766	cell organisation	4.207E-02	NUP93,NUP205,RANBP2,NUP37,EMD,NDC1,CDK1,NUP50,POM121C,NUP62,RAE1,CNEP1R1,NUP43,CCNB1,NUP54	15	up
nuclear export	GO:0051168	cellular transport	1.365E-04	CDKN2A,DHX38,ATXN1,TP53,SUPT6H,LTV1,CASC3,NUP93,SIRT7,NUP205,RANBP2,NUP37,NPM1,EIF4E,EMD,NSUN2,NDC1,IFI27,STRADB,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,GSK3B,SMURF1,POM121C,YTHDC1,RANGAP1,THOC2,RBM15B,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,RAE1,CSE1L,BAG3,NUP43,RBM27,TCF7L2,RAN,POLR2D,SRSF2,NUP54,SMG1,EIF6,FYTTD1,DDX39A,PABPN1	52	up
nuclear import of rev protein	REAC:R-HSA-180746	protein metabolism	2.556E-03	NUP93,NUP205,RANBP2,NUP37,NPM1,NDC1,KPNB1,NUP50,POM121C,NUP62,RAE1,NUP43,RAN,NUP54	14	up
nuclear pore complex (npc) disassembly	REAC:R-HSA-3301854	cell organisation	1.292E-02	NUP93,NUP205,RANBP2,NUP37,NDC1,CDK1,NUP50,POM121C,NUP62,RAE1,NUP43,CCNB1,NUP54	13	up
nuclear pore organisation	GO:0006999	cell organisation	1.881E-02	NUP93,NUP205,NDC1,RTN4,NUP98,NUP54,TMEM170A	7	up
nuclear transport	GO:0051169	cellular transport	5.883E-06	CSE1L,NUP98,SLBP,ZC3H11A,PRKCD,HNRNPA1,RBM26,UFM1,CDH1,ANP32B,NUP62,NUP205,PTPN14,POLR2D,RANGAP1,HMGA1,AKT1,RAN,KPNA1,TNPO1,IPO5,FAM53C,BACH2,ABCE1,SMAD3,STAT3,POM121C,UHMK1,RBM8A,ATXN1,SRSF7,RGPD4,PRICKLE1,APPL1,LMNA,HNRNPA2B1,NUP50,IPO7,NUP210,RSRC1,SNRPD1,TP53,GEMIN4,XPO1,EIF4A3,NUP35,TNPO3,NUP85,FYTTD1,STYX,NXF1,YWHAE,GSK3B,EIF5A,HEATR3,PHAX,EIF4E,SRSF4,XPO6,E2F3	60	both
nuclear-transcribed mrna catabolic process	GO:0000956	catabolic process	2.778E-04	MRTO4,PABPC1,LSM4,CASC3,PPP2CA,RPL29,RPS12,THRAP3,RPL3,RPS7,RPS3A,BTG2,RPLP0,HBS1L,RPL35A,TNKS1BP1,TNRC6B,ETF1,RPS28,CNOT6L,PATL1,DDX6,TNRC6A,AGO2,CNOT4,PNRC2,AGO1,RNPS1,CSDE1,RPL14,CPEB3,EDC3,RPL10,RPL36,RPS5,ATM,RPL37,RPS2,NCBP2,XRN1,EIF4G1,CTIF,CNOT2,RPL9,RPL23,TOB1,RPL24,RPS15A,RPL4,CNOT1,RPS27A,POLR2D,MTPAP,RPS14,SMG1	55	up
nuclear-transcribed mrna catabolic process, nonsense-mediated decay	GO:0000184	catabolic process	7.554E-03	PABPC1,CASC3,PPP2CA,RPL29,RPS12,RPL3,RPS7,RPS3A,RPLP0,RPL35A,ETF1,RPS28,PNRC2,RNPS1,RPL14,RPL10,RPL36,RPS5,RPL37,RPS2,NCBP2,EIF4G1,CTIF,RPL9,RPL23,RPL24,RPS15A,RPL4,RPS27A,RPS14,SMG1	31	up
nuclear-transcribed mrna poly(a) tail shortening	GO:0000289	transcription and translation	3.372E-02	PABPC1,BTG2,TNKS1BP1,TNRC6B,CNOT6L,TNRC6A,AGO2,CNOT4,CPEB3,CNOT2,TOB1,CNOT1	12	up
nucleic acid transport	GO:0050657	cellular transport	2.160E-04	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,SIDT2,POM121C,YTHDC1,THOC2,RBM15B,TGFBR2,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,CKAP5,YBX1,RAE1,NUP43,RBM27,RAN,POLR2D,SRSF2,NUP54,ARC,SMG1,EIF6,FYTTD1,DDX39A,MRPL18,PABPN1,HNRNPA3	46	up
nucleobase-containing compound transport	GO:0015931	cellular transport	1.258E-03	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,SLC19A1,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,SLC29A1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,SIDT2,POM121C,YTHDC1,THOC2,RBM15B,TGFBR2,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,CKAP5,YBX1,RAE1,SLC25A36,NUP43,SLC25A32,RBM27,RAN,POLR2D,SRSF2,NUP54,ARC,SMG1,EIF6,FYTTD1,DDX39A,MRPL18,PABPN1,HNRNPA3	50	up
nucleocytoplasmic transport	GO:0006913	cellular transport	7.789E-06	CSE1L,NUP98,SLBP,ZC3H11A,PRKCD,HNRNPA1,RBM26,UFM1,CDH1,ANP32B,NUP62,NUP205,PTPN14,POLR2D,RANGAP1,AKT1,RAN,KPNA1,TNPO1,IPO5,FAM53C,BACH2,ABCE1,SMAD3,STAT3,POM121C,UHMK1,RBM8A,ATXN1,SRSF7,RGPD4,PRICKLE1,APPL1,LMNA,HNRNPA2B1,NUP50,IPO7,NUP210,RSRC1,SNRPD1,TP53,GEMIN4,XPO1,EIF4A3,NUP35,TNPO3,NUP85,FYTTD1,STYX,NXF1,YWHAE,GSK3B,EIF5A,HEATR3,PHAX,EIF4E,SRSF4,XPO6,E2F3	59	both
nucleoside diphosphate metabolic process	GO:0009132	metabolic process	2.506E-04	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,NME2,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,POM121C,NUDT5,LDHA,GPI,NUP62,TIGAR,NUP98,CMPK1,RAE1,DTYMK,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	36	up
nucleotide phosphorylation	GO:0046939	nucleotide metabolism	3.665E-04	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,NME2,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,POM121C,LDHA,GPI,NUP62,TIGAR,NUP98,CMPK1,RAE1,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	34	up
nucleotide-binding domain, leucine rich repeat containing receptor (nlr) signalling pathways	REAC:R-HSA-168643	nucleotide metabolism	3.662E-07	TNFAIP3,BCL2,MAPK14,IRAK2,TRAF6,NFKB1,IRAK1,TXNIP,UBE2V1,CHUK,CYLD,TAB3,APP,MAP3K7,NLRP3,BIRC3,CASP1,CASP9,RIPK2,NOD1,SUGT1,CASP8,BCL2L1,BIRC2,UBB,RPS27A,UBC,TAB2	28	up
nucleotide-binding domain, leucine rich repeat containing receptor signalling pathway	GO:0035872	nucleotide metabolism	1.701E-05	XIAP,TNFAIP3,IRAK2,TRAF6,IRAK1,UBE2V1,CYLD,TAB3,MAP3K7,BIRC3,RIPK2,NOD1,CASP8,BIRC2,UBB,RPS27A,UBC,ERBIN,TAB2	19	up
nucleotide-binding oligomerization domain containing signalling pathway	GO:0070423	nucleotide metabolism	1.065E-05	XIAP,TNFAIP3,IRAK2,TRAF6,IRAK1,UBE2V1,CYLD,TAB3,MAP3K7,BIRC3,RIPK2,NOD1,CASP8,BIRC2,UBB,RPS27A,UBC,ERBIN,TAB2	19	up
nucleus organisation	GO:0006997	cell organisation	1.805E-02	ETS1,VPS4B,NUP93,PPP2CA,NUP205,EMD,NDC1,SERBP1,SRPK1,PAFAH1B1,CHMP4B,VPS4A,DYRK3,DMPK,CDK1,SUN1,RTN4,CHMP2B,NUP98,UBXN2B,REEP3,CNEP1R1,TOR1B,CCNB1,SUN2,HABP4,NUP54,TMEM170A	28	up
oncogene induced senescence	REAC:R-HSA-2559585	senescence	3.876E-11	CDK6,MAPK1,AGO3,SP1,TNRC6B,AGO4,AGO1,ETS1,MDM2,TP53,MDM4,TFDP2,E2F3	13	both
oncogenic mapk signalling	REAC:R-HSA-6802957	MAPK signalling	3.492E-02	VCL,JAK2,MAP3K11,FXR1,RAF1,KRAS,YWHAB,SPRED1,BCL2L11,TRAK1,ACTG1,MAPK3,SRC,MAP2K1,ITGB3,ATG7,NRAS,ESRP1,QKI,MAPK1,ACTB	21	up
oocyte meiosis	KEGG:04114	endocrine system	1.889E-02	RPS6KA1,CCNE1,PPP2CA,MAPK14,IGF1R,PPP1CA,YWHAB,BTRC,ITPR1,ANAPC13,CDK1,CPEB2,CPEB3,CDC27,YWHAQ,YWHAH,CCNE2,PPP2R5C,RPS6KA3,CDK2,CDC25C,CDC20,MAPK3,AR,MAP2K1,ANAPC5,PPP3R1,CDC23,PPP1CC,CPEB4,AURKA,CCNB1,MAPK1	33	up

organelle fission	GO:0048285	cell cycle	6.843E-03	VPS4B,IGF2,PDS5A,XIAP,MYO19,AURKB,PPP2CA,SIRT7,APC,EMD,SMC2,KPNB1,RHOA,DUSP1,HORMAD2,KIF22,FANCM,MX2,NSL1,TACC3,KIF2C,TGFA,CHEK1,AURKAIP1,CHMP4B,MTFR1L,BCL2L11,CUL3,VPS4A,KIF23,BIRC5,RACGAP1,ACOX1,KIF3B,CDK1,INSR,CDC27,CYP26B1,KDR,CHMP2B,ATM,UBE2S,KIF11,STAG2,MRE11,CDC25C,CDC20,PDGFRB,IK,KIF4A,NUP62,ANAPC5,NCAPG,POGZ,MKI67,RAD51,BNIP3,BAG6,BECN1,BMP7,KIF2A,CDC23,UBXN2B,REEP3,CNEP1R1,AURKA,CCNB1,MFF,STAT2,SLX4,INCENP,NCAPG2,NCAPD2,CHEK2,ZNF711,EDN1,RAN,EREG,NAA50,DSN1,ERCC4,MYBL1,DDX4,PDGFB,KLHDC3,PLCB1,PHF13,TOP2A,SLC25A46	89	up
organic acid transmembrane transport	GO:1903825	cellular transport	3.846E-02	SLC7A1,AKT1,SLC19A1,SLC25A1,SLC7A6,LRP2,ARL6IP1,SLC38A2,SLC25A12,SLC25A22,SLC25A29,SLC7A5,ITGB1,CPT2,ACSL1,SLC1A5,PER2,SLC25A32,SLC38A9,MID1IP1,LRRC8D,ABCD2,SLC46A1,CD36,SLC16A1,THBS1,EMB	27	up
organic hydroxy compound biosynthetic process	GO:1901617	protein metabolism	2.153E-02	ACLY,SPHK1,IP6K1,PSAT1,TNF,IPPK,PTH1R,REST,LSS,CD244,DKK3,KPNB1,NFKB1,OSBPL1A,LBR,FGF2,ALOX12,PRKAA1,OSBPL3,FASN,PNPO,PPIP5K2,FGFR4,SPTLC1,MSMO1,SP1,ERLIN1,SIRT1,DHCR7,ERLIN2,PDXK,CYP51A1,HSD17B10,SNAI1,QDPR,ZEB2,INSIG1,PER2,NFYB,OSBP,IPMK,RAN,NUS1,DHCR24,SC5D,SREBF1,H6PD	47	up
ossification	GO:0001503	organogenesis	2.883E-03	BCOR,BMPR1B,SIRT7,REST,IL6R,ALOX5,CYP24A1,EGFR,GLI1,FGFR2,RHOA,GPM6B,ISG15,IFITM1,SPP1,BGLAP,SFRP1,IL6,NOTCH1,SOX2,DKK1,FGFR3,SKI,CDK6,CRIM1,FASN,RUNX2,TFAP2A,RBPJ,ZBTB16,ACVR2A,EXT1,FZD9,YAP1,TUFT1,IL6ST,MEF2C,RRAS2,CCL3,TMEM64,ITGA11,RRBP1,LEF1,DDX21,EXT2,SNAI1,BMP7,EPHA2,PRKD1,S1PR1,BMPR1A,SOX11,SMOC1,ACVR1,WWTR1,LIMD1,TWIST1,HNRNPC,FFAR4,CHSY1	60	up
osteoblast differentiation	GO:0001649	cell differentiation	2.403E-03	BMPR1B,SIRT7,REST,IL6R,CYP24A1,GLI1,FGFR2,IFITM1,SPP1,BGLAP,SFRP1,IL6,NOTCH1,SOX2,SKI,CDK6,CRIM1,FASN,RUNX2,ACVR2A,YAP1,IL6ST,MEF2C,RRAS2,CCL3,TMEM64,ITGA11,RRBP1,LEF1,DDX21,SNAI1,BMP7,EPHA2,PRKD1,BMPR1A,SOX11,SMOC1,ACVR1,WWTR1,LIMD1,TWIST1,HNRNPC,FFAR4	43	up
osteoclast differentiation	GO:0030316	cell differentiation	1.205E-04	TNF,GAB2,MAPK14,FBN1,TRAF6,BGLAP,TLR4,NOTCH2,IL23R,CSF1,MAFB,SH3PXD2A,PAFAH1B1,OSCAR,FBXW7,CCL3,SRC,CEBPB,EPHA2,CSF1R,TREM2,TLR3,UBASH3B,SIGLEC15	24	up
osteoclast differentiation	GO:0030316	cell differentiation	1.205E-04	TNF,GAB2,MAPK14,FBN1,TRAF6,BGLAP,TLR4,NOTCH2,IL23R,CSF1,MAFB,SH3PXD2A,PAFAH1B1,OSCAR,FBXW7,CCL3,SRC,CEBPB,EPHA2,CSF1R,TREM2,TLR3,UBASH3B,SIGLEC15	24	up
osteoclast differentiation	KEGG:04380	cell differentiation	1.205E-04	TNF,GAB2,MAPK14,FBN1,TRAF6,BGLAP,TLR4,NOTCH2,IL23R,CSF1,MAFB,SH3PXD2A,PAFAH1B1,OSCAR,FBXW7,CCL3,SRC,CEBPB,EPHA2,CSF1R,TREM2,TLR3,UBASH3B,SIGLEC15	24	up
osteoclast differentiation	KEGG:04380	cell differentiation	1.205E-04	TNF,GAB2,MAPK14,FBN1,TRAF6,BGLAP,TLR4,NOTCH2,IL23R,CSF1,MAFB,SH3PXD2A,PAFAH1B1,OSCAR,FBXW7,CCL3,SRC,CEBPB,EPHA2,CSF1R,TREM2,TLR3,UBASH3B,SIGLEC15	24	up
other types of o-glycan biosynthesis	KEGG:00514	protein metabolism	2.451E-02	B4GALT3,GALNT18,ST6GAL2,GXYLT2,LFNG,EOGT,OGT,GALNT1,B4GALT1,GALNT7,C1GALT1C1,POFUT2,GALNT4,POC1B-GALNT4,GALNT8	15	up
outflow tract morphogenesis	GO:0003151	organogenesis	7.835E-03	SMAD4,FGFR2,LRP2,ROBO1,NOTCH1,NRP1,VEGFA,ELN,RBPJ,HEYL,TGFBR3,MEF2C,JAG1,TGFBR2,CTNNB1,BMPR1A,GATA6,SOX11	18	up
ovarian tumor domain proteases	REAC:R-HSA-5689896	cancer	3.197E-06	TP53,TNFAIP3,YOD1,APC,RHOA,TRAF6,PTEN,OTUB1,CDK1,TRAF3,RIPK2,NOD1,OTUD7B,UBB,MAVS,RPS27A,UBC,OTUD3,ESR1,TNIP3,OTUD7A	21	up
oxidative stress induced senescence	REAC:R-HSA-2559580	senescence	2.340E-04	CDK6,CBX4,MAPK1,RBBP4,MAPK14,HIST1H2BJ,CBX6,AGO3,TNRC6B,AGO4,EED,EZH2,SUZ12,AGO1,MAP2K7,HIST1H2BK,PHC3,KDM6B,FOS,MDM2,JUN,CBX2,TP53,MDM4,MAPKAPK5,TFDP2,BMI1,MINK1,E2F3	29	both
p-body assembly	GO:0033962	cell organisation	8.466E-03	LSM4,CNOT6L,PATL1,DDX6,EDC3,ATXN2L,CNOT2,CNOT1,LIMD1	9	up
p53 signalling pathway	KEGG:04115	P53 signalling	7.964E-13	CDK6,EI24,SESN3,IGF1,BID,CD82,CCND1,CASP3,SERPINE1,CCND3,PPM1D,ATM,PTEN,PMAIP1,CCNG1,BCL2,BBC3,MDM2,CCND2,CASP8,TNFRSF10B,CHEK1,SIVA1,CCNG2,TNFRSF10A,GADD45A,CDKN1A,TP53,MDM4,CYCS,THBS1,SHISA5	32	both
p75ntr recruits signalling complexes	REAC:R-HSA-209543	signalling pathways	1.704E-02	TRAF6,IRAK1,SQSTM1,RIPK2,UBB,RPS27A,UBC	7	up
p75ntr signals via nf-kb	REAC:R-HSA-193639	Nfκ	1.599E-02	TRAF6,NFKB1,IRAK1,SQSTM1,RIPK2,UBB,RPS27A,UBC	8	up
pancreatic cancer	KEGG:05212	cancer	2.472E-03	CDKN2A,STAT3,E2F3,TP53,ERBB2,AKT1,BAK1,PIK3CB,RAF1,PIK3CD,SMAD4,EGFR,E2F2,NFKB1,CDKN1A,STAT1,TGFB1,SMAD2,BRCA2,CCND1,KRAS,PIK3R3,TGFA,CDK4,VEGFA,CDK6,SMAD3,RPS6KB1,CHUK,PIK3R1,AKT3,CDC42,E2F1,MAPK3,TGFBR2,MAP2K1,RAD51,CASP9,GADD45A,RALB,BAX,BCL2L1,MAPK1	43	both
pathogenic escherichia coli infection	KEGG:05130	viral of bacterial infection	3.240E-07	SEC24A,TNF,BAK1,MAPK14,TNFRSF10B,Fas,ABL1,RHOA,FOS,ROCK1,TRAF6,NFKB1,FADD,IRAK1,WASF2,MYO6,IL6,CXCL8,TLR4,CASP7,WASL,ACTR3B,ACTR2,MYO5A,PAK2,CHUK,TUBB,TAB3,NCKAP1,TUBB2A,CDC42,MAP3K7,NLRP3,ITGB1,ACTG1,CYTH1,MAPK3,SRC,CASP3,MYO1C,NAIP,CASP1,CASP9,CYCS,TNFRSF10A,TRAF2,ARF6,BAX,FASLG,TNFRSF1A,CYTH3,CTTN,CASP8,ARF1,TIRAP,MYO1B,CYTH2,MAPK1,WIPF2,MYH11,ACTB,TAB2,RAB1A,PAK3	64	up
pathways of neurodegeneration - multiple diseases	KEGG:05022	diseases	3.944E-02	ND6,FZD4,ATXN1,KLC2,GRIN2A,FRAT2,COX7C,SDHB,ZFYVE1,BCL2,TNF,FUS,BAK1,ADRM1,MAPK14,VDAC1,PSMB1,APC,Fas,RAF1,FZD6,CSNK2A1,COX2,NFKB1,FADD,PTGS2,NOS1,SQSTM1,IL6,CASP7,WNT2B,CSF1,DKK1,WNT1,KRAS,FZD5,ATG14,KIF5B,GABARAPL1,WNT7A,MAP2K3,DCTN5,TUBB,AGER,ITPR1,WIPI2,GABARAP,AXIN2,TUBB2A,APP,GSK3B,FZD9,PSMB5,CHMP2B,ALS2,MAPK3,KLC1,CASP3,MAP2K1,MFN2,PLCG1,STX1A,CTNNB1,HSD17B10,ATXN2L,CASP9,CYCS,TRAF2,BECN1,TOMM40,BAX,PPP3R1,FASLG,TNFRSF1A,ATXN1L,CAPN1,CYBB,CASP8,BCL2L1,APAF1,NRAS,CDK5R1,TANK,UQCRFS1,GNAQ,UBB,PRNP,MAPK1,RPS27A,UBC,TRPC3,NRBF2,UQCRB,FIG4,UBA7,TOMM40L,PLCB1,RAB1A,ACTR1A	99	up
pattern recognition receptor signalling pathway	GO:0002221	signalling pathways	2.853E-07	ZDHHC5,XIAP,S100A8,TNFAIP3,MFHAS1,HSPD1,IRAK2,TRAF6,TLR2,FADD,IRAK1,IRF7,RSAD2,ITGB2,PRKCE,TLR4,OTUD4,UBE2D3,COLEC12,HSP90B1,UBE2V1,MAPKAPK2,DDX3X,CHUK,ZCCHC3,CYLD,TAB3,RAB11FIP2,USP15,MAP3K7,RTN4,RPS6KA3,BIRC3,PUM2,CD40,MAP3K1,TRAF3,HMGB1,RIPK2,NOD1,BCL10,CASP8,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,TANK,UBB,IRF1,RNF125,RPS27A,UBC,CXorf21,SFTPA1,ERBIN,UBE2D2,F2RL1,CD36,TNIP3,TAB2	61	up
pd-l1 expression and pd-1 checkpoint pathway in cancer	KEGG:05235	cell cycle	7.513E-06	STAT3,JAK2,AKT1,MAPK14,PIK3CB,RAF1,PIK3CD,RASGRP1,EGFR,CSNK2A1,FOS,TRAF6,NFKB1,TLR2,STAT1,TLR4,KRAS,CD274,PIK3R3,PTEN,RPS6KB1,PDCD1,MAP2K3,CHUK,PIK3R1,AKT3,MAPK3,ZAP70,MAP2K1,PLCG1,PPP3R1,NRAS,TIRAP,MAPK1	34	both
peptidyl-lysine modification	GO:0018205	protein metabolism	2.043E-03	SAE1,SOX4,KMT2A,NUP98,WDR82,SUMO2,EPC1,ATRX,GNL3L,RIF1,EP300,NUP62,KAT6B,NUP205,RPS6KA5,MCRS1,PIAS2,RANGAP1,MEAF6,SENP1,BCL11A,SIRT1,EZH2,KMT2E,SUV39H2,NAA50,MORF4L1,DNMT3B,DOT1L,PER1,NAA40,KMT5C,LOX,MORF4L2,MDM2,TET3,TET2,CHEK1,POM121C,BCOR,KIAA1586,PIAS1,LMNA,JARID2,NUP50,DR1,MTF2,CTNNB1,NUP210,PPARGC1A,NUP35,MSL2,NUP85,SETD7,CREBBP,BRPF3,KMT2B,HCFC1	58	both
peptidyl-serine modification	GO:0018209	protein kinase activity	9.037E-03	PARP1,PAK2,MAPK1,MAPK14,GALNT13,GALNT1,FNIP2,BRSK1,PRKX,PRKCD,MAP3K13,PCK1,MAP2K2,RPS6KA5,PDPK1,PFN2,ROCK2,AKT1,TGFBR1,TGFBR2,ATM,PTEN,CAPRIN2,CSNK1A1,LATS2,GRK2,TFRC,PDK3,HMGA2,RPS6KA3,DDIT4,ULK1,NLK,SGK1,AKT2,AKT3,VEGFA,CAMK1D,UHMK1,CAB39,KDELC2,PDE4D,GALNT3,ROCK1,GADD45A,HSP90AB1,CSNK2A1,ERN1,MAPKAPK5,PARP2,WNK1,GALNT2,GSK3B,MIF,MKNK2,AURKA	56	both
peptidyl-serine phosphorylation	GO:0018105	phosphorylation	5.692E-07	MKNK2,AKT1,AURKB,TNF,WNK1,MAPK14,LIF,CD44,RAF1,DYRK2,TNKS1BP1,HMGA2,NTRK3,EGFR,CSNK2A1,ROCK1,MIF,NOS1,IL6,PRKCE,HSP90AA1,DKK1,RPS6KA4,PTEN,VEGFA,RPS6KB1,STK38,MAPKAPK2,PDE4D,PAK2,CHUK,PRKCD,DYRK3,DMPK,CDK1,AKT3,CAB39,CREBL2,SMAD7,CAMKV,APP,CNKSR3,GSK3B,TLK1,RASSF2,RPS6KA3,CLSPN,HAX1,CDK2,LATS2,ATM,TGFBR2,TFRC,IFNB1,EIF4G1,GADD45A,RICTOR,RIPK2,PRKD1,MAST3,FNIP1,AURKA,CDK5R1,DDIT4,MAPKAPK5,MASTL,MAPK1,CAPRIN2,RPS6KA5,DYRK1A,PRKD2,SMG1,PDGFB,STK4,HIPK1	75	up
peptidyl-threonine modification	GO:0018210	protein metabolism	1.784E-02	SPHK1,AKT1,WNK1,DYRK2,TNKS1BP1,CSNK2A1,ROCK1,EOGT,S1PR2,CHEK1,SPRED1,GALNT1,WNK3,PRKCD,DYRK3,CDK1,CAB39,SMAD7,APP,GSK3B,CAD,TGFBR2,MAP2K1,EIF4G1,BMP7,RIPK2,PRKD1,CDK5R1,DDIT4,MAPK1,ACVR1,GALNT4,DYRK1A,PRKD2,HIPK1	35	both
peptidyl-threonine phosphorylation	GO:0018107	phosphorylation	7.872E-04	SPHK1,AKT1,WNK1,DYRK2,TNKS1BP1,CSNK2A1,ROCK1,S1PR2,CHEK1,SPRED1,WNK3,PRKCD,DYRK3,CDK1,CAB39,SMAD7,APP,GSK3B,CAD,TGFBR2,MAP2K1,EIF4G1,BMP7,RIPK2,PRKD1,CDK5R1,DDIT4,MAPK1,ACVR1,DYRK1A,PRKD2,HIPK1	32	up

peptidyl-tyrosine modification	GO:0018212	protein metabolism	2.249E-06	NF2,STAT3,IGF2,TP53,ERBB2,JAK2,EPO,PPP2CA,TNF,IL6R,IGF1R,ERBB3,LIF,SH3BP5L,CD44,FES,ABL1,EGFR,EPHA7,FGFR2,MIF,ERBB4,CD80,SFRP1,IL6,CCL5,ITGB2,IL23R,GPRC5A,ITGA5,FGFR3,ADAM17,NRP1,TGFA,ABL2,VEGFA,PTPRJ,PAK2,PRKCD,FGFR4,INSR,RAP2C,APP,KDR,SOCS5,IL6ST,HAX1,FBXW7,MAPK3,ZAP70,SRC,PDGFRB,PDGFRA,SOCS4,CD40,ITGB3,RIPK2,CSF1R,KIT,TNFRSF1A,TREM2,AREG,DOCK3,ADNP,SH2B3,PRNP,ACVR1,EREG,SOCS3,DYRK1A,PDGFB,FRK,IL15	73	up
peptidyl-tyrosine phosphorylation	GO:0018108	phosphorylation	1.410E-06	NF2,STAT3,IGF2,TP53,ERBB2,JAK2,EPO,PPP2CA,TNF,IL6R,IGF1R,ERBB3,LIF,SH3BP5L,CD44,FES,ABL1,EGFR,EPHA7,FGFR2,MIF,ERBB4,CD80,SFRP1,IL6,CCL5,ITGB2,IL23R,GPRC5A,ITGA5,FGFR3,ADAM17,NRP1,TGFA,ABL2,VEGFA,PTPRJ,PAK2,PRKCD,FGFR4,INSR,RAP2C,APP,KDR,SOCS5,IL6ST,HAX1,FBXW7,MAPK3,ZAP70,SRC,PDGFRB,PDGFRA,SOCS4,CD40,ITGB3,RIPK2,CSF1R,KIT,TNFRSF1A,TREM2,AREG,DOCK3,ADNP,SH2B3,PRNP,ACVR1,EREG,SOCS3,DYRK1A,PDGFB,FRK,IL15	73	up
pertussis	KEGG:05133	viral of bacterial infection	7.437E-04	TNF,MAPK14,RHOA,FOS,TRAF6,NFKB1,IRAK1,IL6,ITGB2,CXCL8,TLR4,CASP7,ITGA5,NLRP3,ITGB1,CFL1,MAPK3,CASP3,CASP1,NOD1,IL10,TIRAP,CFL2,MAPK1,IRF1,SFTPA1	26	up
phosphatidylinositol 3-kinase signalling	GO:0014065	PI3k signalling	2.722E-04	EPOR,ERBB2,JAK2,AKT1,EPO,TNF,IGF1R,PIK3CB,ERBB3,PIK3CD,NTRK3,EGFR,PIP4K2C,ENTPD5,CCL5,IRS1,FGF2,PTEN,VEGFA,INSR,PIK3R1,PLEKHA1,PPP2R5C,KDR,HAX1,MAZ,MAPK3,SRC,PDGFRB,PDGFRA,SIRT1,PIK3CG,BECN1,KIT,PIP5K1C,MAPK1,EDN1,F2RL1,PDGFB,TWIST1	40	up
phosphatidylinositol biosynthetic process	GO:0006661	PI3k signalling	4.398E-03	ARF3,MTMR12,PLEKHA8,MTMR3,PIK3CB,RAB4A,PIGF,PIK3CD,PIP4K2C,MTMR4,RAB14,TMEM246,FGF2,PIK3R3,PTEN,PI4K2B,OCRL,PIK3R1,PLEKHA1,CDS1,MTMR2,PIGT,PIK3CG,MTMR9,IMPA1,ARF1,PIP5K1C,PIGG,FIG4,PIGA,PDGFB	31	up
phosphatidylinositol metabolic process	GO:0046488	metabolic process	2.204E-04	ARF3,PLA2G4F,MTMR12,IP6K1,PLEKHA8,MTMR3,PIK3CB,RAB4A,PIGF,PIK3CD,PIP4K2C,MTMR4,RAB14,TMEM246,FGF2,PIK3R3,PLA2G12A,PTEN,PI4K2B,OCRL,PIK3R1,PLEKHA1,SOCS5,PIP4P1,CDS1,MTMR2,PDGFRB,SOCS4,PIGT,PLCG1,PIK3CG,MTMR9,PLA2G2D,CSF1R,IMPA1,ARF1,MTMR10,PIP5K1C,LCLAT1,PIGG,FIG4,PIGA,SOCS3,SMG1,PDGFB,SOCS7,PLCB1	47	up
phosphatidylinositol signalling system	KEGG:04070	PI3k signalling	2.696E-02	IP6K1,MTMR3,IPPK,PIK3CB,PIK3CD,PIP4K2C,MTMR4,PIK3R3,PTEN,PI4K2B,PPIP5K2,OCRL,ITPR1,PIK3R1,CDS2,PIP4P1,CDS1,MTMR2,PLCG1,DGKZ,IMPA1,PIP5K1C,IPMK,PLCB1,DGKB,DGKI	26	up
phosphatidylinositol-mediated signalling	GO:0048015	PI3k signalling	2.204E-04	EPOR,ERBB2,JAK2,AKT1,EPO,TNF,GAB2,IGF1R,PIK3CB,ERBB3,PIK3CD,NTRK3,EGFR,PIP4K2C,RHOA,ENTPD5,CCL5,IRS1,FGF2,PTEN,VEGFA,RPS6KB1,OGT,INSR,PIK3R1,PLEKHA1,PPP2R5C,KDR,HAX1,MAZ,MAPK3,SRC,PDGFRB,PDGFRA,KCNH1,SIRT1,PIK3CG,BECN1,CSF1R,KIT,PIP5K1C,MAPK1,EDN1,F2RL1,PDGFB,PLCB1,TWIST1	47	up
phospholipase d signalling pathway	KEGG:04072	signalling pathways	1.348E-04	SPHK1,PLA2G4F,AKT1,GAB2,PIK3CB,RAF1,PIK3CD,EGFR,RHOA,CXCL8,SOS1,KRAS,SOS2,PIK3R3,GRB2,INSR,PIK3R1,AKT3,PLPP3,RRAS2,GRM7,CYTH1,MAPK3,PDGFRB,PDGFRA,RRAS,MAP2K1,PLCG1,PIK3CG,ARF6,RALB,DGKZ,KIT,CYTH3,AGTR1,ARF1,NRAS,CYTH2,PIP5K1C,MAPK1,PDGFB,AGPAT5,PLCB1,DGKB,DGKI	45	up
phospholipid metabolism	REAC:R-HSA-1483257	lipid metabolism	3.187E-02	PCTP,GPAT4,ARF3,PLA2G4F,MTMR12,PLEKHA8,MTMR3,DGAT1,PIK3CB,RAB4A,PIK3CD,PIP4K2C,MTMR4,CSNK2A1,RAB14,PIK3R3,PLA2G12A,PTEN,PISD,PI4K2B,CPNE1,OCRL,SELENOI,PIK3R1,PLEKHA1,ETNK1,MIGA1,CDS2,PNPLA6,PIP4P1,CDS1,MTMR2,DGAT2L6,PIK3CG,GDE1,MTMR9,PLA2G2D,ARF1,MTMR10,PIP5K1C,HADHB,LCLAT1,MIGA2,FIG4,ACP6,TNFAIP8L1,PLEKHA6,AGPAT5,STARD7,CRLS1	50	up
phosphorylation of emi1	REAC:R-HSA-176417	phosphorylation	4.447E-02	CDK1,CDC20,FZR1,CCNB1	4	up
photoperiodism	GO:0009648	transcription and translation	3.376E-02	CLOCK,PER2,PER1,PPP1CB,PPP1CC,FBXL3,CRY2,TP53,RBM4B,PPP1CA	10	down
pi metabolism	REAC:R-HSA-1483255	PI3k signalling	1.818E-03	ARF3,MTMR12,PLEKHA8,MTMR3,PIK3CB,RAB4A,PIK3CD,PIP4K2C,MTMR4,RAB14,PIK3R3,PTEN,PI4K2B,OCRL,PIK3R1,PLEKHA1,PNPLA6,PIP4P1,MTMR2,PIK3CG,GDE1,MTMR9,ARF1,MTMR10,PIP5K1C,FIG4,TNFAIP8L1,PLEKHA6	28	up
pi3k-akt signalling pathway	KEGG:04151	signalling pathways	4.382E-10	EPOR,IGF2,TP53,ERBB2,JAK2,AKT1,CCNE1,ANGPT2,EPO,BCL2,PPP2CA,EIF4EBP1,IL6R,IGF1R,PIK3CB,ERBB3,EIF4E,RAF1,PIK3CD,MCL1,EGFR,FGFR2,LAMC2,NFKB1,TLR2,CDKN1A,ERBB4,SPP1,BRCA1,IL6,CCND1,TLR4,CCND2,SOS1,HSP90AA1,CSF1,IRS1,ITGA5,KRAS,FGFR3,SOS2,HSP90B1,FGF2,CDKN1B,PIK3R3,TGFA,YWHAB,ITGB8,PTEN,CDK4,VEGFA,CCND3,CDK6,RPS6KB1,PRKAA1,BCL2L11,GRB2,GNB1,CHUK,FGFR4,INSR,PIK3R1,AKT3,MYB,ITGA2,PHLPP2,YWHAQ,YWHAH,LAMC1,CCNE2,PPP2R5C,KDR,GSK3B,GNG12,FOXO3,CDK2,MDM2,ITGB1,MYC,MET,ITGA6,ITGA11,MAPK3,PDGFRB,PDGFRA,MAP2K1,IFNB1,ITGB3,MAGI1,PIK3CG,CASP9,EPHA2,CSF1R,KIT,FASLG,AREG,BCL2L1,NRAS,OSMR,CREB1,DDIT4,G6PC,MAPK1,EREG,PDGFB,ITGA1,THBS1,COL4A1,PHLPP1	109	both
pi3k/akt signalling in cancer	REAC:R-HSA-2219528	cancer	3.943E-06	ERBB2,AKT1,PIK3CB,PIK3CD,EGFR,CDKN1A,CD80,IRS1,FGF2,CDKN1B,PIK3R3,TGFA,PTEN,CHUK,FGFR4,PIK3R1,AKT3,GSK3B,FOXO3,FOXO1,MDM2,MET,SRC,PDGFRB,PDGFRA,KLB,CASP9,RICTOR,KIT,AREG,CREB1,EREG,ESR1,PDGFB,AKT1S1,FRS2	36	up
pi5p, pp2a and ier3 regulate pi3k/akt signalling	REAC:R-HSA-6811558	PI3k signalling	2.189E-04	ERBB2,AKT1,PPP2CA,PIK3CB,PIK3CD,EGFR,PIP4K2C,TRAF6,IRAK1,CD80,IRS1,FGF2,PIK3R3,TGFA,FGFR4,INSR,PIK3R1,PPP2R5C,MET,MAPK3,SRC,PDGFRB,PDGFRA,KLB,KIT,AREG,PIP5K1C,MAPK1,EREG,ESR1,PDGFB,FRS2	32	up
pip3 activates akt signalling	REAC:R-HSA-1257604	PI3k signalling	1.214E-03	KLB,TRIM27,CBX4,MAPK1,RBBP4,ESR1,PSMB9,CBX6,MTA3,AGO3,RRAGC,FRK,XIAP,TNRC6B,SLC38A9,PDGFRA,AGO4,PDPK1,FOXO1,EED,EZH2,AKT1,SUZ12,SNAI2,AGO1,FGF19,PPARG,PTEN,KIT,PPP2R5E,PHC3,RHOG,RCOR1,EREG,PDGFRB,MDM2,JUN,REST,AKT2,AKT3,CBX2,CDKN1B,FRS2,PIP4K2C,RRAGD,FOXO3,MET,CDKN1A,IRAK4,CSNK2A1,TP53,EGF,PSMC4,BMI1,GSK3B,PSMD3,PHLPP2,OTUD3	58	both
plasma membrane bounded cell projection morphogenesis	GO:0120039	organogenesis	4.965E-03	SEMA4C,BTBD3,ZSWIM6,SEMA4B,FZD4,NPTN,LYPLA2,GAB2,PLXND1,SMO,PIK3CB,CD44,PIK3CD,ABL1,EPHA7,FGFR2,CXCR4,RHOA,LAMC2,ROCK1,LRP2,PARD6B,ACTBL2,ROBO1,NOTCH2,SOS1,CXCL12,L1CAM,NOTCH1,HSP90AA1,WASL,NPTX1,DICER1,B4GALT5,NRP1,ALCAM,PTEN,VEGFA,TAOK1,PAFAH1B1,KIF5B,WNT7A,PTPRD,CPNE1,GRB2,EFNB2,PAK2,KANK1,SLC9A6,SPTBN1,PIK3R1,NCKAP1,MINK1,ARHGDIA,YWHAH,APP,CDC42,GSK3B,SMURF1,RET,RTN4,BSG,EPB41L3,ARTN,CAPRIN1,ZNF365,ITGB1,SEMA3A,CFL1,EFNB1,ALS2,CORO1B,MOV10,MAPK3,SRC,SPTAN1,SYT1,RAP2A,PLCG1,ANK3,CTNNB1,EPHA5,LLPH,BMP7,MAP1B,EPHA2,GDI1,GFRA3,CTTN,ADNP,GAP43,CDK5R1,PDPN,PLXNA3,NFIB,UBB,GRB10,MAPK1,CAPRIN2,RPS6KA5,RHOH,ARC,ENAH,UNC5C,FRS2,ACTB,RAB10,SDC2,PAK3,ATP7A,EMB	111	both
platelet activation	GO:0030168	platelet activation	6.816E-04	VCL,PIK3CB,RAF1,CD40LG,IL6,PRKCE,TLR4,VAV2,ALOX12,GNB1,PRKCD,ITPR1,PIK3R1,STXBP3,MYL9,VAV3,ACTG1,MAPK3,SRC,PDGFRA,METAP1,CD40,ITGB3,AXL,PIK3CG,SAA1,DGKZ,SH2B3,F11R,PDPN,GNAQ,MAPK1,TRPC3,UBASH3B,PDGFB,CSRP1,ACTB,DGKB,DGKI	39	both
platelet activation	GO:0030168	platelet activation	6.816E-04	VCL,PIK3CB,RAF1,CD40LG,IL6,PRKCE,TLR4,VAV2,ALOX12,GNB1,PRKCD,ITPR1,PIK3R1,STXBP3,MYL9,VAV3,ACTG1,MAPK3,SRC,PDGFRA,METAP1,CD40,ITGB3,AXL,PIK3CG,SAA1,DGKZ,SH2B3,F11R,PDPN,GNAQ,MAPK1,TRPC3,UBASH3B,PDGFB,CSRP1,ACTB,DGKB,DGKI	39	both
platelet activation	KEGG:04611	platelet activation	6.816E-04	VCL,PIK3CB,RAF1,CD40LG,IL6,PRKCE,TLR4,VAV2,ALOX12,GNB1,PRKCD,ITPR1,PIK3R1,STXBP3,MYL9,VAV3,ACTG1,MAPK3,SRC,PDGFRA,METAP1,CD40,ITGB3,AXL,PIK3CG,SAA1,DGKZ,SH2B3,F11R,PDPN,GNAQ,MAPK1,TRPC3,UBASH3B,PDGFB,CSRP1,ACTB,DGKB,DGKI	39	both
platelet activation	KEGG:04611	platelet activation	6.816E-04	VCL,PIK3CB,RAF1,CD40LG,IL6,PRKCE,TLR4,VAV2,ALOX12,GNB1,PRKCD,ITPR1,PIK3R1,STXBP3,MYL9,VAV3,ACTG1,MAPK3,SRC,PDGFRA,METAP1,CD40,ITGB3,AXL,PIK3CG,SAA1,DGKZ,SH2B3,F11R,PDPN,GNAQ,MAPK1,TRPC3,UBASH3B,PDGFB,CSRP1,ACTB,DGKB,DGKI	39	both
platelet aggregation	GO:0070527	platelet activation	1.255E-02	VCL,PIK3CB,ALOX12,PRKCD,STXBP3,MYL9,ACTG1,PDGFRA,METAP1,ITGB3,PIK3CG,SH2B3,F11R,PDPN,UBASH3B,CSRP1,ACTB	17	up
platinum drug resistance	KEGG:01524	drug resistance	1.403E-10	MAPK1,XIAP,BID,PDPK1,CASP3,AKT1,ATM,PMAIP1,BCL2,BBC3,MDM2,AKT2,AKT3,CASP8,REV3L,CDKN1A,TP53,BIRC5,CYCS	19	both
positive regulation of cell migration by vascular endothelial growth factor signalling pathway	GO:0038089	cell adhesion and migration	2.991E-03	PIK3CD,VEGFA,KDR,MYO1C,PRKD1,PRKD2	6	up
positive regulation of cysteine-type endopeptidase activity	GO:2001056	endopeptidase activity	6.775E-07	CDKN2A,PMAIP1,BCL2L13,JAK2,S100A8,GRIN2A,BBC3,TNF,BAK1,REST,TNFRSF10B,Fas,HSPD1,FADD,ROBO1,SMAD3,BCL2L11,DDX3X,RET,F3,NLRP3,MYC,SENP1,SIRT1,DIABLO,CASP1,HMGB1,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,TRAF2,BAX,RIPK2,NOD1,FASLG,CIDEB,DAPK1,BCL10,CFLAR,CASP8,APAF1,CASP10,GRAMD4,DLC1,EGLN3	47	up

positive regulation of cysteine-type endopeptidase activity involved in apoptotic process	GO:0043280	endopeptidase activity	6.731E-07	CDKN2A,PMAIP1,BCL2L13,JAK2,S100A8,BBC3,TNF,REST,TNFRSF10B,Fas,HSPD1,FADD,ROBO1,SMAD3,BCL2L11,DDX3X,RET,F3,NLRP3,MYC,SENP1,SIRT1,DIABLO,CASP1,HMGB1,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,TRAF2,BAX,NOD1,FASLG,DAPK1,BCL10,CFLAR,CASP8,APAF1,CASP10,GRAMD4,DLC1,EGLN3	43	up
positive regulation of dna-binding transcription factor activity	GO:0051091	cell cycle	1.460E-07	SPHK1,STAT3,FZD4,S100A8,AKT1,TNF,DHX33,NPM1,SMO,CRTC1,CEBPG,TRIM22,CD40LG,IRAK2,TRAF6,NFKB1,TLR2,IRAK1,IL1RAP,IL6,TLR4,S100A12,WNT1,CLOCK,RPS6KA4,PTEN,VEGFA,SMAD3,UBE2V1,FLOT2,CHUK,AGER,SLCO3A1,TAB3,CLU,APP,TCF3,MAP3K7,PLPP3,NLRP3,AR,MTDH,CD40,TFRC,CTNNB1,SMARCA4,EPHA5,TRAF2,RBCK1,RIPK2,KIT,NOD1,PRKD1,IL10,BCL10,CFLAR,NEUROD2,TIRAP,UBB,ZBTB7A,TRIM37,MAVS,EDN1,RPS27A,UBC,MTPN,JMY,RPS6KA5,ESR1,CD36,PRKD2,TAB2	72	up
positive regulation of endopeptidase activity	GO:0010950	endopeptidase activity	1.048E-05	CDKN2A,PMAIP1,STAT3,BCL2L13,JAK2,S100A8,GRIN2A,BBC3,TNF,BAK1,REST,TNFRSF10B,Fas,HSPD1,FADD,ROBO1,SMAD3,VSIR,BCL2L11,DDX3X,AGER,RET,F3,NLRP3,MYC,SENP1,SIRT1,DIABLO,CASP1,HMGB1,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,TRAF2,BAX,RIPK2,NOD1,FASLG,CIDEB,DAPK1,BCL10,CFLAR,CASP8,APAF1,CASP10,GRAMD4,DLC1,EGLN3	50	up
positive regulation of membrane permeability	GO:1905710	cell organisation	5.314E-03	TP63,LAPTM5,BID,SLC35F6,YWHAG,PPP1R13B,PMAIP1,BCL2,BLOC1S2,BBC3,CASP8,PPP3R1,BCL2L11,SIVA1,TP53,TFDP2,YWHAE,GSK3B,YWHAB,MOAP1	20	both
positive regulation of mitochondrial membrane permeability	GO:0035794	mitochondrial activity	5.314E-03	TP63,BID,SLC35F6,YWHAG,PPP1R13B,PMAIP1,BCL2,BLOC1S2,BBC3,CASP8,PPP3R1,BCL2L11,SIVA1,TP53,TFDP2,YWHAE,GSK3B,YWHAB,MOAP1	19	both
positive regulation of mitochondrial membrane permeability involved in apoptotic process	GO:1902110	mitochondrial activity	2.967E-03	PMAIP1,BMF,TP53,BBC3,BCL2,BAK1,YWHAB,BCL2L11,YWHAQ,YWHAH,GSK3B,FZD9,E2F1,SFN,BNIP3,TP73,BAX,PPP3R1,CASP8,MOAP1,TP53BP2	21	both
positive regulation of nf-kb transcription factor activity	GO:0051092	Nfκ	5.443E-07	SPHK1,STAT3,S100A8,TNF,DHX33,NPM1,TRIM22,CD40LG,IRAK2,TRAF6,NFKB1,TLR2,IRAK1,IL1RAP,TLR4,S100A12,CLOCK,RPS6KA4,UBE2V1,FLOT2,CHUK,AGER,SLCO3A1,TAB3,CLU,APP,MAP3K7,NLRP3,AR,MTDH,CD40,TFRC,TRAF2,RBCK1,RIPK2,NOD1,PRKD1,BCL10,CFLAR,TIRAP,UBB,ZBTB7A,TRIM37,RPS27A,UBC,MTPN,RPS6KA5,CD36,PRKD2,TAB2	50	up
positive regulation of oxidoreductase activity	GO:0051353	protein metabolism	3.400E-02	VDR,AKT1,TNF,PIK3CB,ABL1,ABL2,RFK,SCARB1,AGTR1,EDN1,PDP2,NUS1,TERF2,ATP7A	14	up
positive regulation of phosphatidylinositol 3-kinase activity	GO:0043552	PI3k signalling	3.844E-02	ERBB4,IRS1,FGFR3,FGF2,ATG14,PDGFRB,PDGFRA,KIT,PRKD1,PDGFB	10	up
positive regulation of protein serine/threonine kinase activity	GO:0071902	protein kinase activity	4.100E-09	DUSP9,MAPK1,MAPK14,DDX3X,MAP3K13,RET,MAP2K2,ADAM17,SYAP1,IGF1,TAOK3,MAP3K2,TAOK1,CCND1,MAP3K11,SIRT1,EZH2,AKT1,CCND3,UBE2V1,FERMT2,MAP2K7,KIT,INCENP,DUSP5,HMGA2,PDGFRB,CCND2,VEGFA,CAB39,RHOA,GADD45A,TRAF7,ERN1,IKBKG,DVL3,CKS1B,SLC27A1,EGF,MUC20,IRAK2,PLCE1,THBS1,WNT5A,S1PR2,TAOK2	46	both
positive regulation of signalling receptor activity	GO:2000273	signalling pathways	3.054E-02	MED1,ADAM17,NRP1,TGFA,ADRA2B,FBXW7,ITGB1,AREG,EREG,ARC	10	up
positive regulation of ubiquitin protein ligase activity	GO:1904668	ubiquitination	3.339E-02	PTEN,BTRC,UBE2S,CDC20,FZR1,RAB1A	6	up
post-transcriptional silencing by small rnas	REAC:R-HSA-426496	miRNA/siRNA biogenesis	1.818E-03	TNRC6B,AGO3,TNRC6A,AGO2,AGO1,AGO4	6	up
post-translational protein modification	GO:0043687	protein metabolism	8.002E-03	FBXO44,DCUN1D3,UBE2F,ANKRD9,DCAF10,KBTBD6,RAB13,ASB8,PSMB9,VCAN,FBXL18,KLHL5,TTL,CKAP4,FEM1A,RAB11B,GPS1,HIF1A,CDH2,FEM1B,PDIA6,HSP90B1,CUL5,DCAF4,FBXO11,ASB1,RHBDD1,IGFBP1,FGG,FBN1,P3H1,CAND1,FGA,WSB2,TMEM132A,VHL,LAMC1,SOCS5,F5,FBXL3,SKP2,KCTD6,GAN,KLHL42,FBXO21,SOCS3,SENP8,TGOLN2,HIF3A,FBXW8,KLHL21,STC2,DNAJC3,QSOX1,SUMF2,ABCA2,WDTC1,PSMC4,FBXW2,C3,APOA5,MATN3,WSB1,PSMD3,CCDC8,KLHL11,SHISA5,CCNF	68	down
postmitotic nuclear pore complex (npc) reformation	REAC:R-HSA-9615933	cell cycle	7.666E-03	NUP93,NUP205,NUP37,NDC1,KPNB1,RANGAP1,TNPO1,NUP62,NUP43,RAN,NUP54	11	up
pou5f1 (oct4), sox2, nanog activate genes related to proliferation	REAC:R-HSA-2892247	cell proliferation	4.207E-02	STAT3,SOX2,FGF2,SALL1,NANOG,POU5F1	6	up
pre-mirna processing	GO:0031054	miRNA/siRNA biogenesis	1.620E-04	LIN28A,LIN28B,PRKRA,AGO3,DICER1,AGO2,TARBP2,AGO1,AGO4,BCDIN3D	10	up
pre-notch expression and processing	REAC:R-HSA-1912422	NOTCH signalling	5.788E-03	E2F3,SEL1L,TP53,CREBBP,TNRC6B,LFNG,CCND1,NOTCH2,NOTCH1,AGO3,FURIN,TNRC6A,AGO2,AGO1,RBPJ,AGO4,B4GALT1,E2F1,MOV10,HIST1H2AC,HIST1H2BJ,SIRT6,RAB6A,MAMLD1	24	up
pre-notch transcription and translation	REAC:R-HSA-1912408	NOTCH signalling	1.346E-02	E2F3,TP53,CREBBP,TNRC6B,CCND1,NOTCH2,NOTCH1,AGO3,TNRC6A,AGO2,AGO1,RBPJ,AGO4,E2F1,MOV10,HIST1H2AC,HIST1H2BJ,SIRT6,MAMLD1	19	up
pre-replicative complex assembly	GO:0036388	cell cycle	2.207E-04	MCMDC2,MCM4,MCM2,MCM7,MCM6,MCM3,MCM5	7	up
pre-replicative complex assembly involved in nuclear cell cycle dna replication	GO:0006267	cell cycle	2.207E-04	MCMDC2,MCM4,MCM2,MCM7,MCM6,MCM3,MCM5	7	up
pri-mirna transcription by rna polymerase ii	GO:0061614	miRNA/siRNA biogenesis	1.310E-04	PPARA,NFIB,TERT,SOX9,HIF1A,FOSL1,NR3C1,PPARG,ETS1,FOS,KLF4,JUN,SMAD3,STAT3,DDX5,FOXO3,ATOH8,TP53,SRF,WT1	20	both
primary mirna processing	GO:0031053	miRNA/siRNA biogenesis	4.808E-02	STAT3,LIN28B,SMAD2,IL6,SMAD3,HNRNPA2B1	6	up
process utilizing autophagic mechanism	GO:0061919	autophagy	1.213E-02	VPS4B,TP53INP1,STAT3,BMF,TP53,S100A8,CHMP3,VPS51,ULK3,AKT1,ZFYVE1,BCL2,EEF1A1,MTMR3,PRKAG1,VDAC1,PIK3CB,HUWE1,EXOC7,YOD1,MCL1,ABL1,DRAM2,PIP4K2C,HK2,MTMR4,TMEM59,CSNK2A1,TRIM22,ROCK1,SQSTM1,ATG9A,PACS2,HSP90AA1,FZD5,VPS37B,ATG14,RAB1B,SESN3,VPS37A,ABL2,RUBCN,CHMP4B,GABARAPL1,STX17,FOXK1,LAMP2,RAB23,PRKAA1,FLCN,VPS4A,SH3BP4,TBC1D14,HSPA8,ITPR1,TAB3,WIPI2,GABARAP,PAFAH1B2,DYNLL2,C6orf106,CLU,KDR,GSK3B,SMURF1,SPTLC1,MAP3K7,FOXO3,HAX1,FBXW7,FOXO1,LGALS8,CHMP2B,ATM,MET,SUPT5H,SRC,CASP3,SIRT1,VPS37D,TPCN2,ATP6V1E1,RAB3GAP2,MTDH,LARP1,ATG5,UBQLN2,RRAGD,RRAGA,MFN2,ATG4B,EIF4G1,BNIP3,HMGB1,MTMR9,STAM2,RALB,BECN1,SESN2,TOMM40,ATG7,PRKD1,BAG3,TREM2,DAPK1,CAPN1,IL10,UBXN2B,KDM4A,BCL2L1,CDK5R1,WDR81,ATP6V1C1,SLC38A9,ATP6V1B2,ATP6V0E1,USP13,QSOX1,ACBD5,ATP6V0D1,NRBF2,SNX5,SMG1,SESN1,TAB2,SREBF1,RAB1A	127	both
processing of capped intron-containing pre-mrna	REAC:R-HSA-72203	transcription and translation	4.099E-03	DHX38,HNRNPK,LSM4,CASC3,NUP93,FUS,NUP205,PCBP2,RANBP2,NUP37,SRRM2,EIF4E,PTBP1,SNRPB,NDC1,PPWD1,ELAVL1,PPIL1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PLRG1,HNRNPA1,U2SURP,NUP50,POLDIP3,POLR2E,HNRNPA2B1,EFTUD2,POM121C,SNRPA1,THOC2,CHERP,SF3B3,NUP62,HNRNPUL1,NCBP2,CDC5L,YBX1,RAE1,WBP11,NUP43,SNRPD1,PRPF38A,PRPF4,POLR2D,SF3A1,SRSF2,NUP54,FYTTD1,DDX39A,SNRNP48,PABPN1,ELAVL2,PAPOLA,HNRNPC,SF1,HNRNPA3	60	up
production of mirnas involved in gene silencing by mirna	GO:0035196	miRNA/siRNA biogenesis	3.553E-04	STAT3,LIN28A,NCOR2,LIN28B,TP53,TNF,TRIM71,PRKRA,EGFR,SMAD2,IL6,AGO3,DICER1,AGO2,TARBP2,SMAD3,AGO1,AGO4,HNRNPA2B1,MYCN,PUM2,MAP2K1,ESR1,BCDIN3D	24	both
production of small rna involved in gene silencing by rna	GO:0070918	miRNA/siRNA biogenesis	2.400E-04	STAT3,LIN28A,NCOR2,LIN28B,TP53,TNF,TRIM71,PRKRA,EGFR,SMAD2,IL6,AGO3,DICER1,AGO2,TARBP2,SMAD3,AGO1,AGO4,HNRNPA2B1,MYCN,PUM2,TSN,MAP2K1,ESR1,BCDIN3D	25	both

progesterone-mediated oocyte maturation	KEGG:04914	endocrine system	4.242E-04	RPS6KA1,AKT1,MAPK14,IGF1R,PIK3CB,RAF1,PIK3CD,KIF22,CCNA2,HSP90AA1,KRAS,PIK3R3,ANAPC13,CDK1,CDC25A,CPEB2,CPEB3,PIK3R1,CDC27,AKT3,RPS6KA3,CDK2,CDC25C,FZR1,MAPK3,MAP2K1,ANAPC5,CDC23,CPEB4,AURKA,CCNB1,MAPK1	32	up
programmed cell death	REAC:R-HSA-5357801	apoptosis	5.087E-04	CDKN2A,PMAIP1,STAT3,BMF,TP53,XIAP,BBC3,AKT1,BCL2,BAK1,TNFRSF10B,PSMB1,APC,Fas,KPNB1,ROCK1,FADD,TLR4,CASP7,YWHAB,BCL2L11,PAK2,PRKCD,AKT3,DYNLL2,YWHAQ,YWHAH,KPNA1,PSMB5,CLSPN,E2F1,HIST1H1E,SFN,BIRC3,MAPK3,CASP3,DSP,SPTAN1,DIABLO,CTNNB1,TJP2,HMGB1,CASP9,CYCS,TP73,TNFRSF10A,TRAF2,BAX,PPP3R1,FASLG,DAPK1,DFFA,CASP6,CASP8,BCL2L1,APAF1,BIRC2,TP53BP2,UBB,MAPK1,RPS27A,UBC	62	both
prolactin signalling pathway	KEGG:04917	endocrine system	3.835E-02	STAT3,JAK2,AKT1,MAPK14,PIK3CB,RAF1,PIK3CD,FOS,NFKB1,STAT1,CCND1,CCND2,SOS1,KRAS,SOS2,PIK3R3,GRB2,PIK3R1,AKT3,GSK3B,SOCS5,FOXO3,STAT5A,MAPK3,SRC,SOCS4,MAP2K1,NRAS,MAPK1,IRF1,ESR1,SOCS3,SOCS7	33	both
prolonged erk activation events	REAC:R-HSA-169893	MAPK signalling	2.644E-02	YWHAB,CRKL,CRK,MAPK3,MAP2K1,MAPK1,FRS2	7	up
prostate cancer	KEGG:05215	cancer	4.198E-05	E2F3,TP53,ERBB2,AKT1,CCNE1,BCL2,CREBBP,IGF1R,PIK3CB,RAF1,PIK3CD,EGFR,FGFR2,E2F2,NFKB1,CDKN1A,CCND1,SOS1,HSP90AA1,KRAS,SOS2,HSP90B1,CDKN1B,PIK3R3,TGFA,PTEN,GRB2,CHUK,PIK3R1,AKT3,CCNE2,GSK3B,ZEB1,FOXO1,CDK2,MDM2,E2F1,LEF1,MAPK3,PDGFRB,PDGFRA,AR,MAP2K1,CTNNB1,CASP9,TCF7,NRAS,CREB1,TCF7L2,MAPK1,PDGFB	51	both
proteasomal protein catabolic process	GO:0010498	catabolic process	1.757E-02	PMAIP1,RYBP,RMND5A,CEBPA,SEL1L,FBXL20,FBXO38,HSPBP1,AURKB,EDEM1,PCBP2,RNF144A,FBXL18,HUWE1,PSMB1,YOD1,MAN1B1,TRIM71,ANAPC16,ARIH2,IFI27,EDEM3,FAF1,UBE2D3,CLOCK,HSP90B1,RAD23B,OGT,N4BP1,BTRC,CUL3,ARIH1,UBE4A,CUL2,CBFA2T3,CDK1,CDC27,RNF41,KLHL15,SMAD7,KLHL40,CLU,PPP2R5C,UBR3,GSK3B,SMURF1,SOCS5,TBL1XR1,DNAJC10,PSMB5,ZNRF1,FBXW7,CDK2,MDM2,BAG2,TMEM67,UBE2S,CDC20,FZR1,ERLIN1,SIRT1,ERLIN2,UBQLN2,ANAPC5,CTNNB1,BAG6,RBCK1,TREM2,SIRT6,BFAR,CDC23,UBXN2B,DDA1,BIRC2,UBXN4,GID4,DNAJB9,AURKA,CCNB1,RNF4,TMF1,DDI2,LTN1,UBB,USP13,KCTD10,RPS27A,UBC,DNAJC18,TRIM72,DERL2,AREL1	92	up
proteasome-mediated ubiquitin-dependent protein catabolic process	GO:0043161	ubiquitination	7.129E-03	RYBP,RMND5A,CEBPA,SEL1L,FBXL20,FBXO38,HSPBP1,AURKB,EDEM1,PCBP2,RNF144A,FBXL18,HUWE1,PSMB1,YOD1,MAN1B1,TRIM71,ANAPC16,ARIH2,IFI27,EDEM3,FAF1,UBE2D3,CLOCK,HSP90B1,RAD23B,OGT,N4BP1,BTRC,CUL3,ARIH1,UBE4A,CUL2,CBFA2T3,CDK1,CDC27,KLHL15,SMAD7,KLHL40,CLU,PPP2R5C,UBR3,GSK3B,SMURF1,SOCS5,TBL1XR1,DNAJC10,PSMB5,ZNRF1,FBXW7,CDK2,MDM2,TMEM67,UBE2S,CDC20,FZR1,ERLIN1,SIRT1,ERLIN2,UBQLN2,ANAPC5,CTNNB1,BAG6,RBCK1,SIRT6,BFAR,CDC23,UBXN2B,DDA1,BIRC2,UBXN4,GID4,DNAJB9,AURKA,CCNB1,RNF4,LTN1,UBB,KCTD10,RPS27A,UBC,DNAJC18,TRIM72,DERL2,AREL1	85	both
protein acetylation	GO:0006473	protein metabolism	3.228E-02	SPHK1,CREBBP,LIF,SMAD4,MUC1,SET,NOS1,BRCA2,BRCA1,CLOCK,RPS6KA4,CHEK1,TAOK1,MSL1,OGT,PRKAA1,DDX3X,FLCN,TADA2B,NAA25,GSK3B,MAP3K7,FOXO1,LEF1,MAPK3,SPI1,SIRT1,KANSL2,PER1,BAG6,SOX4,SUPT7L,RPS6KA5,NAA50,BRPF1,HAT1,NAA30	37	up
protein acylation	GO:0043543	protein metabolism	3.967E-02	ZDHHC5,SPHK1,CREBBP,LIF,SMAD4,MUC1,SET,NOS1,BRCA2,BRCA1,CLOCK,ZDHHC6,RPS6KA4,CHEK1,TAOK1,MSL1,OGT,PRKAA1,DDX3X,PPM1A,FLCN,TADA2B,NAA25,GSK3B,MAP3K7,ZDHHC16,FOXO1,LEF1,MAPK3,SPI1,SIRT1,KANSL2,PER1,BAG6,SOX4,ZDHHC21,ZDHHC24,SUPT7L,RPS6KA5,NAA50,BRPF1,HAT1,NAA30,PPM1B	44	up
protein alkylation	GO:0008213	protein metabolism	4.829E-02	EHMT1,BCOR,SUV39H1,SUPT6H,SIRT7,CREBBP,TET2,KMT2D,SMAD4,ETF1,SNRPB,BRCA1,JARID2,DNMT1,SETDB1,TET3,OGT,ASH1L,PHF19,CARM1,PCMT1,PAGR1,PRDM4,MYB,SETD1B,RIF1,MTHFR,SIRT1,SETD3,CTNNB1,TET1,RAB6A	32	up
protein autophosphorylation	GO:0046777	phosphorylation	3.345E-06	DDR2,PAK2,YES1,DDX3X,PRKX,MAP3K13,FRK,MAP2K2,TAOK3,PDGFRA,PDPK1,TAOK1,MAP3K11,MYO3A,AKT1,IGF1R,PTK2,ATM,KIT,PPP2R5E,ULK1,MAP3K3,PDGFRB,VEGFA,RAP2C,UHMK1,PIM3,TXK,ERN1,EIF2AK2,MRE11,MAK,TYRO3,STK17B,MAPKAPK5,WNK1,PTK6,MINK1,GSK3B,TAOK2,MOB1B,MKNK2,AURKA	43	both
protein deacetylation	GO:0006476	protein metabolism	1.981E-02	SIRT7,REST,AKAP8,MTA2,VEGFA,SPRED1,BAZ2A,PRKAA1,RCOR1,ELK4,SIRT4,TBL1XR1,HDAC1,SIRT1,TPPP,PER1,PRKD1,SIRT6,PER2,ZBTB7B,DYRK1A,PRKD2,BRMS1L	23	up
protein deacylation	GO:0035601	protein metabolism	1.797E-02	SIRT7,LYPLA2,REST,AKAP8,MTA2,VEGFA,SPRED1,BAZ2A,PRKAA1,RCOR1,ELK4,SIRT4,TBL1XR1,HDAC1,SIRT1,TPPP,PER1,PRKD1,SIRT6,PER2,ZBTB7B,DYRK1A,PRKD2,BRMS1L,LYPLAL1	25	up
protein dephosphorylation	GO:0006470	phosphorylation	8.483E-03	CTDSP1,PPP2CA,DUSP6,TNF,MTMR3,CDH5,PTBP1,MFHAS1,PPP1CA,MTMR4,DUSP1,ROCK1,PPP1R11,HSP90B1,PPP6R1,YWHAB,PTEN,PTPRJ,PTPRD,RPRD1B,PPM1A,BTRC,PRKCD,PPP6R3,FKBP1A,PPP2R5C,GSK3B,PPP6C,SSU72,MTMR2,CAMTA1,PDGFRB,FKBP1B,PPP1CC,CNEP1R1,DUSP5,PPP1R7,MASTL,PTPN4,PPP1R15B,TIMM50,DLC1,PTPRG,DUSP18,PTPRB,UBASH3B,ARPP19,ITGA1,PPM1B	49	both
protein depolymerization	GO:0051261	protein metabolism	4.533E-02	VPS4B,NES,APC,KIF24,MICAL2,KIF2C,TAOK1,VPS4A,CAMSAP1,CAPZA2,STMN1,TWF1,CFL1,CAPZB,CAPG,CKAP5,MAP1B,KIF2A,CFL2,MID1IP1,CAMSAP2,MTPN,F2RL1	23	up
protein deubiquitination	GO:0016579	ubiquitination	4.013E-03	TP53,TNFAIP3,ADRM1,PSMB1,YOD1,APC,USP8,SMAD4,RHOA,TRAF6,USP48,SMAD2,BRCA1,CCNA2,OTUD4,PTEN,USP42,RAD23B,SMAD3,FOXK1,OGT,OTUB1,CDK1,CDC25A,CYLD,SMAD7,USP15,TADA2B,ASXL1,MAP3K7,USP3,USP31,PSMB5,CLSPN,NLRP3,MDM2,CFTR,MYC,YY1,MDM4,CDC20,BIRC3,SNX3,AR,TRAF3,USP47,TRAF2,STAM2,BECN1,MBD6,BIRC2,USP28,OTUD7B,TANK,UBB,USP13,USP32,RPS27A,UBC,OTUD3,ESR1,TNIP3,ACTB,OTUD7A	64	up
protein export from nucleus	GO:0006611	protein metabolism	4.517E-04	CDKN2A,DHX38,TP53,SUPT6H,LTV1,CASC3,NUP93,SIRT7,NUP205,RANBP2,NUP37,NPM1,EIF4E,EMD,NSUN2,NDC1,IFI27,STRADB,RNPS1,SRSF1,NUP50,POLDIP3,HNRNPA2B1,GSK3B,SMURF1,POM121C,YTHDC1,RANGAP1,THOC2,RBM15B,NUP62,NCBP2,NUP98,RAE1,CSE1L,BAG3,NUP43,TCF7L2,RAN,POLR2D,SRSF2,NUP54,SMG1,EIF6,FYTTD1,DDX39A,PABPN1	47	up
protein folding	GO:0006457	protein metabolism	1.232E-02	SPHK1,HSPBP1,GANAB,QSOX2,HSPD1,CSNK2A1,ENTPD5,HSP90AA1,MLEC,HSP90B1,CCT6A,HSPA4L,RAD23B,CDC37L1,GNB1,DNAJA1,HSPA8,BAG4,PPIG,GNAT1,FKBP1A,CLU,CANX,PDIA6,DNAJC10,BAG2,FKBP8,CCT3,DNAJB6,AIP,FKBP1B,BAG3,FUT10,DFFA,BAG1,HSPA13,PPIC,FKBP9,POFUT2,QSOX1,PRKCSH,DNAJC18,LMAN1,DNAJC21,DNAJB4,PFDN2	46	up
protein import	GO:0017038	protein metabolism	9.914E-04	STAT3,E2F3,AKT1,TIMM23,NUP93,RANBP2,TNPO3,HSPD1,KPNB1,HSP90AA1,KPNA4,SMAD3,LAMP2,RAB23,PEX13,HSPA8,PRKCD,PIK3R1,NUP50,PEX12,CLU,KPNA1,KPNA3,POM121C,ECT2,TNPO1,PPP1R10,NUP62,AIFM1,TOMM40,CSE1L,BAG3,RANBP6,RPL23,MAVS,ROMO1,TIMM50,RAN,NUP54,IPO7,TOMM40L,KPNA2,TNPO2	43	up
protein insertion into mitochondrial membrane involved in apoptotic signalling pathway	GO:0001844	mitochondrial activity	4.773E-05	PMAIP1,BMF,TP53,BBC3,BCL2,YWHAB,BCL2L11,YWHAQ,YWHAH,E2F1,SFN,TP73,BAX,PPP3R1,CASP8,MOAP1,TP53BP2	17	both
protein kinase b signalling	GO:0043491	protein kinase activity	7.982E-07	LIN28A,IGF2,ERBB2,AKT1,SFRP5,TNF,IGF1R,PIK3CB,ERBB3,PIK3CD,MFHAS1,NTRK3,EGFR,FGFR2,ERBB4,LRP2,CD80,CCL5,HSP90AA1,IRS1,HLA-G,FGFR3,FGF2,PIK3R3,TGFA,PTEN,VEGFA,PTPRJ,CPNE1,GRB2,FLCN,FGFR4,INSR,PIK3R1,RNF41,PLEKHA1,PHLPP2,PPP2R5C,KDR,RET,RTN4,F3,HAX1,ITGB1,CCL3,MET,MAZ,SRC,PDGFRB,PDGFRA,SIRT1,KLB,MTDH,RRAS,GATA4,AXL,PIK3CG,RICTOR,EPHA2,KIT,AREG,PPARA,SH2B3,TCF7L2,OTUD3,EREG,ESR1,PDGFB,FRS2,THBS1,PHLPP1	71	up
protein localization to cell-cell junction	GO:0150105	protein localization	8.466E-03	VCL,CDH5,PAK2,CGNL1,ACTG1,DSP,TJP2,F11R,ACTB	9	up
protein localization to endoplasmic reticulum	GO:0070972	protein localization	3.061E-02	RPL29,RPS12,EDEM1,RPL3,RPS7,RPS3A,RPLP0,RPL35A,RPS28,SRPRB,CHMP4B,SRPRA,SEC61A1,RPL14,RPL10,RPL36,RTN4,RPS5,RAB3GAP2,RPL37,RPS2,RPL9,INSIG1,SPCS3,RPL23,RPL24,RPS15A,RPL4,RPS27A,KDELR1,SEC16A,RPS14,RAB10	33	up
protein localization to mitochondrion	GO:0070585	mitochondrial activity	3.554E-05	PMAIP1,BMF,TP53,BBC3,AKT1,BCL2,TIMM23,TIMM10,HUWE1,HSPD1,HK2,ARIH2,HSP90AA1,UBE2D3,FZD5,YWHAB,BCL2L11,DNAJA1,BAG4,TIMM13,YWHAQ,YWHAH,HAX1,FBXW7,E2F1,SFN,MFN2,TP73,AIFM1,TOMM40,BAX,AIP,PPP3R1,CASP8,MOAP1,TP53BP2,MFF,ROMO1,TIMM50,TOMM40L,SREBF1,LMAN1	42	up
protein localization to nucleolus	GO:1902570	protein localization	1.633E-02	GLUL,MCRS1,TERT,NVL,RAN,RPF2,POLR1A	7	down
protein localization to nucleus	GO:0034504	protein localization	2.407E-06	CDKN2A,MEPCE,STAT3,E2F3,BCL3,AKT1,NUP93,SIX1,RANBP2,NPM1,LIF,TNPO3,MFHAS1,KPNB1,CARD10,KPNA4,CCT6A,ARL2,SMAD3,RAB23,FLCN,PRKCD,CDK1,SUN1,PIK3R1,NUP50,TBRG1,C6orf106,GSK3B,KPNA1,KPNA3,POM121C,YAP1,LATS2,MDM2,RANGAP1,ECT2,TNPO1,PPP1R10,NUP62,CCT3,TFRC,BMP7,SESN2,CSE1L,BAG3,CNEP1R1,RANBP6,TOR1B,TAF8,OTUD7B,RPL23,SUPT7L,SUN2,ZBTB7A,MAVS,RPF2,RAN,NUP54,IPO7,WWTR1,DTX3L,KPNA2,TOR1AIP1,TNPO2	65	both

protein localization to plasma membrane	GO:0072659	protein localization	2.632E-02	ZDHHC5,AKT1,TNF,SLC9A3R2,EHD1,EGFR,TMEM59,ROCK1,NUMB,SQSTM1,PRKCE,PACS2,RAB34,RAB12,KIF5B,RAB15,MYO5A,WNK3,FLOT2,VPS4A,SPTBN1,PIK3R1,RAB40B,GGA3,SMURF1,BSG,EPB41L3,ITGB1,GORASP2,VAMP2,AR,AP2M1,RAP2A,ANK3,PKP2,ARF6,TSPAN14,EPHA2,TNFRSF1A,TREM2,CACNB3,BCL2L1,F11R,RAB3D,MAP7,KIF13A,SEC16A,C16orf70,KCNB1,EMP2,RAB31,ACTB,RAB10	53	up
protein methylation	GO:0006479	epigenetic mechanism	4.829E-02	EHMT1,BCOR,SUV39H1,SUPT6H,SIRT7,CREBBP,TET2,KMT2D,SMAD4,ETF1,SNRPB,BRCA1,JARID2,DNMT1,SETDB1,TET3,OGT,ASH1L,PHF19,CARM1,PCMT1,PAGR1,PRDM4,MYB,SETD1B,RIF1,MTHFR,SIRT1,SETD3,CTNNB1,TET1,RAB6A	32	up
protein modification by small protein removal	GO:0070646	protein metabolism	2.889E-03	TP53,TNFAIP3,ADRM1,PSMB1,YOD1,APC,USP8,SMAD4,RHOA,COPS8,TRAF6,USP48,SMAD2,BRCA1,CCNA2,OTUD4,PTEN,USP42,RAD23B,SMAD3,FOXK1,OGT,OTUB1,CDK1,CDC25A,CYLD,SMAD7,USP15,TADA2B,ASXL1,MAP3K7,USP3,USP31,PSMB5,CLSPN,NLRP3,MDM2,CFTR,MYC,YY1,MDM4,CDC20,BIRC3,SNX3,SENP1,AR,TRAF3,USP47,TRAF2,STAM2,BECN1,MBD6,BIRC2,USP28,OTUD7B,TANK,UBB,USP13,USP32,RPS27A,UBC,OTUD3,ESR1,SENP6,TNIP3,ACTB,COPS7B,OTUD7A	68	up
protein monoubiquitination	GO:0006513	ubiquitination	1.937E-02	BCOR,RYBP,HUWE1,UHRF1,KDM2B,CDC73,FANCM,UBE2D3,CUL3,RNF168,PEX12,RNF40,BIRC2,RAG1,UBB,TRIM37,MGRN1,DTX3L	18	up
protein polyubiquitination	GO:0000209	ubiquitination	8.465E-03	CDKN2A,CBFB,RMND5A,XIAP,FBXL20,FBXO38,TNFAIP3,BCL2,RNF144A,UNKL,FBXL18,HUWE1,PSMB1,TRIM71,ARIH2,ZNF738,TRIM22,IFI27,TRAF6,BRCA1,LNPEP,UBE2D3,UBE2V1,RBBP6,DDX3X,BTRC,CUL3,ARIH1,UBE2Q1,OTUB1,UBE4A,UBE3C,ANAPC13,CDC27,ZNRF2,RNF168,RNF41,UBE2Q2,SMURF1,UBE2H,PSMB5,ZNRF1,FBXW7,MDM2,UBE2S,RNF167,FZR1,ANAPC5,TRAF3,CTNNB1,TRAF2,RBCK1,BFAR,CDC23,DDA1,BIRC2,MYLIP,FBXW2,SASH1,RNF4,RLIM,TRIM36,UBB,RNF125,RPS27A,UBC,UBE2D2,FBXO28,DTX3L,WSB1,AREL1	71	both
protein processing in endoplasmic reticulum	KEGG:04141	protein metabolism	1.834E-02	SEL1L,SEC24A,HSPBP1,SSR3,BCL2,EDEM1,GANAB,BAK1,YOD1,MAN1B1,MAN1C1,EDEM3,HSP90AA1,UBE2D3,HSP90B1,HSPA4L,RAD23B,DNAJA1,SEC61A1,HSPA8,TRAM1,CANX,HYOU1,PDIA6,DNAJC10,BAG2,RRBP1,UBQLN2,TRAF2,SAR1A,CRYAA,BAX,CAPN1,BAG1,DNAJC5,UBXN4,SEC23B,DAD1,PRKCSH,UBE2D2,LMAN1,DERL2	42	up
protein stabilization	GO:0050821	protein metabolism	2.967E-03	CDKN2A,SEL1L,RPS7,NPM1,PRKRA,HSPD1,CDKN1A,HSP90AA1,CCT6A,PTEN,NAPG,LAMP2,CDC37L1,FLOT2,PRKCD,BAG4,PIK3R1,TBRG1,CREBL2,SMAD7,CLU,RASSF2,PLPP3,RTN4,FBXW7,BAG2,ZSWIM7,MDM4,CCT3,BAG6,MTMR9,CRYAA,BAG3,SUGT1,BAG1,SOX4,ATF7IP,WDR81,CREB1,RPL23,GNAQ,CHEK2,USP13,SEC16A,OTUD3,STK4	46	up
protein sumoylation	GO:0016925	SUMOylation	1.892E-02	CDKN2A,NUP93,NUP205,RANBP2,NUP37,PIAS3,NDC1,NUP50,POM121C,RANGAP1,SENP1,NUP62,STX1A,NUP98,CTNNB1,RAE1,UBA2,NUP43,RNF4,KIAA1586,NUP54	21	up
protein targeting	GO:0006605	protein metabolism	7.458E-03	SCARB2,ERBB2,TIMM23,TIMM10,RPL29,RPS12,EDEM1,RPL3,RPS7,HUWE1,RPS3A,RPLP0,RPL35A,HSPD1,ARIH2,RPS28,SRPRB,ITGB2,HSP90AA1,ARL6IP1,UBE2D3,FZD5,VPS37B,ZDHHC6,VPS37A,CHMP4B,SRPRA,LAMP2,PEX13,VPS4A,SEC61A1,HSPA8,BAG4,ACOX1,RPL14,GABARAP,TIMM13,AP3M1,PEX12,TRAK1,GGA3,RAB3IP,CLU,TRAM1,SMURF1,RPL10,RPL36,SNX16,RPS5,HAX1,FBXW7,VPS37D,RPL37,RPS2,MFN2,ANK3,MYO1C,AIFM1,TOMM40,AIP,GDI1,FUT10,RPL9,ZDHHC21,MFF,SPCS3,RPL23,ZDHHC24,RPL24,UBB,PRNP,RPS15A,RPL4,ROMO1,RPS27A,UBC,GNPTAB,TIMM50,KCNB1,UBE2D2,RPS14,TOMM40L,SREBF1,LMAN1	84	up
protein targeting to er	GO:0045047	protein metabolism	3.124E-02	RPL29,RPS12,EDEM1,RPL3,RPS7,RPS3A,RPLP0,RPL35A,RPS28,SRPRB,CHMP4B,SRPRA,SEC61A1,RPL14,RPL10,RPL36,RPS5,RPL37,RPS2,RPL9,SPCS3,RPL23,RPL24,RPS15A,RPL4,RPS27A,RPS14	27	up
protein-containing complex disassembly	GO:0032984	protein metabolism	3.671E-05	VPS4B,SMARCD2,CHMP3,FRAT2,TNF,MTRF1L,NES,IGF1R,APC,KIF24,PPP1CA,ETF1,HMGA1,SET,MRPL10,MICAL2,MRPS30,MRPS27,WNT1,FZD5,KIF2C,ATG14,TAOK1,RUBCN,SUPT16H,KIF5B,AURKAIP1,GABARAPL1,STX17,LAMP2,VPS4A,AMER1,HSPA8,MRPL40,DYRK3,INSR,GABARAP,CAMSAP1,GSK3B,CAPZA2,STMN1,TWF1,SMARCD1,CHMP2B,CFL1,MYC,PTCD3,OGFOD1,SMARCC2,KLC1,CAPZB,CAPG,APEH,MRPS26,CTNNB1,SMARCA4,SMARCC1,CKAP5,BNIP3,MAP1B,KIF2A,MRPS21,MRPS16,RPL23,CFL2,MRPL37,MRPS35,MID1IP1,CAMSAP2,MTPN,MRPL52,F2RL1,ARID1A,MRPL18,GRWD1,MRRF	76	up
protein-dna complex disassembly	GO:0032986	cell cycle	1.019E-04	SMARCD2,HMGA1,SET,SUPT16H,SMARCD1,MYC,SMARCC2,SMARCA4,SMARCC1,RPL23,ARID1A,GRWD1	12	up
proteoglycans in cancer	KEGG:05205	cancer	1.164E-14	WNT4,MYC,PDCD4,MAPK1,MAPK14,ESR1,TWIST1,MAP2K2,IGF1,PDPK1,COL1A1,CCND1,CASP3,TWIST2,HIF1A,ROCK2,AKT1,IGF1R,PTK2,KRAS,COL1A2,CDC42,ITGB1,MMP2,MDM2,FZD5,TIAM1,FZD4,AKT2,AKT3,VEGFA,PPP1CB,PPP1CC,SMAD2,STAT3,FRS2,ITPR1,DDX5,CTTN,MET,RHOA,ROCK1,CTNNB1,CDKN1A,TP53,ACTG1,FZD7,RRAS,PLCE1,THBS1,WNT5A,PPP1CA	52	both
pten regulation	REAC:R-HSA-6807070	PTEN expression	1.499E-02	TRIM27,CBX4,MAPK1,RBBP4,PSMB9,CBX6,MTA3,AGO3,RRAGC,FRK,XIAP,TNRC6B,SLC38A9,AGO4,EED,EZH2,AKT1,SUZ12,SNAI2,AGO1,PPARG,PTEN,PHC3,RCOR1,JUN,REST,AKT2,AKT3,CBX2,RRAGD,CSNK2A1,TP53,PSMC4,BMI1,PSMD3,OTUD3	36	both
ptk6 regulates cell cycle	REAC:R-HSA-8849470	cell cycle	6.376E-03	CCNE1,CCND1,CDKN1B,CDK4,CDK2	5	up
purine nucleoside diphosphate metabolic process	GO:0009135	metabolic process	1.115E-03	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,POM121C,LDHA,GPI,NUP62,TIGAR,NUP98,RAE1,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	32	up
purine ribonucleoside diphosphate metabolic process	GO:0009179	metabolic process	9.348E-04	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,POM121C,LDHA,GPI,NUP62,TIGAR,NUP98,RAE1,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	32	up
pyrimidine deoxyribonucleotide metabolic process	GO:0009219	nucleotide metabolism	3.844E-02	TDG,UNG,MBD4,TYMS,DCTPP1,DTYMK,DUT	7	up
pyrimidine metabolism	KEGG:00240	nucleotide metabolism	3.109E-02	NME2,UMPS,ENTPD5,ENTPD1,ENTPD6,UCK2,NT5C2,CAD,TYMS,RRM2,NT5E,CMPK1,DCTPP1,DTYMK,DUT,NT5C1B,NT5C1B-RDH14	17	up
pyrimidine nucleotide metabolic process	GO:0006220	nucleotide metabolism	1.390E-02	TDG,UNG,MBD4,UMPS,CAD,TYMS,CMPK1,DCTPP1,DTYMK,DUT,PRPS1	11	up
pyruvate metabolic process	GO:0006090	metabolic process	1.812E-03	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,VDAC1,PFKM,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,BSG,POM121C,LDHA,GPI,NUP62,TIGAR,NUP98,RAE1,ME1,PPARA,NUP43,PGAM4,ZBTB7A,PDP2,NUP54,EIF6,SLC16A1	37	up
raf-independent mapk1/3 activation	REAC:R-HSA-112409	MAPK signalling	3.832E-03	JAK2,DUSP6,IL6R,DUSP1,IL6,CDK1,PEA15,MAPK3,MAP2K1,DUSP5,MAPK1	11	up
rap1 signalling pathway	KEGG:04015	signalling pathways	2.853E-04	MAPK1,MAPK14,GNAQ,CDH1,MAGI3,MAP2K2,IGF1,PDGFRA,PARD3,PFN2,AKT1,IGF1R,GNAI2,FGF19,KIT,ADCY9,KRAS,RAP1B,SIPA1L1,CTNND1,CDC42,ITGB1,PDGFRB,TIAM1,AKT2,AKT3,VEGFA,MET,PRKD3,CRKL,RHOA,CALML4,CTNNB1,CRK,EGF,ACTG1,GNAI3,ANGPT4,RRAS,PLCE1,MAGI2,THBS1,PFN1	43	both
ras protein signal transduction	GO:0007265	signalling pathways	2.592E-08	CDKN2A,EPOR,TP53,JAK2,EPO,STARD13,MAPK14,PIK3CB,RAF1,RASGRP1,RHOV,USP8,PLEKHG5,ABL1,STARD8,KPNB1,RHOA,ROCK1,CDKN1A,GRAP2,SQSTM1,ROBO1,NOTCH2,SOS1,NOTCH1,CCNA2,DNMT1,KRAS,FGF2,NRP1,SETDB1,ABL2,OGT,GRB2,GNB1,CUL3,FLCN,KANK1,CRKL,NCKAP1,RAP2C,ARHGDIA,SHOC2,CDC42,RTN4,STMN1,RHOB,CDK2,RRAS2,ITGB1,CFL1,MET,ARHGAP1,ALS2,NUP62,ARHGDIB,RRAS,EPS8L2,RAP2A,MFN2,PIK3CG,ARF6,RALB,PRKD1,G3BP2,GDI1,AGTR1,USP28,NRAS,F11R,PDPN,MAPKAPK5,KCTD10,DLC1,ERBIN,F2RL1,RHOH,G3BP1,LRRC59,DENND4B	80	both
ras signalling pathway	KEGG:04014	signalling pathways	1.654E-05	ETS1,IGF2,PLA2G4F,GRIN2A,AKT1,ANGPT2,GAB2,RASAL2,IGF1R,PIK3CB,RAF1,PIK3CD,RASGRP1,ABL1,EGFR,FGFR2,RHOA,NFKB1,SOS1,CSF1,KRAS,FGFR3,SOS2,FGF2,PIK3R3,PLA2G12A,TGFA,ABL2,VEGFA,RASSF5,GRB2,GNB1,PAK2,CHUK,FGFR4,INSR,PIK3R1,REL,AKT3,SHOC2,CDC42,KDR,GNG12,RRAS2,MET,MAPK3,ZAP70,PDGFRB,PDGFRA,RRAS,MAP2K1,PLCG1,ARF6,RALB,PLA2G2D,EPHA2,CSF1R,KIT,FASLG,BCL2L1,NRAS,RAB5B,MAPK1,ETS2,PDGFB,STK4,PAK3	67	up
reactive oxygen species metabolic process	GO:0072593	oxygen levels	9.211E-03	PMAIP1,PRDX2,STAT3,TP53,JAK2,AKT1,TNF,MAPK14,KHSRP,ALOX5,NNT,CDKN1A,PTGS2,NOS1,BRCA1,ITGB2,TLR4,HSP90AA1,SH3PXD2A,KLF4,SMAD3,ALOX12,TFAP2A,GRB2,PRKCD,ACOX1,INSR,RNF41,CLU,PDGFRB,TGFBR2,DDAH2,BNIP3,GADD45A,BMP7,SESN2,CYB5B,DDAH1,CYBB,PPARA,AGTR1,ROMO1,ABCD2,EDN1,F2RL1,CD36,EIF6,PDGFB,SOD2,SESN1,THBS1,ATP7A	52	up

recombinational repair	GO:0000725	cell cycle	4.947E-04	RFWD3,FUS,PARP1,FANCM,BRCA2,BRCA1,ZFYVE26,MCMDC2,CHEK1,ACTR2,NUCKS1,RNF138,KLHL15,RIF1,AP5Z1,ZNF365,MRE11,ZSWIM7,YY1,MRNIP,MCM4,POLL,MCM2,MCM7,FEN1,FIGN,MCM6,XRCC1,RAD51,MMS19,MCM3,SIRT6,MCM5,POLQ,REV3L,SLX4,NABP1,ERCC4,XRCC2	39	up
recycling pathway of l1	REAC:R-HSA-437239	signalling pathways	1.127E-02	RPS6KA1,NUMB,L1CAM,RPS6KA4,AP2B1,TUBB2A,RPS6KA3,AP2A1,ACTG1,KIF4A,AP2M1,AP2A2,CLTA,MAPK1,DPYSL2,RPS6KA5,ACTB	17	up
regulated necrosis	REAC:R-HSA-5218859	apoptosis	2.485E-05	XIAP,TNFRSF10B,Fas,FADD,BIRC3,TNFRSF10A,TRAF2,FASLG,CASP8,BIRC2,UBB,RPS27A,UBC	13	up
regulation by c-flip	REAC:R-HSA-3371378	signalling pathways	3.238E-03	TNFRSF10B,Fas,FADD,TNFRSF10A,TRAF2,FASLG,CASP8	7	up
regulation of actin cytoskeleton	KEGG:04810	cytoskeleton	3.532E-06	VCL,PIK3CB,APC,RAF1,PIK3CD,PPP1CA,EGFR,PIP4K2C,FGFR2,CXCR4,RHOA,ROCK1,WASF2,MYLK,ITGB2,SOS1,CXCL12,WASL,ITGA5,KRAS,FGFR3,SOS2,FGF2,PIK3R3,ITGB8,ACTR3B,ACTR2,VAV2,PAK2,FGFR4,CRKL,PIK3R1,NCKAP1,ITGA2,CDC42,CRK,GNG12,DIAPH1,SLC9A1,RRAS2,ITGB1,MYL9,CFL1,ITGA6,VAV3,ITGA11,ACTG1,MAPK3,SRC,PDGFRB,PDGFRA,RRAS,MAP2K1,ITGB3,PPP1CC,NRAS,PIP5K1C,CFL2,MAPK1,MYH11,ENAH,PDGFB,ACTB,SPATA13,ITGA1,PAK3	66	up
regulation of actin cytoskeleton reorganisation	GO:2000249	cell organisation	1.342E-02	FES,ABL1,NTRK3,NOTCH2,NRP1,ABL2,ARHGDIA,CDC42,HAX1,PDGFRA,ARHGDIB,CSF1R,F11R	13	up
regulation of adaptive immune response	GO:0002819	adaptive immune system	2.994E-03	FBXO38,SUPT6H,TNFAIP3,HSPD1,TRAF6,FADD,CD80,IRF7,IL6,RSAD2,IL23R,HLA-A,HLA-G,FZD5,CD274,AGER,RIF1,SMAD7,SOCS5,MAP3K7,IL6ST,NLRP3,MEF2C,SIRT1,CD40,TFRC,IFNB1,HMGB1,TRAF2,IL10,CD226,IRF1,B2M,PVR	34	up
regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	GO:0002822	adaptive immune system	6.547E-03	FBXO38,SUPT6H,TNFAIP3,HSPD1,TRAF6,FADD,CD80,IL6,RSAD2,IL23R,HLA-A,HLA-G,FZD5,CD274,AGER,RIF1,SMAD7,SOCS5,MAP3K7,NLRP3,MEF2C,CD40,TFRC,IFNB1,HMGB1,TRAF2,IL10,CD226,B2M,PVR	30	up
regulation of alternative mrna splicing, via spliceosome	GO:0000381	transcription and translation	3.625E-02	THRAP3,REST,FXR1,PTBP1,RNPS1,SRSF1,HNRNPA1,YTHDC1,NOVA2,RBM15B,IK,KHDRBS1,RBFOX2,SMU1,ZBTB7A,QKI,MBNL1,MBNL3,SRSF2,SF1	20	up
regulation of androgen receptor signalling pathway	GO:0060765	signalling pathways	1.633E-02	EP300,DAB2,RNF14,PIAS2,SIRT1,RNF6,ARRB2,DDX5,FOXH1,HEYL	10	down
regulation of apoptotic dna fragmentation	GO:1902510	apoptosis	2.991E-03	CDKN2A,IL6,AIFM1,CIDEA,BAX,DFFA	6	up
regulation of atp metabolic process	GO:1903578	metabolic process	9.448E-03	STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PARP1,NDC1,ENTPD5,OGT,PRKAA1,FLCN,CBFA2T3,INSR,NUP50,APP,POM121C,NUP62,TIGAR,NUP98,RAE1,TREM2,PPARA,NUP43,ZBTB7A,NUP54,EIF6,ATP7A	28	up
regulation of attachment of spindle microtubules to kinetochore	GO:0051988	cytoskeleton	2.092E-03	AURKB,APC,RCC2,RACGAP1,CDC42,ECT2,BECN1,CCNB1	8	both
regulation of autophagy	GO:0010506	autophagy	4.311E-02	LARP1,TRIM27,ABL2,FBXL2,CALCOCO2,TP53INP1,SESN3,RRAGC,EP300,SPTLC2,TRIM13,SLC38A9,HMGB1,TRIM38,FOXO1,SNX5,CASP3,IL10RA,SIRT1,AKT1,DRAM1,ATM,BCL2,ULK1,SMCR8,GAPDH,MCL1,PRKAB2,FZD5,HUWE1,SH3GLB1,STAT3,RAB3GAP2,ITPR1,PIP4K2C,RRAGD,FOXO3,MET,CHMP4B,IL4,ROCK1,EXOC8,LRSAM1,ERN1,TRIM65,IKBKG,ATP6V0D2,QSOX1,TMEM59,GNAI3,TPCN2,GSK3B,UBQLN4,FOXK2,RAB3GAP1,CAPNS1	56	both
regulation of binding	GO:0051098	cell adhesion and migration	6.314E-03	TWIST1,FMR1,PRKCD,GNL3L,DTX3L,EP300,IGF1,DAB2,HMGB1,NEUROD1,TERT,RARA,AKT1,FOXC1,PPARG,NVL,RAN,FKBP1A,CAPRIN2,CSNK1A1,PER2,ARRB2,HMGA2,RSF1,DOT1L,AMFR,CTNNBIP1,ZFPM1,JUN,TIAM1,STMN1,SMAD2,SKI,B2M,MET,ROCK1,CTNNB1,CDKN1A,CRK,NUCKS1,FLOT1,HJURP,TMBIM6,EGF,SLPI,STYX,GSK3B,PPP1CA,DVL1,AURKA	50	both
regulation of biological process involved in symbiotic interaction	GO:0043903	signalling pathways	5.037E-04	VPS4B,CHMP3,PABPC1,TNF,REST,EXOC7,HMGA2,TRIM22,IFI27,IFIT5,ISG15,IFITM3,IFITM1,SLPI,STAT1,OASL,RSAD2,CCL5,IFIT1,CXCL8,VPS37B,SETDB1,TARBP2,SRPK1,CHMP4B,CCL4,CCNT1,TRIM35,NUCKS1,DDX3X,VPS4A,POLR2E,TBC1D20,BSG,SP1,HEXIM1,CCL3,CHMP2B,CFL1,HDAC1,NELFCD,SUPT5H,RRP1B,LEF1,SNX3,UBP1,LARP1,IFNB1,SMARCA4,ADARB1,PPARA,APOBEC3F,MAVS,IGF2R,POLR2D,F2RL1,KPNA2,TOP2A	58	up
regulation of body fluid levels	GO:0050878	homeostasis	1.146E-03	VCL,GPAT4,JAK2,PABPC4,APLN,WNK1,SCNN1A,PIK3CB,RAF1,EHD1,ADM,CD40LG,ERBB4,COPA,IL6,PRKCE,TLR4,PLAUR,VEGFA,VAV2,ALOX12,DOCK11,RCOR1,PRKAR2A,GNB1,MAFK,PRKCD,ENTPD1,ITPR1,PIK3R1,ITGA2,RAB11FIP2,CDC42,STXBP3,CAPZA2,STMN1,F3,MYL9,CFTR,MET,HDAC1,VAV3,HNF4A,SFN,ACTG1,VPS45,MAPK3,SRC,PDGFRA,CAPZB,GPI,METAP1,CD40,IFNB1,GATA4,ITGB3,MFN2,AXL,PIK3CG,SAA1,DGKZ,GGCX,SH2B3,GATA6,F11R,PDPN,AKAP10,GNAQ,MAPK1,EDN1,IRF1,ENPP4,ZBTB7B,TRPC3,F2RL1,CD36,UBASH3B,PDGFB,CBX5,HAS2,CSRP1,EMP2,CYP4F11,ACTB,THBS1,DGKB,DGKI,LMAN1	88	up
regulation of canonical wnt signalling pathway	GO:0060828	Wnt signalling	4.889E-02	TMEM9,FZD4,XIAP,SFRP5,WNK1,PSMB1,APC,EMD,NRARP,FZD6,USP8,PPP1CA,EGFR,GLI1,FGFR2,DKK3,NFKB1,SFRP1,SOX2,DKK1,DDX3X,PPM1A,BTRC,CUL3,AMER1,CCDC88C,KANK1,NKD1,CYLD,TLE4,AXIN2,GSK3B,FZD9,TBL1XR1,ZNRF3,PSMB5,LATS2,TMEM64,HDAC1,CTNNB1,USP47,POU5F1,TLE3,SOX4,GNAQ,TCF7L2,MCC,CAPRIN2,KREMEN1,WWTR1,STK4,ZNF703,TMEM170B,LIMD1,PPM1B	55	up
regulation of carbohydrate metabolic process	GO:0006109	metabolic process	4.392E-02	NUP98,SLC2A6,PPARA,PTPN2,RORA,EP300,NUP62,IGF1,NUP205,PHKG2,SIRT1,HIF1A,NFKB1,AKT1,SLC45A3,PMAIP1,PDK3,AKT2,STAT3,POM121C,NUP50,ZBTB20,SCARB2,NUP210,PPARGC1A,ENTPD5,TP53,EGF,NUP35,NUP85,ARPP19,GSK3B,FOXK2	33	both
regulation of cell cycle arrest	GO:0071156	cell cycle	7.099E-08	CDKN2A,E2F7,TP53,ARID3A,ZNF385A,BTG2,TNKS1BP1,HMGA2,MUC1,MIF,CDKN1A,BRCA1,CNOT6L,CCND1,RBM38,CDKN1B,CNOT4,CDK4,CARM1,CDK1,PPP2R5C,FZD9,CDK2,MDM2,E2F1,ATM,CDC25C,SFN,MDM4,CRADD,GADD45A,TP73,BAX,CNOT2,SOX4,AURKA,GATA6,CCNB1,RPL23,CHEK2,CNOT1,CRLF3	42	both
regulation of cell cycle g1/s phase transition	GO:1902806	cell cycle	1.924E-07	DCUN1D3,SOX4,CDK6,WEE1,DDX3X,LSM10,TP63,ARID3A,FAM107A,EP300,ADAM17,ZNF655,FAM83D,CCND1,EZH2,AKT1,CCND3,ATM,PTEN,KMT2E,CARM1,BTG2,MDM2,KLF4,CNOT6,CCND2,CDKN1B,APPL1,RFWD3,GADD45A,CDKN1A,KANK2,TP53,CDC73,MDM4,RBM38,TFDP2,AURKA	38	both
regulation of cell cycle phase transition	GO:1901987	cell cycle	1.885E-04	DCUN1D3,KNTC1,SOX4,CDK6,CCP110,WEE1,DDX3X,ACTR1A,LSM10,TP63,APC,BRSK1,ARID3A,PSMB9,CEP41,DUSP1,FAM107A,EP300,ADAM17,PCM1,FGFR1OP,TAOK3,ZNF655,TAOK1,FAM83D,YWHAG,CCND1,EZH2,AKT1,CCND3,MECP2,ATM,PTEN,PHOX2B,KMT2E,TOPBP1,ZFP36L2,TUBB,HMGA2,CARM1,HECW2,ZFP36L1,CDC23,BTG2,RCC2,MDM2,KLF4,CNOT6,CCND2,CDKN1B,CHEK1,DONSON,HAUS8,APPL1,BUB1,RFWD3,GADD45A,CDKN1A,KANK2,CDC27,TP53,CDC73,DYNC1H1,MDM4,ESPL1,HAUS3,RBM38,MRNIP,MRE11,HUS1,PSMC4,TFDP2,YWHAE,NDE1,PSMD3,TAOK2,AURKA	77	both
regulation of cell development	GO:0060284	organogenesis	4.854E-04	SEMA6B,NUMBL,NPTN,SEMA6A,METRN,LIMS1,CLOCK,HOOK3,SEMA3E,CAPRIN1,MAP3K13,NOTCH1,PDE3A,L1CAM,IGF1,ZDHHC21,PCM1,TIAM2,SPRY4,BCL11A,ADGRA2,SEMA4C,YAP1,ROCK2,RELN,PTEN,RNF6,LDLR,CAPRIN2,PER2,NOTCH2,CDC42,FGG,RCC2,DICER1,FBN1,FGB,FGA,NUMB,TIAM1,REST,DYNLT1,VEGFA,NEDD9,SEMA7A,PTPRD,SKI,B2M,CRKL,RHOA,ROCK1,CTNNB1,CRK,RREB1,NF1,HES2,SEMA4G,FBXW8,ARHGDIA,RFLNB,MYADM,HEYL,F2,GSK3B,ACTN4,S1PR2,SPEN,HES7	68	down
regulation of cell division	GO:0051302	cell cycle	6.688E-03	E2F7,MYO19,AURKB,HDGF,FGFR2,RHOA,PRKCE,TXNIP,ZFYVE26,CUL3,FLCN,VPS4A,KIF23,RACGAP1,CDC42,TAL1,ECT2,MYC,DLL1,SFN,RAB11FIP4,NUP62,BIRC6,BECN1,POU5F1,BCL2L1,AURKA,OR2A4,KLHL21,CDK2AP2,CSPP1,KIF13A	32	up
regulation of cell morphogenesis	GO:0022604	organogenesis	4.854E-04	ALDOA,FGD6,NTNG2,MYO10,LIMS1,SEMA3E,CAPRIN1,MAP3K13,EPS8,FGD4,CDC42EP3,NTNG1,SPRY4,PHIP,RND2,PTK2,RHOC,RELN,FERMT2,KIT,CAPRIN2,RHOG,FMNL3,CDC42,FGG,RCC2,SPARC,ENPP2,FGB,FGA,FZD4,VEGFA,NEDD9,PDZD8,PTPRD,DLC1,CRKL,RHOA,MKLN1,PARVB,CRK,WDPCP,RREB1,FBXW8,DVL3,MYADM,TBCCD1,BVES,PDPN,WNT5A,ACTN4,TAOK2,DVL1,PRAG1	54	down
regulation of cell morphogenesis involved in differentiation	GO:0010769	organogenesis	8.579E-03	LIMS1,CAPRIN1,SPRY4,PTK2,RELN,CAPRIN2,CDC42,FGG,RCC2,FGB,FGA,NEDD9,PTPRD,CRKL,CRK,RREB1,FBXW8,MYADM,PDPN,ACTN4	20	down
regulation of cell projection organisation	GO:0031344	cell organisation	3.584E-02	SEMA6B,PAK2,CCP110,NPTN,ABL2,SEMA6A,NTNG2,NSMF,METRN,MYO10,APC,BRSK1,FMR1,VLDLR,PRKCD,SEMA3E,CAPRIN1,MAP3K13,RET,EPS8,ZDHHC15,EP300,L1CAM,CDC42EP3,TIAM2,NTNG1,HOMER1,S100A9,PFN2,BCL11A,SEMA4C,YAP1,AKT1,CDH2,RELN,PLEKHM1,PTEN,RNF6,CAPRIN2,ATP8B1,TBC1D7,ARF6,HECW2,SIPA1L1,CDC42,HECW1,P3H1,FSCN1,ENPP2,TIAM1,FZD4,ITGA6,VEGFA,CAMK1D,MYLIP,WASL,SEMA7A,PTPRD,OCLN,RHOA,SCARB2,RREB1,SEMA4G,FBXW8,ARHGDIA,DVL3,SCARF1,PDPN,PTK6,NDEL1,PLCE1,MAGI2,WNT5A,GSK3B,CEP97,PTPN9,ARSB,PFN1,DVL1,PRAG1	80	down

regulation of cell-cell adhesion	GO:0022407	cell adhesion and migration	9.711E-03	SOX4,PAK2,LAX1,ADAMTS18,YES1,SOX12,LAPTM5,GRAP2,PRKCD,PPARA,PTPN2,NOTCH1,CDH1,DUSP10,PCK1,IGF1,ZDHHC21,ZNF703,SH2B3,HMGB1,PDPK1,NFKBID,CD274,RARA,AKT1,PTK2,NOTCH4,TGFBR2,PLPP3,IL1A,TFRC,VCAM1,ETS1,IL7,SLC7A1,IL2,TESPA1,CDC42,CD276,FGG,DENND6A,KLF4,FGB,FGA,VEGFA,SOCS5,PRKAR1A,CD46,CD55,RHOA,IL4,MAP3K8,NFAT5,BTLA,FLOT1,MYADM,CD209,AKNA,DLG5,PDPN,PYCARD,WNK1,TNFRSF13C,MINK1,FAM49B,ZBTB7B,CITED2,PIEZO1	68	both
regulation of cell-matrix adhesion	GO:0001952	cell adhesion and migration	3.695E-04	CDKN2A,VCL,NF2,PIK3CB,ABL1,RHOA,GPM6B,ROCK1,SFRP1,CSF1,PHLDB2,RCC2,NRP1,PTEN,VEGFA,CDK6,PTPRJ,CASK,MINK1,KDR,GSK3B,SLC9A1,JAG1,ACTG1,SRC,RRAS,ADAM15,DLC1,CD36,PLET1,EMP2,THBS1	32	up
regulation of cell-substrate adhesion	GO:0010810	cell adhesion and migration	2.177E-03	CDKN2A,VCL,NF2,FZD4,JAK2,PIK3CB,ABL1,RHOA,GPM6B,ROCK1,SFRP1,NOTCH1,CSF1,PHLDB2,WNT1,RCC2,NRP1,PTEN,ARL2,VEGFA,CDK6,PTPRJ,KANK1,CRKL,CASK,MINK1,CDC42,KDR,GSK3B,CRK,SLC9A1,JAG1,ACTG1,SRC,RRAS,RSU1,ADAM15,PDPN,DLC1,CD36,PDGFB,PLET1,EMP2,THBS1	44	both
regulation of cell-substrate junction organisation	GO:0150116	cell organisation	3.376E-02	VCL,ABL1,RHOA,GPM6B,ROCK1,SFRP1,PHLDB2,RCC2,NRP1,PTEN,VEGFA,PTPRJ,PIK3R1,KDR,SLC9A1,ACTG1,SRC,ARF6,DLC1,THBS1	20	both
regulation of cellular response to heat	GO:1900034	cellular response to external stimuli	9.759E-04	NUP98,MAPK1,EP300,NUP62,NUP205,DNAJB6,BAG4,SIRT1,BAG1,CCAR2,RPA1,ATM,POM121C,HSPA8,NUP50,NUP210,HSP90AB1,NUP35,CHORDC1,NUP85,YWHAE,GSK3B,HSBP1,CREBBP	24	both
regulation of cellular response to transforming growth factor β stimulus	GO:1903844	TGF signalling	9.970E-04	CREBBP,SMAD4,MTMR4,FBN1,DKK3,SMAD2,ADAM17,SKI,SMAD3,SPRED1,PPM1A,FLCN,TGFBR3,SMAD7,SMURF1,LATS2,VASN,STRAP,SIRT1,TGFBR2,PEG10,CIDEA,PPARA,SOX11,PMEPA1,DAND5,UBB,ZBTB7A,RPS27A,UBC,TRIM33,ZNF703,THBS1	33	up
regulation of chemokine (c-x-c motif) ligand 2 production	GO:2000341	cell adhesion and migration	4.808E-02	TNF,TLR4,KLF4,HMGB1,TIRAP,F2RL1	6	up
regulation of cholesterol biosynthesis by srebp (srebf)	REAC:R-HSA-1655829	lipid metabolism	1.381E-02	MTF1,SEC24A,CREBBP,MED1,LSS,KPNB1,FASN,CARM1,TBL1XR1,SP1,NCOA1,DHCR7,CYP51A1,PPARA,INSIG1,NFYB,RAN,SC5D	18	up
regulation of chromatin organisation	GO:1902275	chromatin organisation	1.094E-04	BCOR,IGF2,SUPT6H,PHF8,LIF,SMAD4,MUC1,HMGA1,SET,NOS1,AKAP8,BRCA1,JARID2,DNMT1,SETDB1,RPS6KA4,CHEK1,VEGFA,OGT,SSRP1,FLCN,PHF19,OTUB1,MYB,RIF1,TADA2B,MTHFR,TLK1,TAL1,HIST1H1E,MAPK3,SPI1,SIRT1,RNF40,CTNNB1,MKI67,POU5F1,PRKD1,SIRT6,ATF7IP,ZBTB7B,RPS6KA5,TET1,PRKD2,TWIST1	45	up
regulation of chromosome organisation	GO:0033044	cell organisation	9.457E-06	AURKB,PHF8,LIF,APC,SMAD4,MUC1,PARP1,DUSP1,NOS1,AKAP8,BRCA1,JARID2,DNMT1,TACC3,CCT6A,SETDB1,RPS6KA4,VEGFA,OGT,CUL3,PHF19,HNRNPA1,CDC27,MYB,HMBOX1,RIF1,AXIN2,TADA2B,HNRNPA2B1,TAL1,ATM,MYC,MRE11,CDC20,MAPK3,SRC,FEN1,SIRT1,IK,RNF40,PPP1R10,CCT3,ANAPC5,CTNNB1,XRN1,BECN1,POU5F1,PRKD1,SIRT6,CDC23,ATF7IP,CCNB1,SLX4,RNF4,MAPKAPK5,MAPK1,ZBTB7B,RPS6KA5,TERF2,TET1,ERCC4,PRKD2,SMG1,SENP6,CTC1,TOP2A,HNRNPC	67	up
regulation of circadian rhythm	GO:0042752	endocrine system	5.000E-02	ZFHX3,CLOCK,GNAQ,PPARA,RORA,EZH2,ROCK2,CCAR2,PPARG,PER2,SUV39H2,PER1,PPP1CB,PPP1CC,KLF10,FBXL3,CRY2,PPARGC1A,TP53,RBM4B,GSK3B,KDM2A,PPP1CA	23	down
regulation of cyclin-dependent protein kinase activity	GO:1904029	cyclin signalling pathway	1.136E-05	APC,NR2F2,GTF2H1,CCNI,ADAM17,CCND1,CEBPA,AKT1,CCND3,CCNK,PTEN,LATS2,IPO5,CCNG1,CCNT2,CCNA2,CCND2,CDKN1B,CCNG2,IPO7,GADD45A,CDKN1A,HSP90AB1,CKS1B,CCNT1,HEXIM1,SERTAD1,CCNF	28	both
regulation of cyclin-dependent protein serine/threonine kinase activity	GO:0000079	cyclin signalling pathway	2.474E-04	CDKN2A,CEBPA,AKT1,CCNE1,CDKN2D,APC,EGFR,CCNJ,CDKN1A,CDKN3,CCND1,CCND2,CCNA2,ADAM17,CDKN1B,PTEN,CCND3,CCNT1,CDC25A,CCNT2,CCNE2,LATS2,HEXIM1,CDC25C,GADD45A,CDKN2C,CDK5R1,CCNB1,MAPRE3,CCNI,IPO7,PDGFB,ACTB	33	both
regulation of cysteine-type endopeptidase activity	GO:2000116	endopeptidase activity	2.082E-13	CDKN2A,PMAIP1,RPS6KA1,XIAP,BCL2L13,JAK2,S100A8,GRIN2A,BBC3,AKT1,TNF,CDKN2D,BAK1,REST,TNFRSF10B,Fas,CD44,RAF1,HSPD1,EPHA7,CSNK2A1,FADD,ROBO1,PLAUR,SOX2,ARL6IP1,KLF4,VEGFA,SMAD3,BCL2L11,DDX3X,PAK2,BIRC5,BCL2L12,RET,RPS6KA3,F3,NLRP3,MYC,SFN,BIRC3,SENP1,SRC,SIRT1,MAGEA3,DIABLO,NAIP,DNAJB6,CASP1,HMGB1,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,USP47,TRAF2,BAX,RIPK2,NOD1,FASLG,NOL3,CIDEB,DAPK1,BCL10,CFLAR,CASP8,APAF1,BIRC2,CASP10,FNIP1,GRAMD4,DLC1,EGLN3,DHCR24,THBS1	76	up
regulation of cysteine-type endopeptidase activity involved in apoptotic process	GO:0043281	endopeptidase activity	1.722E-02	CDKN2A,PMAIP1,RPS6KA1,XIAP,BCL2L13,JAK2,S100A8,BBC3,AKT1,TNF,CDKN2D,REST,TNFRSF10B,Fas,CD44,RAF1,HSPD1,EPHA7,CSNK2A1,FADD,ROBO1,PLAUR,SOX2,ARL6IP1,KLF4,VEGFA,SMAD3,BCL2L11,DDX3X,PAK2,BIRC5,BCL2L12,RET,RPS6KA3,F3,NLRP3,MYC,SFN,BIRC3,SENP1,SRC,SIRT1,MAGEA3,DIABLO,NAIP,DNAJB6,CASP1,HMGB1,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,USP47,TRAF2,BAX,NOD1,FASLG,NOL3,DAPK1,BCL10,CFLAR,CASP8,APAF1,BIRC2,CASP10,FNIP1,GRAMD4,DLC1,EGLN3,DHCR24,THBS1	72	both
regulation of cytoskeleton organisation	GO:0051493	cell organisation	9.910E-05	VPS4B,NF2,S100A8,NES,CDH5,NPM1,APC,FES,SMAD4,ABL1,NTRK3,RHOA,GPM6B,ROCK1,RHOBTB3,WASF2,SFRP1,BRCA1,PRKCE,NOTCH2,CXCL12,TACC3,PHLDB2,NRP1,ABL2,ARL2,TAOK1,PAFAH1B1,ACTR2,CHMP4B,PRKAA1,MECP2,PAK2,KANK1,PRKCD,AMOT,CYLD,PIK3R1,NCKAP1,CGNL1,ARHGDIA,CAMSAP1,CDC42,GSK3B,CRK,DIAPH1,CAPZA2,SLC9A1,STMN1,RHOB,HAX1,TWF1,TMEM67,CHMP2B,MET,TPM1,ACTG1,CORO1B,MAPK3,PDGFRB,PDGFRA,CAPZB,CAPG,NUP62,ARHGDIB,TPPP,CKAP5,RICTOR,EPHA5,ARF6,RAE1,GMFB,MAP1B,CSF1R,CTTN,ARF1,CDK5R1,OR2A4,RNF4,TRIM36,F11R,CLIC4,CFL2,MID1IP1,MAPRE3,TRIM37,MAPK1,EDN1,CDK2AP2,CAMSAP2,MTPN,JMY,DLC1,CLIP1,F2RL1,RHOH,DYRK1A,SENP6,SIGLEC15,FSCN1,SKA2,PAK3,PFDN2	103	up
regulation of deoxyribonuclease activity	GO:0032070	cell cycle	1.281E-02	AKT1,NPM1,PRKCD,SIRT1,HMGB1,DFFA	6	up
regulation of dephosphorylation	GO:0035303	phosphorylation	7.363E-03	PPP1R37,ZFYVE1,TNF,MTMR3,WNK1,CDH5,CSRNP2,PTBP1,MFHAS1,MTMR4,ROCK1,PPP1R11,HSP90B1,PPP6R1,YWHAB,SPRED1,PRKCD,PPP6R3,FKBP1A,GSK3B,MEF2C,RRP1B,MTMR2,CAMTA1,SRC,PDGFRB,RBM26,MTMR9,FKBP1B,CNEP1R1,WDR81,PPP1R7,MASTL,PPP1R15B,DLC1,ARPP19,ITGA1,ELL	38	up
regulation of dna recombination	GO:0000018	cell cycle	3.636E-02	SUPT6H,FUS,PARP1,CHEK1,ACTR2,KLHL15,RIF1,KPNA1,ZNF365,MRE11,HIST1H1E,MRNIP,CD40,TFRC,FIGN,RAD51,MMS19,SIRT6,IL10,POLQ,ZNF711,TERF2,KPNA2	23	up
regulation of dna-binding transcription factor activity	GO:0051090	cell cycle	8.110E-06	CDKN2A,SPHK1,STAT3,FZD4,S100A8,AKT1,TNFAIP3,SFRP5,TNF,DHX33,NPM1,MAPK14,SMO,CRTC1,FZD6,CEBPG,TRIM22,CD40LG,FOS,IRAK2,TRAF6,NFKB1,TLR2,IRAK1,IL1RAP,IL6,TLR4,S100A12,FAF1,SIK1,WNT1,CLOCK,KLF4,RPS6KA4,PTEN,VEGFA,SMAD3,UBE2V1,BTRC,FLOT2,BHLHE40,CHUK,AGER,SLCO3A1,CYLD,TAB3,HEYL,SMAD7,CLU,APP,TCF3,MAP3K7,PIM1,PLPP3,ADORA3,NLRP3,ANXA4,MAPK3,SIRT1,AR,MTDH,CD40,TFRC,TRAF3,CTNNB1,SMARCA4,EPHA5,TRAF2,BMP7,RBCK1,RIPK2,KIT,NLRC5,NOD1,PRKD1,G3BP2,IL10,BCL10,CFLAR,ADGRG3,NEUROD2,TIRAP,UBB,PRNP,ZBTB7A,TRIM37,MAVS,TCF7L2,MAPK1,EDN1,RPS27A,UBC,MTPN,JMY,RPS6KA5,ERBIN,ESR1,ZNF431,CD36,PRKD2,TAB2	101	up
regulation of dna-templated transcription, initiation	GO:2000142	cell cycle	2.096E-02	ESR1,TWIST1,HMGB1,FOSL1,JUN,MITF,MED17,CTNNB1,TP53,MED16,SRF,PSMC4	12	down
regulation of embryonic development	GO:0045995	organogenesis	1.827E-02	EHMT1,TDG,RAB14,PHLDB2,WNT1,B4GALT5,PAFAH1B1,RACGAP1,CDK1,NR2C2,INSR,CFL1,SEPT7,BAG6,PLCB1	15	up
regulation of endodeoxyribonuclease activity	GO:0032071	cell cycle	2.287E-02	AKT1,NPM1,PRKCD,SIRT1,HMGB1	5	up
regulation of endopeptidase activity	GO:0052548	endopeptidase activity	3.976E-08	CDKN2A,PMAIP1,RPS6KA1,STAT3,XIAP,BCL2L13,JAK2,S100A8,GRIN2A,BBC3,AKT1,TNF,CDKN2D,BAK1,REST,NRDC,TNFRSF10B,Fas,CD44,RAF1,HSPD1,EPHA7,CSNK2A1,FADD,ROBO1,SERPINA4,PLAUR,SOX2,ARL6IP1,FURIN,KLF4,VEGFA,SMAD3,VSIR,BCL2L11,DDX3X,RECK,PAK2,BIRC5,AGER,BCL2L12,RET,RPS6KA3,F3,NLRP3,MYC,HDAC1,SFN,BIRC3,SERPINB1,SENP1,SRC,SIRT1,MAGEA3,DIABLO,NAIP,DNAJB6,CASP1,HMGB1,CASP9,CRADD,CYCS,AIFM1,TNFRSF10A,USP47,TRAF2,BAX,RIPK2,NOD1,FASLG,NOL3,CIDEB,DAPK1,BCL10,CFLAR,CASP8,APAF1,BIRC2,CASP10,FNIP1,GRAMD4,DLC1,EGLN3,DHCR24,THBS1	85	up
regulation of endoplasmic reticulum tubular network organisation	GO:1903371	cell organisation	3.967E-02	ARL6IP1,LNPK,RAB3GAP2,TMEM33	4	both

regulation of endothelial cell migration	GO:0010594	cell adhesion and migration	3.997E-02	ETS1,AKT1,ANGPT2,TNF,STARD13,PIK3CB,PIK3CD,ABL1,RHOA,PTGS2,CARD10,NOTCH1,ADAM17,FGF2,KLF4,NRP1,VEGFA,MECP2,MAP2K3,AMOT,AKT3,KDR,PLPP3,BSG,RHOB,MEF2C,SP1,STAT5A,SCARB1,MET,GPI,SIRT1,RRAS,CD40,ITGB3,PLCG1,PIK3CG,HMGB1,GADD45A,EPHA2,PRKD1,SASH1,EDN1,NUS1,PRKD2,PDGFB,EMP2,THBS1,ADAMTS9	49	up
regulation of epithelial cell proliferation	GO:0050678	cell proliferation	6.870E-03	VDR,STAT3,IGF2,ERBB2,AKT1,APLN,MED1,NME2,NRARP,PIK3CD,ALOX5,EGFR,FGFR2,UHRF1,CDC73,STAT1,SFRP1,BRCA2,TLR4,ROBO1,NOTCH2,SOX2,ADAM17,FGF2,NRP1,TGFA,VEGFA,CDK6,WNT7A,CASK,AKT3,TGFBR3,LAMC1,KDR,RTN4,YAP1,F3,FBXW7,MEF2C,SP1,STAT5A,MYC,STRAP,SIRT1,ITGB3,PLCG1,HMGB1,GDF5,PRKD1,SIRT6,WDR77,AREG,AGTR1,NRAS,SOX11,NFIB,TCF7L2,MCC,EREG,PRKD2,PDGFB,B2M,ZNF703,THBS1,MTSS1	65	up
regulation of epithelial to mesenchymal transition	GO:0010717	organogenesis	2.017E-02	PPP2CA,SMAD4,SFRP1,SMAD2,IL6,NOTCH1,PHLDB2,PTEN,SMAD3,SPRED1,AXIN2,SMAD7,JAG1,VASN,LEF1,STRAP,TGFBR2,CTNNB1,SNAI1,PDPN,TCF7L2,ACVR1,WWTR1,ZNF703,TWIST1	25	up
regulation of erythrocyte differentiation	GO:0045646	cell differentiation	4.002E-02	ETS1,STAT3,MED1,MAPK14,STAT1,MAFB,CDK6,ACVR2A,FOXO3,TAL1,SPI1,HOXA5	12	up
regulation of establishment of endothelial barrier	GO:1903140	blood brain barrier	2.076E-03	VCL,TNF,CDH5,ROCK1,S1PR2,VEGFA,TNFRSF1A,ZDHHC21,F11R	9	up
regulation of establishment of protein localization	GO:0070201	protein localization	1.812E-03	CDKN2A,PMAIP1,KCNS3,TP53,ERBB2,BBC3,BCL2,SIRT7,TNF,EDEM1,REST,HUWE1,YOD1,EMD,ALOX5,ARIH2,IFI27,TLR2,SFRP1,IL6,RSAD2,CCL5,ITGB2,TLR4,IRS1,UBE2D3,FZD5,CLOCK,CCT6A,YWHAB,ARL2,CREBRF,SMAD3,RAB23,DNAJA1,HSPA8,PRKCD,BAG4,ITPR1,TM7SF3,PIK3R1,CD2AP,SIRT4,YWHAQ,YWHAH,GSK3B,BSG,HAX1,FBXW7,E2F1,CFTR,RANGAP1,ECT2,VAMP2,SNX12,HNF4A,SFN,SNX3,ACSL4,CCT3,ITGB3,STX1A,ANK3,CYP51A1,FRMD4A,MYO1C,SAA1,INHBB,TP73,EPHA5,ARF6,SAR1A,PPP3R1,BAG3,GDI1,TREM2,GAPVD1,CASP8,TP53BP2,SOX4,INSIG1,MFF,PER2,BMP8A,TMEM30A,PRNP,MAVS,TCF7L2,RAB11FIP1,SEC16A,RAN,KCNB1,F2RL1,MIDN,KCNA5,SREBF1,LMAN1,DERL2,PCNT	99	up
regulation of execution phase of apoptosis	GO:1900117	apoptosis	1.033E-02	TP53,PAK2,CIDEA,DFFA,BCL2L1,TP53BP2,DLC1,MTRNR2L10,MTRNR2L11,MTRNR2L7,MTRNR2L3	11	up
regulation of extrinsic apoptotic signalling pathway	GO:2001236	apoptosis	2.244E-04	PMAIP1,ZMYND11,AKT1,TNFAIP3,BCL2,TNF,TNFRSF10B,Fas,MCL1,FADD,SFRP1,BRCA1,ICAM1,PTEN,DDX3X,PAK2,CYLD,BCL2L12,GSK3B,RET,ITGA6,PEA15,SRC,AR,BIRC6,TNFRSF10A,TRAF2,LTBR,FASLG,NOL3,BCL10,CFLAR,CASP8,BCL2L1,TCF7L2,ACVR1,THBS1	37	both
regulation of extrinsic apoptotic signalling pathway via death domain receptors	GO:1902041	apoptosis	5.924E-03	PMAIP1,TNFAIP3,TNFRSF10B,Fas,FADD,SFRP1,BRCA1,ICAM1,PTEN,DDX3X,GSK3B,PEA15,TNFRSF10A,TRAF2,FASLG,CFLAR,CASP8,BCL2L1,THBS1	19	both
regulation of fat cell differentiation	GO:0045598	cell differentiation	1.729E-03	AKT1,TNF,SIX1,ZNF385A,ALOX5,PTGS2,SFRP1,IL6,WNT1,PPARD,SMAD3,FLCN,CARM1,ZBTB16,CREBL2,ASXL1,PIM1,RUNX1T1,YAP1,FOXO1,E2F1,CDS1,TMEM64,SIRT1,CEBPB,BMP7,TAF8,ZADH2,CREB1,ZBTB7B,WWTR1	31	up
regulation of fibroblast proliferation	GO:0048145	cell proliferation	5.098E-03	MYC,DDR2,CDK6,IGF1,PDGFRA,EREG,PEX2,SKI,CTNNB1,CDKN1A,NF1,TP53,CDC73,NLRC3,WNT5A,BMI1,MIF	17	both
regulation of foxo transcriptional activity by acetylation	REAC:R-HSA-9617629	FoxO signalling pathway	2.273E-02	EP300,FOXO1,SIRT1,TXNIP,FOXO3,CREBBP	6	down
regulation of g0 to g1 transition	GO:0070316	cell cycle	2.623E-02	RBBP4,RYBP,EPC1,EED,EZH2,SUZ12,PHC3,CHEK1,PCGF2,CBX3,TFDP2,BMI1,RAD51	13	down
regulation of gene expression by hypoxia-inducible factor	REAC:R-HSA-1234158	gene expression	3.844E-02	EP300,HIF1A,VEGFA,HIF3A,CREBBP,CITED2	6	down
regulation of gene expression, epigenetic	GO:0040029	gene expression	2.771E-02	TRIM27,RBBP4,EPC1,RIF1,HIST1H2AH,EP300,HMGB1,DEK,HMGA1,SIRT1,EED,EZH2,SUZ12,POLR2E,PPM1D,MECP2,RLIM,MORF4L1,DNMT3A,DNMT3B,TFAP2C,DOT1L,TDG,DDX21,MORF4L2,CHEK1,PCGF2,JARID2,ASF1A,CREBZF,SERTAD2,MTF2,POLR1E,SMARCD1,CD3EAP,SERTAD1,POLR1A,BMI1,H2AFY2	39	down
regulation of gene silencing by rna	GO:0060966	miRNA/siRNA biogenesis	2.957E-02	NUP98,ESR1,FMR1,MAP2K2,TNRC6B,NUP62,NUP205,POLR2D,TERT,AGO1,POLR2E,PPARG,DDX6,MYCN,STAT3,POM121C,DDX5,PUM2,ELAVL1,PUM1,NUP50,NUP210,LIN28A,TP53,NUP35,NUP85	26	both
regulation of generation of precursor metabolites and energy	GO:0043467	metabolic process	5.938E-03	STAT3,IGF2,TP53,AKT1,NUP93,NUP205,RANBP2,NUP37,PRKAG1,DYRK2,NDC1,ENTPD5,IRS1,OGT,PRKAA1,EPM2AIP1,CBFA2T3,CDK1,INSR,NUP50,APP,GSK3B,POM121C,NUP62,TIGAR,NUP98,RAE1,PPARA,NUP43,CCNB1,PPP1R3D,ZBTB7A,GRB10,NUP54,EIF6,ATP7A	36	up
regulation of glucokinase by glucokinase regulatory protein	REAC:R-HSA-170822	protein metabolism	3.007E-02	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,NUP62,RAE1,NUP43,NUP54	11	up
regulation of growth	GO:0040008	cell proliferation	3.933E-03	CDKN2A,SEMA4C,RPS6KA1,SPHK1,STAT3,SEMA4B,TP53,ERBB2,S100A8,BBC3,AKT1,BCL2,PPP2CA,DUSP6,SIX1,CDKN2D,NPM1,SMAD4,ABL1,EGFR,GLI1,FGFR2,CSNK2A1,CDKN1A,ERBB4,SFRP1,SERTAD2,NOTCH2,L1CAM,NOTCH1,FGFR3,ADAM17,FGF2,CDKN1B,NRP1,DCUN1D3,PTEN,VEGFA,PAFAH1B1,SMAD3,PTPRJ,DDX3X,FLCN,SH3BP4,RBPJ,NKD1,INSR,TGFBR3,APP,CDC42,GSK3B,SMURF1,CRK,PIM1,RTN4,RPS6KA3,MEF2C,LATS2,STAT5A,SEMA3A,DLL1,HNF4A,SIRT1,ACSL4,SYT1,CDKN2AIP,SMARCA4,EIF4G1,TP73,USP47,SESN2,CDKN2C,CTTN,ADNP,AGTR1,UBAP2,KIAA1109,SERTAD3,BMPR1A,ADAM15,DCBLD2,EDN1,MTPN,CAPRIN2,BTG1,FGFR1OP,GHSR,PLCB1,CRLF3,DERL2,VGLL4	91	up
regulation of hippo signalling	GO:0035330	signalling pathways	3.023E-02	NF2,MAPK14,MAP2K3,SOX11,DLG5,MOB3B,LIMD1,VGLL4	8	up
regulation of histone methylation	GO:0031060	epigenetic mechanism	4.704E-02	BCOR,SUPT6H,SMAD4,BRCA1,JARID2,DNMT1,OGT,PHF19,MYB,RIF1,MTHFR,SIRT1,CTNNB1,TET1	14	up
regulation of hsf1-mediated heat shock response	REAC:R-HSA-3371453	signalling pathways	7.751E-04	NUP93,NUP205,RANBP2,NUP37,NDC1,HSPA4L,MAPKAPK2,HSPA8,BAG4,NUP50,GSK3B,POM121C,BAG2,ATM,MAPK3,SIRT1,NUP62,DNAJB6,RAE1,BAG3,BAG1,HSPA13,NUP43,MAPK1,NUP54	25	up
regulation of i-κb kinase/nf-κb signalling	GO:0043122	Nfκ	4.245E-05	TMEM101,ZMYND11,TNFAIP3,TNF,TNFRSF10B,PLEKHG5,RHOA,TRIM22,IFIT5,TRAF6,FADD,IRAK1,STAT1,SQSTM1,S100A12,UBE2V1,CPNE1,PPM1A,CHUK,LITAF,TAB3,REL,FKBP1A,MAP3K7,ECT2,BIRC3,DDX21,C18orf32,SIRT1,NUP62,MTDH,CD40,MAP3K14,TFRC,TRAF3,PER1,CASP1,TRAF2,RBCK1,RIPK2,NOD1,LTBR,FASLG,TNFRSF1A,PRKD1,BCL10,CFLAR,CASP8,BIRC2,CASP10,TIRAP,OTUD7B,TANK,MAVS,ESR1,F2RL1,RHOH,TMEM9B,TNIP3,TAB2,OTUD7A,PPM1B	62	up
regulation of interferon-α production	GO:0032647	interferon signalling	2.358E-02	HSPD1,STAT1,IRF7,TLR4,DDX3X,CHUK,RIPK2,IL10,TLR3,MAVS	10	up
regulation of interferon-β production	GO:0032648	interferon signalling	2.359E-02	TLR2,IRF7,TLR4,DDX3X,REL,POLR3G,YY1,TRAF3,RIPK2,TIRAP,TLR3,MAVS,IRF1,PPM1B	14	up
regulation of interleukin-12 production	GO:0032655	interleukin signalling	1.680E-02	MAPK14,HSPD1,CD40LG,TLR2,TLR4,IL23R,HLA-G,AGER,CD40,HMGB1,RIPK2,IL10,TIRAP,TLR3,PLCB1,THBS1	16	up
regulation of intracellular steroid hormone receptor signalling pathway	GO:0033143	signalling pathways	1.765E-02	ESR1,STRN3,CLOCK,UFM1,EP300,DAB2,RNF14,PIAS2,SIRT1,YAP1,RNF6,ARRB2,CARM1,PER1,DDX5,KCTD6,CRY2,KANK2,FOXH1,HEYL	20	both
regulation of ire1-mediated unfolded protein response	GO:1903894	protein metabolism	6.547E-03	BBC3,BAK1,BCL2L11,BAX,BFAR,FICD,DNAJB9,TMEM33	8	up

regulation of jnk cascade	GO:0046328	signalling pathways	1.379E-03	ZMYND11,MAP3K11,IGF1R,RASGRP1,MFHAS1,EGFR,TRAF6,PDCD4,TAOK1,PAFAH1B1,WNT7A,ZNF622,DNAJA1,AGER,CYLD,MINK1,APP,MAP4K2,RASSF2,SEMA3A,RAP2A,TRAF3,PER1,HMGB1,GADD45A,TRAF2,LTBR,CD27,TIRAP,FKTN,F2RL1,PLCB1,PHLPP1	33	up
regulation of lamellipodium organisation	GO:1902743	cell organisation	8.998E-03	CD44,WASF2,WNT1,ACTR2,KANK1,PIK3R1,NCKAP1,CDC42,TWF1,CORO1B,SRC,CAPZB,EPHA2,PDPN,FSCN1,AKIRIN1	16	up
regulation of leukocyte adhesion to arterial endothelial cell	GO:1904997	cell adhesion and migration	3.967E-02	TNF,ALOX5,KLF4,ZDHHC21	4	up
regulation of leukocyte adhesion to vascular endothelial cell	GO:1904994	cell adhesion and migration	2.736E-02	ETS1,TNF,ALOX5,RHOA,TRAF6,NFAT5,IRAK1,IL6,ITGB2,CXCL12,KLF4,ZDHHC21	12	up
regulation of leukocyte apoptotic process	GO:2000106	apoptosis	4.820E-03	CDKN2A,TP53,BBC3,AURKB,PIK3CB,PIK3CD,FADD,IRF7,CCL5,CXCL12,ADAM17,CD274,PDCD1,MEF2C,SIRT1,AXL,IL10,BCL10,FNIP1	19	up
regulation of leukocyte cell-cell adhesion	GO:1903037	cell adhesion and migration	1.164E-05	ETS1,CDKN2A,SLC7A1,CBFB,IGF2,AKT1,TNF,WNK1,CD44,ALOX5,HSPD1,RHOA,CD40LG,TRAF6,NFAT5,FADD,IRAK1,GRAP2,CD80,BTN2A2,IL6,CCL5,ITGB2,CXCL12,IL23R,HLA-A,HLA-G,CD274,KLF4,VSIR,PDCD1,TNFSF9,PAG1,GRB2,PAK2,FLOT2,AGER,PIK3R1,MYB,SMAD7,CDC42,SOCS5,IL6ST,NLRP3,LEF1,ZAP70,SRC,TGFBR2,CEBPB,TFRC,IFNB1,HMGB1,CD24,TNFRSF21,PLA2G2D,IL10,CD70,PPARA,SOX4,LAX1,ZDHHC21,TNFRSF13C,NKAP,DLG5,PRNP,IRF1,ZBTB7B,RHOH,HAS2,SDC4,PAK3,IL15	72	up
regulation of leukocyte proliferation	GO:0070663	cell proliferation	7.811E-04	CDKN2A,CD320,SLC7A1,IGF2,IKZF3,TNFAIP3,BCL2,CD40LG,MIF,FADD,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,CSF1,HLA-G,CD274,VSIR,TNFSF9,AGER,TCF3,IL6ST,MEF2C,ATM,VAV3,MAPK3,TGFBR2,CEBPB,CD40,TFRC,HMGB1,CD24,TNFRSF21,PLA2G2D,CSF1R,IL10,CD70,TIRAP,TNFRSF13C,SOX11,DLG5,PRNP,MAPK1,IRF1,ZBTB7B,SDC4,IL15	49	up
regulation of lipid kinase activity	GO:0043550	lipid metabolism	2.197E-02	ERBB4,IRS1,FGFR3,FGF2,ATG14,PIK3R3,RUBCN,PIK3R1,PDGFRB,PDGFRA,DGKZ,KIT,PRKD1,WDR81,PDGFB	15	up
regulation of lipid metabolic process	GO:0019216	lipid metabolism	2.761E-03	SPHK1,LACTB,NCOR2,AKT1,TNF,MTMR3,CREBBP,MED1,REST,LSS,MTMR4,DKK3,ADM,KPNB1,NFKB1,ERBB4,PTGS2,BRCA1,LDLR,IRS1,SIK1,FGFR3,FGF2,PPARD,ATG14,RUBCN,PRKAA1,FASN,CARM1,PRKCD,ACOX1,FGFR4,SIRT4,CREBL2,TBL1XR1,FBXW7,SP1,SCARB1,HNF4A,MTMR2,ERLIN1,NCOA1,PDGFRB,PDGFRA,CPT2,SIRT1,DHCR7,ACSL1,ERLIN2,CYP51A1,TXNRD1,MTMR9,SNAI1,TNFRSF21,DGKZ,CIDEA,KIT,TNFRSF1A,PRKD1,ME1,PPARA,AGTR1,CNEP1R1,OPA3,CREB1,NFYB,MID1IP1,ABCD2,SAMD8,PDP2,RAN,CD36,EIF6,PDGFB,SC5D,SREBF1,TWIST1,H6PD	78	up
regulation of localization of foxo transcription factors	REAC:R-HSA-9614399	FoxO signalling pathway	1.059E-02	YWHAG,FOXO1,AKT1,AKT2,AKT3,FOXO3,YWHAB	7	both
regulation of lymphocyte mediated immunity	GO:0002706	leukocyte activation	4.668E-02	FBXO38,SUPT6H,RASGRP1,HSPD1,TRAF6,FADD,IL6,RSAD2,IL23R,HLA-A,HLA-G,FZD5,AGER,RIF1,SMAD7,MAP3K7,NLRP3,CD40,TFRC,IFNB1,HMGB1,TRAF2,IL10,CD226,CLEC12B,B2M,PVR	27	up
regulation of macroautophagy	GO:0016241	autophagy	3.572E-03	LARP1,CALCOCO2,SESN3,RRAGC,SPTLC2,TRIM13,SLC38A9,SNX5,CASP3,SIRT1,AKT1,ULK1,SMCR8,GAPDH,PRKAB2,HUWE1,SH3GLB1,RAB3GAP2,PIP4K2C,RRAGD,CHMP4B,IL4,EXOC8,LRSAM1,ERN1,IKBKG,ATP6V0D2,QSOX1,GNAI3,UBQLN4,RAB3GAP1,CAPNS1	32	both
regulation of map kinase activity	GO:0043405	MAPK signalling	2.219E-06	MAP3K2,ERBB2,PPP2CA,DUSP6,TNF,MAP3K11,MAPK14,IGF1R,PIK3CB,RASGRP1,NTRK3,EGFR,CXCR4,CD40LG,DUSP1,IRAK2,TRAF6,IRAK1,TLR4,ROBO1,S100A12,DKK1,FGF2,TGFA,S1PR2,MAP3K9,PDCD4,VEGFA,TAOK1,UBE2V1,SPRED1,STK38,PTPRJ,PRKAA1,MAPKAPK2,MAP2K3,DNAJA1,PRKCD,CDK1,INSR,TAB3,MAP4K2,RET,MAP3K7,MEF2C,PEA15,MAPK3,PDGFRB,CD40,MAP2K1,PIK3CG,SAA1,GADD45A,CD24,TRAF2,BMP7,RIPK2,KIT,NOD1,LAX1,DUSP5,SH2B3,SASH1,MAP2K4,UBB,MAPK1,EDN1,RPS27A,UBC,PDGFB,THBS1,TAB2	72	up
regulation of mecp2 expression and activity	REAC:R-HSA-9022692	signalling pathways	5.695E-03	NCOR2,AURKB,TNRC6B,LBR,AGO3,TNRC6A,AGO2,AGO1,AGO4,TBL1XR1,HDAC1,MOV10,CREB1	13	up
regulation of membrane permeability	GO:0090559	cell organisation	6.556E-03	PMAIP1,STAT3,BMF,TP53,BBC3,BCL2,BAK1,YWHAB,BCL2L11,YWHAQ,YWHAH,GSK3B,FZD9,E2F1,SFN,TJP2,BNIP3,TP73,BAX,PPP3R1,CASP8,MOAP1,BCL2L1,TP53BP2,F11R	25	both
regulation of mesenchymal cell proliferation	GO:0010464	cell proliferation	8.146E-03	MYC,NFIB,SOX9,TGFBR2,CTNNBIP1,VEGFA,LMNA,WNT5A	8	down
regulation of mesenchymal stem cell differentiation	GO:2000739	cell differentiation	4.578E-02	SOX6,PDGFRA,SOX9,REST	4	down
regulation of microtubule-based process	GO:0032886	neuronal architecture	1.839E-02	VPS4B,ERBB2,CHMP3,CDH5,NPM1,APC,FES,ABL1,ROCK1,BRCA1,TACC3,PHLDB2,ARL2,TAOK1,PAFAH1B1,CHMP4B,PRKAA1,MECP2,CYLD,CAMSAP1,GSK3B,DIAPH1,STMN1,TMEM67,CHMP2B,MET,SIRT1,NUP62,TPPP,CKAP5,RAE1,MAP1B,AURKA,CDK5R1,PGAM4,RNF4,TRIM36,MID1IP1,MAPRE3,TRIM37,CDK2AP2,CAMSAP2,CLIP1,CCR6,DYRK1A,SENP6,SKA2	47	up
regulation of mitochondrial membrane permeability involved in apoptotic process	GO:1902108	mitochondrial activity	7.423E-03	PMAIP1,BMF,TP53,BBC3,BCL2,BAK1,YWHAB,BCL2L11,YWHAQ,YWHAH,GSK3B,FZD9,E2F1,SFN,BNIP3,TP73,BAX,PPP3R1,CASP8,MOAP1,TP53BP2	21	both
regulation of mitochondrion organisation	GO:0010821	mitochondrial activity	3.555E-02	TP63,EP300,IGF1,BID,SLC35F6,YWHAG,PPP1R13B,AKT1,TFRC,PMAIP1,SPIRE1,BCL2,BBC3,FZD5,HUWE1,CASP8,PPP3R1,BCL2L11,LMNA,SIVA1,PPARGC1A,TP53,PYCARD,CLU,STAT2,TFDP2,YWHAE,GSK3B,YWHAB,FAM49B,MOAP1	31	both
regulation of mononuclear cell proliferation	GO:0032944	cell proliferation	1.295E-03	CDKN2A,CD320,SLC7A1,IGF2,IKZF3,BCL2,CD40LG,MIF,FADD,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,CSF1,HLA-G,CD274,VSIR,TNFSF9,AGER,TCF3,IL6ST,MEF2C,ATM,VAV3,TGFBR2,CEBPB,CD40,TFRC,HMGB1,CD24,TNFRSF21,PLA2G2D,IL10,CD70,TIRAP,TNFRSF13C,SOX11,DLG5,PRNP,IRF1,ZBTB7B,SDC4,IL15	45	up
regulation of mrna metabolic process	GO:1903311	metabolic process	1.003E-04	LARP1,NUP98,IGF2BP3,MAPK14,PDE12,GDNF,FMR1,PSMB9,PRKCD,ANGEL2,DIS3,PTCD2,HNRNPA1,IGF2BP2,DCP1A,RBMXL1,EXOSC6,TNRC6B,TBRG4,VIM,IGF2BP1,CELF1,ROCK2,AKT1,PTBP3,TNPO1,ZFP36L2,RBM25,ZFP36L1,SRSF10,BTG2,REST,RBM8A,DDX5,SRSF7,PUM2,ELAVL1,PTBP1,PUM1,HSPA8,ACIN1,SON,ELAVL4,ROCK1,QKI,PNPT1,SERBP1,XPO1,CDC73,RBM38,RBM4B,CCNT1,EXOSC2,PABPC1,PSMC4,PSMD3,RNF40,ZC3HAV1,YWHAB,ZC3H14,SRSF4,CELF3	62	both
regulation of mrna processing	GO:0050684	transcription and translation	8.307E-03	SUPT6H,HNRNPK,THRAP3,REST,NPM1,FXR1,PTBP1,CDC73,RBM23,SRPK1,CPSF7,CCNT1,RNPS1,SRSF1,CPEB3,HNRNPA1,YTHDC1,NOVA2,SUPT5H,RBM15B,IK,RNF40,KHDRBS1,SON,NCBP2,NUP98,RBFOX2,SMU1,ZBTB7A,QKI,MBNL1,MBNL3,SRSF2,PABPN1,RBM3,PAPOLA,SF1	37	up
regulation of mrna stability	GO:0043488	transcription and translation	2.036E-02	LARP1,IGF2BP3,MAPK14,PDE12,GDNF,FMR1,PSMB9,PRKCD,ANGEL2,DIS3,IGF2BP2,DCP1A,EXOSC6,TBRG4,VIM,IGF2BP1,CELF1,ROCK2,AKT1,TNPO1,ZFP36L2,ZFP36L1,PUM2,ELAVL1,PUM1,HSPA8,ELAVL4,ROCK1,SERBP1,XPO1,RBM38,EXOSC2,PABPC1,PSMC4,PSMD3,YWHAB,ZC3H14	37	both
regulation of myeloid cell apoptotic process	GO:0033032	apoptosis	1.022E-02	CDKN2A,EPO,PIK3CB,PIK3CD,IRF7,ADAM17,MEF2C,SIRT1	8	up
regulation of necroptotic cell death	REAC:R-HSA-5675482	apoptosis	3.943E-06	XIAP,TNFRSF10B,Fas,FADD,BIRC3,TNFRSF10A,TRAF2,FASLG,CASP8,BIRC2,UBB,RPS27A,UBC	13	up
regulation of neuron death	GO:1901214	apoptosis	2.750E-04	STAT3,BBC3,AKT1,BCL2,TNF,SIX1,REST,ERBB3,MCL1,EPHA7,SET,FOS,KDM2B,CCL5,ITGB2,TLR4,CSF1,DKK1,CHMP4B,Bace1,SNCG,TFAP2A,EFNB2,CLU,LANCL1,GSK3B,FZD9,FOXO3,FBXW7,MEF2C,RRAS2,CCL3,CTNNB1,NAIP,EIF4G1,AIFM1,TRAF2,BAX,IL10,ADNP,CPEB4,CDK5R1,DDIT4,GPR75,UBB,PRNP,FOXQ1,EGLN3,KCNB1,AKT1S1,DHCR24,SOD2	52	up
regulation of neuron projection development	GO:0010975	organogenesis	4.517E-02	SEMA6B,PAK2,NPTN,ABL2,SEMA6A,NTNG2,NSMF,METRN,BRSK1,VLDLR,SEMA3E,CAPRIN1,MAP3K13,RET,ZDHHC15,EP300,L1CAM,TIAM2,NTNG1,S100A9,BCL11A,SEMA4C,AKT1,CDH2,RELN,PTEN,RNF6,CAPRIN2,HECW2,SIPA1L1,HECW1,P3H1,TIAM1,ITGA6,VEGFA,CAMK1D,MYLIP,SEMA7A,PTPRD,RHOA,SCARB2,SEMA4G,FBXW8,ARHGDIA,SCARF1,PTK6,NDEL1,MAGI2,WNT5A,GSK3B,PTPN9,ARSB,PRAG1	53	down

regulation of nik/nf-κb signalling	GO:1901222	Nfκ	2.236E-03	SPHK1,BCL3,TNF,EGFR,RHOA,TRAF6,TLR2,NFAT5,IRAK1,TLR4,PDCD4,CPNE1,AGO1,DDX3X,PPM1A,AGER,CYLD,APP,NLRP3,HMGB1,BMP7,NOD1,ADGRG3,CD27,TLR3,SASH1,PPM1B	27	up
regulation of nitric-oxide synthase biosynthetic process	GO:0051769	oxygen levels	2.731E-02	JAK2,TLR2,STAT1,TLR4,KDR,NAMPT,EDN1	7	up
regulation of nuclear-transcribed mrna poly(a) tail shortening	GO:0060211	transcription and translation	6.547E-03	PABPC1,BTG2,TNRC6B,TNRC6A,AGO2,CPEB3,TOB1,CNOT1	8	up
regulation of nucleocytoplasmic transport	GO:0046822	cellular transport	8.183E-03	CDKN2A,TP53,SUPT6H,SIRT7,EMD,NSUN2,IFI27,MX2,SMAD3,RAB23,PRKCD,PIK3R1,GSK3B,RANGAP1,ECT2,RBM26,KHDRBS1,NCBP2,BAG3,RBM27,MAVS,TCF7L2,RAN	23	up
regulation of ossification	GO:0030278	organogenesis	1.064E-02	BCOR,BMPR1B,ALOX5,GPM6B,ISG15,SFRP1,NOTCH1,DKK1,TFAP2A,RBPJ,ZBTB16,ACVR2A,FZD9,MEF2C,CCL3,BMP7,S1PR1,BMPR1A,SOX11,ACVR1,TWIST1,CHSY1	22	up
regulation of osteoblast differentiation	GO:0045667	cell differentiation	1.798E-02	BMPR1B,REST,IL6R,FGFR2,IFITM1,IL6,NOTCH1,SKI,CDK6,CRIM1,RUNX2,ACVR2A,YAP1,IL6ST,MEF2C,TMEM64,BMP7,PRKD1,BMPR1A,SOX11,SMOC1,ACVR1,WWTR1,LIMD1,TWIST1,FFAR4	26	both
regulation of osteoclast differentiation	GO:0045670	cell differentiation	3.741E-02	TNF,FBN1,TRAF6,BGLAP,TLR4,IL23R,CSF1,MAFB,FBXW7,CCL3,CEBPB,TLR3,UBASH3B	13	up
regulation of pattern recognition receptor signalling pathway	GO:0062207	signalling pathways	9.280E-03	ZDHHC5,XIAP,TNFAIP3,MFHAS1,TLR2,IRF7,RSAD2,TLR4,OTUD4,DDX3X,ZCCHC3,USP15,RTN4,BIRC3,PUM2,HMGB1,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,IRF1,RNF125,CXorf21,ERBIN,F2RL1,CD36	27	up
regulation of peptide transport	GO:0090087	cellular transport	2.076E-03	CDKN2A,PMAIP1,KCNS3,TP53,ERBB2,BBC3,BCL2,SIRT7,TNF,EDEM1,REST,HUWE1,YOD1,EMD,ALOX5,ARIH2,IFI27,TLR2,SFRP1,IL6,RSAD2,CCL5,ITGB2,TLR4,IRS1,UBE2D3,FZD5,CLOCK,YWHAB,ARL2,CREBRF,SMAD3,RAB23,DNAJA1,HSPA8,PRKCD,BAG4,ITPR1,TM7SF3,PIK3R1,CD2AP,SIRT4,YWHAQ,YWHAH,GSK3B,BSG,HAX1,FBXW7,E2F1,CFTR,RANGAP1,ECT2,VAMP2,SNX12,HNF4A,SFN,SNX3,ACSL4,ITGB3,STX1A,ANK3,CYP51A1,FRMD4A,MYO1C,SAA1,INHBB,TP73,EPHA5,ARF6,SAR1A,PPP3R1,BAG3,GDI1,TREM2,GAPVD1,CASP8,TP53BP2,SOX4,INSIG1,MFF,PER2,BMP8A,TMEM30A,PRNP,MAVS,CHD7,TCF7L2,RAB11FIP1,SEC16A,RAN,KCNB1,F2RL1,MIDN,KCNA5,SREBF1,LMAN1,DERL2,FFAR4,PCNT	99	up
regulation of peptidyl-lysine acetylation	GO:2000756	protein metabolism	5.810E-03	LIF,SMAD4,MUC1,SET,NOS1,BRCA1,RPS6KA4,CHEK1,PRKAA1,FLCN,TADA2B,MAPK3,SPI1,SIRT1,SOX4,RPS6KA5	16	up
regulation of peptidyl-serine phosphorylation	GO:0033135	phosphorylation	3.406E-03	AKT1,TNF,LIF,CD44,RAF1,TNKS1BP1,NTRK3,EGFR,MIF,NOS1,IL6,HSP90AA1,DKK1,PTEN,VEGFA,PDE4D,CREBL2,SMAD7,APP,CNKSR3,RASSF2,HAX1,TFRC,IFNB1,EIF4G1,GADD45A,RIPK2,PRKD1,FNIP1,DDIT4,CAPRIN2,PRKD2,STK4	33	up
regulation of peptidyl-threonine phosphorylation	GO:0010799	phosphorylation	3.741E-02	SPHK1,TNKS1BP1,S1PR2,SPRED1,WNK3,CAB39,SMAD7,APP,EIF4G1,BMP7,RIPK2,DDIT4,MAPK1	13	up
regulation of peptidyl-tyrosine phosphorylation	GO:0050730	phosphorylation	2.261E-05	NF2,STAT3,IGF2,TP53,JAK2,EPO,PPP2CA,TNF,IL6R,ERBB3,LIF,SH3BP5L,CD44,ABL1,EGFR,EPHA7,MIF,ERBB4,CD80,SFRP1,IL6,CCL5,ITGB2,IL23R,GPRC5A,ITGA5,FGFR3,ADAM17,NRP1,TGFA,VEGFA,PTPRJ,PAK2,PRKCD,RAP2C,APP,SOCS5,IL6ST,HAX1,FBXW7,SRC,SOCS4,CD40,ITGB3,RIPK2,CSF1R,KIT,TNFRSF1A,TREM2,AREG,DOCK3,ADNP,SH2B3,PRNP,ACVR1,EREG,SOCS3,PDGFB,IL15	59	up
regulation of phosphatidylinositol 3-kinase activity	GO:0043551	PI3k signalling	1.008E-02	ERBB4,IRS1,FGFR3,FGF2,ATG14,PIK3R3,RUBCN,PIK3R1,PDGFRB,PDGFRA,KIT,PRKD1,WDR81,PDGFB	14	up
regulation of phosphatidylinositol 3-kinase signalling	GO:0014066	PI3k signalling	1.913E-04	EPOR,JAK2,EPO,TNF,IGF1R,PIK3CB,ERBB3,PIK3CD,NTRK3,EGFR,PIP4K2C,ENTPD5,CCL5,FGF2,PTEN,VEGFA,INSR,PIK3R1,PPP2R5C,KDR,HAX1,MAZ,MAPK3,SRC,PDGFRB,PDGFRA,SIRT1,PIK3CG,BECN1,KIT,PIP5K1C,MAPK1,F2RL1,PDGFB,TWIST1	35	up
regulation of phosphoprotein phosphatase activity	GO:0043666	phosphorylation	3.069E-02	BOD1,ROCK2,FKBP1A,HSP90B1,TIPRL,PDGFRB,CRY2,ROCK1,HSP90AB1,PPP1R15B,PPP1R15A,MAGI2,GSK3B,MGAT5	14	down
regulation of plasma membrane bounded cell projection organisation	GO:0120035	cell organisation	4.697E-02	SEMA6B,PAK2,CCP110,NPTN,ABL2,SEMA6A,NTNG2,NSMF,METRN,MYO10,APC,BRSK1,FMR1,VLDLR,PRKCD,SEMA3E,CAPRIN1,MAP3K13,RET,EPS8,ZDHHC15,EP300,L1CAM,CDC42EP3,TIAM2,NTNG1,HOMER1,S100A9,PFN2,BCL11A,SEMA4C,YAP1,AKT1,CDH2,RELN,PLEKHM1,PTEN,RNF6,CAPRIN2,ATP8B1,TBC1D7,ARF6,HECW2,SIPA1L1,CDC42,HECW1,P3H1,FSCN1,ENPP2,TIAM1,ITGA6,VEGFA,CAMK1D,MYLIP,WASL,SEMA7A,PTPRD,OCLN,RHOA,SCARB2,RREB1,SEMA4G,FBXW8,ARHGDIA,SCARF1,PDPN,PTK6,NDEL1,PLCE1,MAGI2,WNT5A,GSK3B,CEP97,PTPN9,ARSB,PFN1,PRAG1	77	down
regulation of positive chemotaxis	GO:0050926	cell adhesion and migration	3.023E-02	ANGPT2,NTRK3,CXCL8,CXCL12,VEGFA,KDR,F3,F2RL1	8	up
regulation of posttranscriptional gene silencing	GO:0060147	miRNA/siRNA biogenesis	2.957E-02	STAT3,LIN28A,NCOR2,LIN28B,TP53,NUP93,TNF,NUP205,RANBP2,NUP37,FXR1,TRIM71,TNRC6B,EGFR,NDC1,IL6,ELAVL1,DDX6,TNRC6A,AGO2,AGO1,NUP50,POLR2E,POM121C,MYCN,NUP62,PUM2,MAP2K1,NUP98,EIF4G1,RAE1,POU5F1,NUP43,POLR2D,ESR1,NUP54,BCDIN3D,LIMD1	38	both
regulation of pri-mirna transcription by rna polymerase ii	GO:1902893	miRNA/siRNA biogenesis	2.018E-05	PPARA,NFIB,TERT,SOX9,HIF1A,FOSL1,NR3C1,PPARG,ETS1,FOS,KLF4,JUN,SMAD3,STAT3,FOXO3,ATOH8,TP53,SRF,WT1	19	both
regulation of production of mirnas involved in gene silencing by mirna	GO:1903798	miRNA/siRNA biogenesis	1.019E-04	STAT3,LIN28A,NCOR2,LIN28B,TP53,TNF,EGFR,IL6,MYCN,MAP2K1,ESR1,BCDIN3D	12	both
regulation of protein acetylation	GO:1901983	protein metabolism	8.618E-03	LIF,SMAD4,MUC1,SET,NOS1,BRCA1,RPS6KA4,CHEK1,TAOK1,PRKAA1,DDX3X,FLCN,TADA2B,GSK3B,MAPK3,SPI1,SIRT1,SOX4,RPS6KA5	19	up
regulation of protein binding	GO:0043393	protein metabolism	2.204E-02	AKT1,AURKB,PPP2CA,NES,PPP1CA,ABL1,ROCK1,CDKN1A,SLPI,IFIT1,DKK1,SNAPIN,NRP1,PRKCD,FKBP1A,APP,GSK3B,CRK,BAG2,LEF1,RALB,BAX,RIPK2,IL10,ADNP,AURKA,ADAM15,TCF7L2,CAPRIN2,RAN,PDGFB,DTX3L,STK4,B2M,ACTB	35	up
regulation of protein kinase b signalling	GO:0051896	protein kinase activity	6.956E-07	LIN28A,IGF2,ERBB2,AKT1,SFRP5,TNF,IGF1R,PIK3CB,ERBB3,PIK3CD,MFHAS1,NTRK3,EGFR,FGFR2,ERBB4,LRP2,CD80,HSP90AA1,IRS1,HLA-G,FGFR3,FGF2,TGFA,PTEN,VEGFA,PTPRJ,CPNE1,GRB2,FLCN,FGFR4,INSR,PIK3R1,RNF41,PLEKHA1,PHLPP2,PPP2R5C,RET,RTN4,F3,HAX1,ITGB1,CCL3,MET,MAZ,SRC,PDGFRB,PDGFRA,SIRT1,KLB,MTDH,RRAS,GATA4,AXL,PIK3CG,RICTOR,EPHA2,KIT,AREG,PPARA,SH2B3,TCF7L2,OTUD3,EREG,ESR1,PDGFB,FRS2,THBS1,PHLPP1	68	up
regulation of protein localization to membrane	GO:1905475	protein localization	1.889E-03	ZDHHC5,PMAIP1,TP53,ERBB2,BBC3,AKT1,BCL2,TNF,EGFR,TMEM59,NUMB,SQSTM1,ITGB2,PRKCE,YWHAB,KIF5B,WNK3,VPS4A,SPTBN1,PIK3R1,YWHAQ,YWHAH,FZD9,E2F1,ITGB1,SFN,AR,AP2M1,ANK3,MYO1C,TP73,ARF6,EPHA2,PPP3R1,GDI1,TREM2,CASP8,BCL2L1,TP53BP2,MFF,PRNP,KCNB1,ACTB	43	up
regulation of protein localization to nucleolus	GO:1904749	protein localization	4.060E-02	GLUL,MCRS1,TERT,NVL,POLR1A	5	down
regulation of protein localization to nucleus	GO:1900180	protein localization	6.316E-03	CDKN2A,MEPCE,AKT1,NPM1,LIF,MFHAS1,CARD10,CCT6A,SMAD3,RAB23,FLCN,PRKCD,CDK1,PIK3R1,C6orf106,GSK3B,YAP1,LATS2,ECT2,CCT3,TFRC,SESN2,BAG3,OTUD7B,MAVS,RAN,WWTR1,DTX3L	28	up
regulation of protein modification by small protein conjugation or removal	GO:1903320	protein metabolism	1.661E-04	CDKN2A,SPHK1,XIAP,HSPBP1,AKT1,TNFAIP3,SIRT7,RPS7,NPM1,HUWE1,PIAS3,ABL1,SPRTN,TRAF6,ISG15,FANCM,SQSTM1,BRCA1,HSP90AA1,OTUD4,DCUN1D3,PTEN,IVNS1ABP,OGT,N4BP1,DDX3X,BTRC,CUL3,AMER1,DNAJA1,OTUB1,FKBP1A,SMAD7,KLHL40,FBXW7,BAG2,UBE2S,CDC20,FZR1,BIRC3,RNF40,RPS2,CTNNB1,RIPK2,UBA2,BCL10,BIRC2,SOX4,SASH1,TANK,RNF4,RPL23,PER2,UBB,DTX3L,RAB1A	56	up

regulation of protein serine/threonine kinase activity	GO:0071900	protein kinase activity	8.261E-10	CDKN2A,MAP3K2,CEBPA,ERBB2,AKT1,CCNE1,PPP2CA,DUSP6,TNF,CDKN2D,MAP3K11,MAPK14,IGF1R,PIK3CB,APC,RASGRP1,HMGA2,ABL1,NTRK3,EGFR,CCNJ,CXCR4,RHOA,CD40LG,DUSP1,IRAK2,TRAF6,CDKN1A,IRAK1,CDKN3,CCND1,TLR4,ROBO1,CCND2,S100A12,CCNA2,DKK1,ADAM17,FGF2,CDKN1B,TGFA,S1PR2,MAP3K9,PTEN,PDCD4,VEGFA,TAOK1,CCND3,UBE2V1,SPRED1,CCNT1,STK38,PTPRJ,PRKAA1,MAPKAPK2,PRKAR2A,MAP2K3,DDX3X,DNAJA1,PRKCD,CDK1,CDC25A,CCNT2,INSR,TAB3,CAB39,CCNE2,MAP4K2,RET,MAP3K7,MEF2C,LATS2,HEXIM1,CDC25C,PEA15,MAPK3,SRC,PDGFRB,SIRT1,CD40,MAP2K1,PIK3CG,SAA1,GADD45A,CD24,TRAF2,RALB,BMP7,CDKN2C,RIPK2,CSF1R,KIT,NOD1,LAX1,DUSP5,CDK5R1,SH2B3,CCNB1,INCENP,SASH1,MAP2K4,UBB,MAPRE3,MAPK1,EDN1,RPS27A,UBC,CCNI,IPO7,PDGFB,ACTB,THBS1,TAB2	113	both
regulation of protein stability	GO:0031647	protein metabolism	1.098E-03	CDKN2A,SEL1L,CREBBP,RPS7,NPM1,LSS,PRKRA,USP8,HSPD1,CDC73,CDKN1A,HSP90AA1,KRAS,B4GALT5,CCT6A,PTEN,NAPG,LAMP2,CDC37L1,BTRC,FLOT2,CUL3,CCDC88C,HSPA8,PRKCD,BAG4,PIK3R1,TBRG1,CREBL2,SMAD7,GGA3,CLU,RASSF2,PLPP3,USP3,RTN4,FBXW7,MDM2,BAG2,ZSWIM7,MDM4,CASP3,SIRT1,CCT3,CDKN2AIP,BAG6,USP47,MTMR9,CRYAA,PRKD1,BAG3,SUGT1,BAG1,SOX4,USP28,ATF7IP,AURKA,WDR81,CREB1,RPL23,GNAQ,DDI2,PRNP,CHEK2,USP13,MAPK1,SEC16A,DAD1,OTUD3,STK4,SREBF1	71	both
regulation of protein ubiquitination	GO:0031396	ubiquitination	1.534E-04	CDKN2A,SPHK1,XIAP,HSPBP1,AKT1,TNFAIP3,SIRT7,RPS7,NPM1,HUWE1,ABL1,SPRTN,TRAF6,ISG15,FANCM,SQSTM1,BRCA1,HSP90AA1,DCUN1D3,PTEN,IVNS1ABP,OGT,N4BP1,DDX3X,BTRC,CUL3,AMER1,DNAJA1,OTUB1,FKBP1A,SMAD7,KLHL40,FBXW7,BAG2,UBE2S,CDC20,FZR1,BIRC3,RNF40,RPS2,RIPK2,BCL10,BIRC2,SOX4,SASH1,RPL23,PER2,UBB,DTX3L,RAB1A	50	up
regulation of pten gene transcription	REAC:R-HSA-8943724	PTEN expression	2.692E-03	CBX4,MAPK1,RBBP4,CBX6,MTA3,RRAGC,SLC38A9,EED,EZH2,SUZ12,SNAI2,PPARG,PHC3,RCOR1,JUN,REST,CBX2,RRAGD,TP53,BMI1	20	down
regulation of pten localization	REAC:R-HSA-8948747	PTEN expression	4.467E-02	XIAP,PTEN,UBB,RPS27A,UBC	5	up
regulation of pten mrna translation	REAC:R-HSA-8943723	PTEN expression	1.113E-04	TNRC6B,AGO3,TNRC6A,AGO2,PTEN,AGO1,AGO4,MOV10	8	up
regulation of purine nucleotide metabolic process	GO:1900542	nucleotide metabolism	4.138E-03	STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PARP1,NDC1,NOS1,ENTPD5,OGT,PRKAA1,FLCN,CBFA2T3,INSR,NUP50,APP,POM121C,NUP62,TIGAR,NUP98,RAE1,TREM2,PPARA,NUP43,ZBTB7A,PDP2,NUP54,EIF6	29	up
regulation of ras protein signal transduction	GO:0046578	protein metabolism	5.313E-04	EPOR,JAK2,EPO,STARD13,PIK3CB,RAF1,RASGRP1,ABL1,STARD8,SQSTM1,ROBO1,NOTCH2,NOTCH1,NRP1,ABL2,OGT,GRB2,CUL3,FLCN,KANK1,CRKL,ARHGDIA,SHOC2,RTN4,STMN1,ITGB1,MET,ALS2,NUP62,ARHGDIB,EPS8L2,MFN2,PIK3CG,ARF6,F11R,KCTD10,DLC1,ERBIN,F2RL1,LRRC59,DENND4B	41	both
regulation of reactive oxygen species metabolic process	GO:2000377	oxygen levels	1.011E-02	STAT3,TP53,JAK2,AKT1,TNF,MAPK14,KHSRP,ALOX5,CDKN1A,PTGS2,BRCA1,ITGB2,TLR4,HSP90AA1,KLF4,SMAD3,TFAP2A,GRB2,PRKCD,INSR,RNF41,CLU,PDGFRB,TGFBR2,DDAH2,GADD45A,BMP7,DDAH1,PPARA,AGTR1,ROMO1,ABCD2,EDN1,F2RL1,CD36,EIF6,PDGFB,THBS1	38	up
regulation of release of cytochrome c from mitochondria	GO:0090199	mitochondrial activity	1.134E-03	PMAIP1,BMF,TP53,BBC3,AKT1,PLAUR,BCL2L11,CLU,HRK,BNIP3,BAX,BIK,NOL3,CIDEB,MOAP1,BCL2L1,MFF	17	up
regulation of response to cytokine stimulus	GO:0060759	cellular response to external stimuli	1.881E-03	CBFB,SPHK1,LIFR,JAK2,TNFAIP3,TNF,CXCR4,IRAK2,TLR2,FADD,IRAK1,STAT1,IL6,TLR4,ROBO1,CSF1,OTUD4,ADAM17,KLF4,PAFAH1B1,CPNE1,CHUK,CYLD,IL6ST,SPPL2A,TRAIP,BIRC3,TTLL12,AXL,HIST1H2BJ,CASP1,CD24,TRAF2,RBCK1,NLRC5,TNFRSF1A,TREM2,CASP8,BIRC2,SH2B3,MAVS,EDN1,F2RL1,SOCS3,HIPK1	45	up
regulation of response to dna damage stimulus	GO:2001020	cell cycle	1.667E-05	CDKN2A,PMAIP1,BCL2,SIRT7,RFWD3,FUS,ZNF385A,CDKN2D,NPM1,FXR1,CD44,MCL1,HMGA2,CEBPG,ABL1,MUC1,EGFR,PARP1,MIF,BRCA1,BCLAF1,CXCL12,CHEK1,UBE2V1,ACTR2,SPRED1,OTUB1,PRKCD,RNF168,KLHL15,RIF1,AXIN2,CLU,MDM2,ZNF365,ATM,MYC,MRNIP,SIRT1,PPP1R10,TIGAR,FIGN,XRCC1,RAD51,HMGB1,CASP9,MMS19,SNAI1,SIRT6,RNF169,BCL2L1,POLQ,NACC2,TERF2,ERCC4,DYRK1A,SMG1,DTX3L,TWIST1	59	up
regulation of rho protein signal transduction	GO:0035023	Rho GTPase signalling	3.625E-02	STARD13,RAF1,ABL1,STARD8,ROBO1,NRP1,ABL2,CUL3,FLCN,KANK1,ARHGDIA,STMN1,ITGB1,MET,ARHGDIB,EPS8L2,F11R,KCTD10,DLC1,F2RL1	20	up
regulation of runx1 expression and activity	REAC:R-HSA-8934593	RUNX metabolism	2.452E-02	CBFB,TNRC6B,CCND1,CCND2,AGO3,TNRC6A,AGO2,CCND3,CDK6,AGO1,AGO4,MOV10,SRC	13	both
regulation of signal transduction by p53 class mediator	GO:1901796	apoptosis	1.130E-05	RBBP4,MAPK14,TP63,TWIST1,TP53INP1,EP300,MEAF6,SIRT1,PPP1R13B,AKT1,SNAI2,RPA1,ATM,TOPBP1,PMAIP1,BCL2,PRKAB2,MDM2,CHEK1,DDX5,TAF13,RPF2,SPRED3,CSNK2A1,TP53,MDM4,DNA2,PAK1IP1,MRE11,HUS1,HEXIM1,MAPKAPK5,RFC2,SETD9,MIF,AURKA	36	both
regulation of signalling by cbl	REAC:R-HSA-912631	signalling pathways	2.698E-02	PIK3CB,PIK3CD,PIK3R3,CRKL,PIK3R1,CRK,UBB,RPS27A,UBC	9	up
regulation of signalling receptor activity	GO:0010469	signalling pathways	3.997E-02	GRIN2A,MED1,NPTX1,CHRFAM7A,GPRC5A,ADAM17,NRP1,TGFA,PDE4D,PRKCD,MINK1,APP,ADRA2B,SOCS5,DLGAP3,FBXW7,MEF2C,CACNG8,ITGB1,SOCS4,HMGB1,DAPK1,CAPN1,AREG,IL10,CLEC12B,EREG,ARC,NPTXR	29	up
regulation of skeletal muscle cell proliferation	GO:0014857	cell proliferation	3.859E-02	STAT3,SIX1,FGF2,CFLAR,AKIRIN1	5	up
regulation of small gtpase mediated signal transduction	GO:0051056	Rho GTPase signalling	5.740E-04	EPOR,JAK2,EPO,STARD13,PIK3CB,RAF1,RASGRP1,RHOV,PLEKHG5,ABL1,STARD8,RHOA,SQSTM1,ROBO1,NOTCH2,SOS1,NOTCH1,SOS2,NRP1,ABL2,OGT,VAV2,ARHGAP12,GRB2,OCRL,CUL3,FLCN,KANK1,RACGAP1,CRKL,CD2AP,CGNL1,ARHGDIA,SHOC2,CDC42,ARHGAP32,TRIP10,RTN4,STMN1,RHOB,ITGB1,ECT2,MET,VAV3,ARHGAP1,ALS2,SRC,NUP62,ARHGDIB,EPS8L2,MFN2,PIK3CG,ARF6,GDI1,F11R,KCTD10,ARHGEF26,DLC1,ERBIN,F2RL1,DEPDC1B,RHOH,LRRC59,DENND4B	64	up
regulation of small molecule metabolic process	GO:0062012	metabolic process	1.383E-02	PMAIP1,STAT3,NCOR2,IGF2,AKT1,NUP93,SIRT7,TNF,NUP205,RANBP2,PTH1R,REST,NUP37,PRKAG1,PSMB1,LSS,DYRK2,CD244,DKK3,PARP1,ADM,NDC1,KPNB1,NFKB1,PTGS2,NOS1,ENTPD5,BRCA1,PRKCE,IRS1,SIK1,PPARD,FOXK1,OGT,PRKAA1,FASN,FLCN,EPM2AIP1,CBFA2T3,FGFR4,INSR,NUP50,SIRT4,APP,GSK3B,PSMB5,POM121C,SP1,ERLIN1,SIRT1,NUP62,DHCR7,ERLIN2,TIGAR,CYP51A1,NUP98,RAE1,SNAI1,TREM2,PPARA,NUP43,PPP1R3D,NFYB,MID1IP1,ZBTB7A,GRB10,ABCD2,PDP2,RAN,NUP54,EIF6,ARPP19,MIDN,SC5D,SREBF1,TWIST1,H6PD	77	up
regulation of smooth muscle cell proliferation	GO:0048660	cell proliferation	1.402E-02	AKT1,TNFAIP3,APLN,TNF,IL6R,MMP2,CDKN1A,STAT1,IL6,CCL5,DNMT1,FGF2,CDKN1B,IGFBP5,PTEN,PDCD4,ELN,MEF2C,TPM1,PDGFRB,MFN2,CTNNB1,IL10,BMPR1A,TCF7L2,EDN1,EREG,PDGFB,SOD2,THBS1	30	up
regulation of t cell activation	GO:0050863	leukocyte activation	1.531E-03	CDKN2A,SLC7A1,CBFB,IRF4,IGF2,AKT1,PRDM1,ABL1,HSPD1,CD40LG,FADD,GRAP2,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,HLA-G,CD274,VSIR,PDCD1,TNFSF9,PAG1,GRB2,PAK2,FLOT2,AGER,PIK3R1,MYB,SMAD7,CDC42,SOCS5,IL6ST,NLRP3,TOX,LEF1,ZAP70,SRC,TGFBR2,CEBPB,TFRC,IFNB1,HMGB1,CD24,TNFRSF21,PLA2G2D,IL10,CD70,TCF7,SOX4,LAX1,TNFRSF13C,NKAP,DLG5,PRNP,IRF1,ZBTB7B,RHOH,SDC4,PAK3,IL15	62	up
regulation of telomere maintenance via telomere lengthening	GO:1904356	telomere	2.282E-02	AURKB,PARP1,CCT6A,HNRNPA1,HMBOX1,HNRNPA2B1,ATM,MAPK3,SRC,CCT3,XRN1,SLX4,MAPKAPK5,MAPK1,TERF2,ERCC4,CTC1,HNRNPC	18	up
regulation of the apoptosome activity	REAC:R-HSA-9627069	apoptosis	6.225E-03	XIAP,MAPK3,DIABLO,CASP9,CYCS,APAF1,MAPK1	7	up
regulation of tnfr1 signalling	REAC:R-HSA-5357905	signalling pathways	3.051E-04	XIAP,TNFAIP3,TNF,CHUK,CYLD,SPPL2A,BIRC3,TRAF2,RBCK1,TNFRSF1A,CASP8,BIRC2,OTUD7B,UBB,RPS27A,UBC	16	up
regulation of toll-like receptor signalling pathway	GO:0034121	TLR signalling	2.127E-02	TNFAIP3,MFHAS1,TLR2,IRF7,RSAD2,TLR4,OTUD4,DDX3X,RTN4,BIRC3,HMGB1,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,IRF1,CXorf21,F2RL1,CD36	20	up
regulation of tp53 activity	REAC:R-HSA-5633007	P53 signalling	2.263E-04	CDKN2A,TP53INP1,EHMT1,TP53,AKT1,AURKB,PPP2CA,ZNF385A,PRKAG1,MAPK14,TAF15,PRDM1,DYRK2,PIP4K2C,CSNK2A1,MTA2,BRCA1,CCNA2,CHEK1,SUPT16H,PRKAA1,SSRP1,TAF13,GATAD2A,CDK1,AKT3,PPP2R5C,PIP4P1,CDK2,MDM2,ATM,HDAC1,MRE11,MDM4,RICTOR,TP73,TP53BP2,AURKA,CDK5R1,GATAD2B,MAPKAPK5,UBB,CHEK2,RPS27A,UBC,RFC2,JMY,BRPF1,HIPK1	49	up

regulation of tp53 activity through methylation	REAC:R-HSA-6804760	epigenetic mechanism	4.071E-03	EHMT1,TP53,MDM2,ATM,MDM4,UBB,CHEK2,RPS27A,UBC,JMY	10	up
regulation of tp53 activity through phosphorylation	REAC:R-HSA-6804756	phosphorylation	4.099E-03	TP53INP1,TP53,AURKB,PRKAG1,MAPK14,TAF15,DYRK2,CSNK2A1,BRCA1,CCNA2,CHEK1,SUPT16H,PRKAA1,SSRP1,TAF13,CDK2,MDM2,ATM,MRE11,MDM4,AURKA,CDK5R1,MAPKAPK5,UBB,CHEK2,RPS27A,UBC,RFC2,HIPK1	29	up
regulation of tp53 degradation	REAC:R-HSA-6804757	P53 signalling	4.144E-04	CDKN2A,TP53,AKT1,PPP2CA,CCNA2,CDK1,AKT3,PPP2R5C,CDK2,MDM2,ATM,MDM4,RICTOR,UBB,CHEK2,RPS27A,UBC	17	up
regulation of tp53 expression and degradation	REAC:R-HSA-6806003	P53 signalling	1.625E-04	CDKN2A,TP53,AKT1,PPP2CA,PRDM1,CCNA2,CDK1,AKT3,PPP2R5C,CDK2,MDM2,ATM,MDM4,RICTOR,UBB,CHEK2,RPS27A,UBC	18	up
regulation of translation in response to stress	GO:0043555	cellular response to external stimuli	1.235E-02	RPS6KA1,SLC35A4,NPM1,PPP1CA,DDX3X,RPS6KA3,EIF4G1,SESN2,PPP1R15B	9	up
regulation of translational initiation	GO:0006446	transcription and translation	3.189E-02	EIF5,EIF4EBP1,NPM1,PPP1CA,CCL5,AGO2,RPS6KB1,DDX3X,EIF2B2,LARP1,KHDRBS1,NCBP2,EIF4G1,CTIF,EIF1,PAIP1,EIF4EBP2,PPP1R15B,HABP4,POLR2D	20	up
regulation of transmembrane receptor protein serine/threonine kinase signalling pathway	GO:0090092	protein kinase activity	2.166E-04	XIAP,JAK2,NUP93,CREBBP,CDH5,SMAD4,MTMR4,FBN1,DKK3,LRP2,SMAD2,NOTCH1,DKK1,WNT1,ADAM17,BMP3,SKI,SMAD3,SPRED1,CRIM1,PPM1A,FLCN,RBPJ,ACVR2A,FKBP1A,TGFBR3,SMAD7,SMURF1,LATS2,VASN,STRAP,SIRT1,TGFBR2,PEG10,INHBB,BMP7,GDF5,CIDEA,POU5F1,PPARA,BMPR1A,BMP8A,SOX11,PMEPA1,DAND5,UBB,PCSK6,ZBTB7A,SPART,RPS27A,UBC,ACVR1,LEFTY1,TRIM33,ZNF703,THBS1	56	up
regulation of tumor necrosis factor superfamily cytokine production	GO:1903555	apoptosis	4.829E-02	STAT3,JAK2,TNFAIP3,RASGRP1,TLR2,MIF,FADD,IL6,TLR4,DICER1,FZD5,CD274,VSIR,PTPRJ,MAPKAPK2,AGER,C6orf106,CLU,APP,CCL3,HMGB1,CIDEA,IL10,BCL10,LILRA2,TIRAP,TLR3,MAVS,GHSR,POMC,THBS1,TWIST1	32	up
regulation of tumor necrosis factor-mediated signalling pathway	GO:0010803	signalling pathways	7.200E-03	SPHK1,TNFAIP3,TNF,ADAM17,CPNE1,CHUK,CYLD,SPPL2A,TRAIP,BIRC3,HIST1H2BJ,CASP1,TRAF2,RBCK1,TNFRSF1A,CASP8,BIRC2,F2RL1,HIPK1	19	up
regulation of type i interferon production	GO:0032479	interferon signalling	2.969E-04	TNFAIP3,DHX33,PCBP2,CREBBP,HSPD1,NFKB1,TLR2,IRAK1,ISG15,STAT1,IRF7,TLR4,DTX4,DDX3X,CHUK,CYLD,REL,POLR2E,C6orf106,POLR3G,MRE11,YY1,POLR3E,TRAF3,CTNNB1,RIPK2,NLRC5,IL10,LRRFIP1,TIRAP,TLR3,MAVS,IRF1,RNF125,UBA7,PPM1B	36	up
regulation of tyrosine phosphorylation of stat protein	GO:0042509	phosphorylation	2.507E-02	NF2,STAT3,JAK2,EPO,PPP2CA,TNF,IL6R,LIF,ERBB4,IL6,CCL5,IL23R,FGFR3,IL6ST,CD40,CSF1R,KIT,TNFRSF1A,SH2B3,SOCS3,IL15	21	up
regulation of ubiquitin protein ligase activity	GO:1904666	ubiquitination	6.870E-03	CDKN2A,RPS7,PTEN,BTRC,BAG2,UBE2S,CDC20,FZR1,RPL23,RAB1A	10	up
regulation of ubiquitin-dependent protein catabolic process	GO:2000058	ubiquitination	4.980E-02	RYBP,ZYG11B,SUMO2,LAPTM5,DAB2,RNF14,NFE2L2,CEBPA,PTK2,CCAR2,PTEN,CSNK1A1,RNF19A,MDM2,SOCS5,PIAS1,PRICKLE1,HSP90AB1,GIPC1,CSNK2A1,XPO1,CAMLG,RAD23B,CLU,STYX,SH3RF2,GSK3B,UBQLN4,DVL1	29	down
regulation of ubiquitin-protein transferase activity	GO:0051438	ubiquitination	1.680E-02	CDKN2A,RPS7,ABL1,DCUN1D3,PTEN,BTRC,SMAD7,FBXW7,BAG2,UBE2S,CDC20,FZR1,RPS2,RPL23,DTX3L,RAB1A	16	up
regulation of vasculature development	GO:1901342	organogenesis	4.136E-02	ETS1,SPHK1,PKM,STAT3,ERBB2,TNFAIP3,TNF,CDH5,PLXND1,PIK3CB,TMEM2,RNH1,PIK3CD,HMGA2,ALOX5,HK2,E2F2,ROCK1,STAT1,SFRP1,BRCA1,IL6,CXCL8,ITGA5,HLA-G,FGF2,KLF4,AGO2,ITGB8,VEGFA,SPRED1,MECP2,AGO1,AMOT,KDR,RTN4,RHOB,F3,SP1,ITGB1,DLL1,SIRT1,MTDH,RRAS,CD40,GATA4,PLCG1,CTNNB1,EPHA2,FASLG,PRKD1,SIRT6,GATA6,SASH1,BTG1,HOXA5,ADM2,PRKD2,EMP2,THBS1,TWIST1,ADAMTS9,HIPK1	63	up
regulation of viral genome replication	GO:0045069	viral of bacterial infection	9.280E-03	PABPC1,TNF,HMGA2,IFI27,IFIT5,ISG15,IFITM3,IFITM1,SLPI,OASL,RSAD2,CCL5,IFIT1,CXCL8,SETDB1,TARBP2,SRPK1,NUCKS1,DDX3X,TBC1D20,LARP1,IFNB1,ADARB1,PPARA,APOBEC3F,MAVS,TOP2A	27	up
regulation of viral life cycle	GO:1903900	viral of bacterial infection	1.875E-02	VPS4B,CHMP3,PABPC1,TNF,HMGA2,TRIM22,IFI27,IFIT5,ISG15,IFITM3,IFITM1,SLPI,OASL,RSAD2,CCL5,IFIT1,CXCL8,VPS37B,SETDB1,TARBP2,SRPK1,CHMP4B,TRIM35,NUCKS1,DDX3X,VPS4A,TBC1D20,BSG,CHMP2B,SNX3,LARP1,IFNB1,ADARB1,PPARA,APOBEC3F,MAVS,KPNA2,TOP2A	38	up
regulation of viral process	GO:0050792	viral of bacterial infection	5.144E-04	VPS4B,CHMP3,PABPC1,TNF,REST,HMGA2,TRIM22,IFI27,IFIT5,ISG15,IFITM3,IFITM1,SLPI,STAT1,OASL,RSAD2,CCL5,IFIT1,CXCL8,VPS37B,SETDB1,TARBP2,SRPK1,CHMP4B,CCL4,CCNT1,TRIM35,NUCKS1,DDX3X,VPS4A,POLR2E,TBC1D20,BSG,SP1,HEXIM1,CCL3,CHMP2B,CFL1,HDAC1,NELFCD,SUPT5H,RRP1B,LEF1,SNX3,UBP1,LARP1,IFNB1,SMARCA4,ADARB1,PPARA,APOBEC3F,MAVS,IGF2R,POLR2D,KPNA2,TOP2A	56	up
regulation of viral transcription	GO:0046782	viral of bacterial infection	7.938E-03	REST,HMGA2,IFITM3,CCL5,TARBP2,CCL4,CCNT1,NUCKS1,POLR2E,SP1,HEXIM1,CCL3,HDAC1,NELFCD,SUPT5H,RRP1B,LEF1,UBP1,SMARCA4,POLR2D	20	up
regulation of wnt signalling pathway	GO:0030111	Wnt signalling	7.594E-03	CBFB,TMEM9,FZD4,XIAP,TNFAIP3,SFRP5,PPP2CA,WNK1,PSMB1,APC,EMD,NRARP,FZD6,USP8,LBX2,PPP1CA,EGFR,GLI1,FGFR2,DKK3,CSNK2A1,NFKB1,TLR2,CDC73,SFRP1,SOX2,DKK1,SKI,DDX3X,PPM1A,BTRC,CUL3,AMER1,CCDC88C,KANK1,NKD1,CYLD,TLE4,AXIN2,APP,GSK3B,FZD9,TBL1XR1,SALL1,ZNRF3,PSMB5,LATS2,TMEM64,HDAC1,SNX3,CTNNB1,SMARCA4,USP47,POU5F1,TLE3,SOX4,GNAQ,CBY1,GRB10,TCF7L2,MCC,CAPRIN2,ESR1,KREMEN1,DEPDC1B,WWTR1,STK4,ZNF703,TMEM170B,LIMD1,VGLL4,PPM1B	72	both
relaxin signalling pathway	KEGG:04926	signalling pathways	1.239E-02	AKT1,MAPK14,PIK3CB,MMP13,MMP2,RAF1,PIK3CD,EGFR,FOS,NFKB1,NOS1,TGFB1,SMAD2,SOS1,KRAS,SOS2,PIK3R3,VEGFA,GRB2,GNB1,PIK3R1,AKT3,GNG12,MAPK3,SRC,TGFBR2,MAP2K1,NRAS,CREB1,MAP2K4,MAPK1,EDN1,PLCB1,COL4A1	34	both
release of cytochrome c from mitochondria	GO:0001836	mitochondrial activity	1.601E-05	PMAIP1,BMF,TP53,BBC3,AKT1,BCL2,BAK1,PLAUR,BCL2L11,CLU,FZD9,SFN,HRK,BNIP3,BAX,BIK,NOL3,CIDEB,MOAP1,BCL2L1,MFF,TIMM50,SOD2	23	up
renal cell carcinoma	KEGG:05211	cancer	5.819E-08	ETS1,AKT1,CREBBP,PIK3CB,RAF1,PIK3CD,CDKN1A,TGFB1,SOS1,KRAS,SOS2,PIK3R3,TGFA,VEGFA,GRB2,PAK2,FLCN,CUL2,CRKL,PIK3R1,AKT3,CDC42,CRK,MET,MAPK3,MAP2K1,FH,NRAS,MAPK1,EGLN3,PDGFB,PAK3	32	both
renal system development	GO:0072001	organogenesis	3.437E-02	ANGPT2,SIX1,ENPEP,IL6R,SMO,PODXL,LIF,FGFR2,STAT1,FGF2,VEGFA,TFAP2A,FLCN,SEC61A1,ZBTB16,RET,SALL1,MEF2C,MYC,JAG1,DLL1,PDGFRB,PDGFRA,CTNNB1,BAG6,CD24,BMP7,AGTR1,SOX4,HOXD11,AHI1,PDGFB,HAS2,COL4A1,MTSS1	35	up
replicative senescence	GO:0090399	senescence	4.808E-02	CDKN2A,TP53,CHEK1,ATM,CHEK2,ROMO1	6	up
repression of wnt target genes	REAC:R-HSA-4641265	Wnt signalling	4.207E-02	TLE4,HDAC1,LEF1,TLE3,TCF7,TCF7L2	6	up
response to bmp	GO:0071772	cellular response to external stimuli	7.685E-04	BMPR1B,XIAP,CDH5,SMAD4,FBN1,LRP2,SFRP1,SMAD2,NOTCH1,WNT1,UBE2D3,SKI,PDCD4,SMAD3,CRIM1,RUNX2,RBPJ,ACVR2A,TMEM100,TGFBR3,SMAD7,USP15,SMURF1,MAPK3,BMP7,GDF5,POU5F1,HIVEP1,BMPR1A,SLC33A1,BMP8A,SOX11,DAND5,PCSK6,SPART,ACVR1,LEFTY1,TRIM33	38	up
response to decreased oxygen levels	GO:0036293	oxygen levels	2.814E-02	PMAIP1,TP53,SUV39H1,BBC3,EPO,CREBBP,REST,BACH1,PIK3CB,PSMB1,MMP2,SMAD4,CXCR4,PTGS2,SFRP1,NOS1,NOTCH1,ADAM17,HSP90B1,NDRG1,VEGFA,SMAD3,PRKAA1,RBPJ,CUL2,CBFA2T3,ITPR1,CPEB2,HIGD1A,HYOU1,RTN4,PSMB5,MDM2,MYC,MDM4,SIRT1,TIGAR,BNIP3,CD24,AIFM1,BMP7,NOL3,DDAH1,CPEB4,HP1BP3,GATA6,DDIT4,UBB,RPS27A,UBC,EGLN3,THBS1,LIMD1,TWIST1	54	both
response to drug	GO:0042493	cellular response to external stimuli	2.625E-02	STAT3,TP53,BCL2,SLC19A1,REST,HMGA2,ABCC1,STAT1,NOS1,CCND1,ADAM17,CDK4,ABCC6,MEF2C,ABCB1,MYC,VAV3,TGFBR2,TFRC,RAP2A,GATA4,CTNNB1,KCNH2,USP47,GATA6,CYP2C19,TMEM30A,SLC46A1,CYP2E1,CYP2U1,THBS1	31	up

response to electrical stimulus	GO:0051602	cellular response to external stimuli	4.578E-02	NEUROD2,NSMF,PTEN,REST	4	down
response to endoplasmic reticulum stress	GO:0034976	cellular response to external stimuli	1.597E-03	PMAIP1,SEL1L,TP53,BBC3,BCL2,EXTL3,EDEM1,BAK1,TNFRSF10B,YOD1,MAN1B1,HDGF,ALOX5,SRPRB,EDEM3,CXCL8,HSP90B1,SCAMP5,CREBRF,SRPRA,BCL2L11,DDX3X,CHAC1,UBE4A,ITPR1,PIK3R1,CLU,CANX,GSK3B,HYOU1,PDIA6,DNAJC10,CFTR,TMEM67,GORASP2,ERLIN1,GFPT1,CEBPB,ERLIN2,MAGEA3,UBQLN2,EIF4G1,TATDN2,BAG6,AIFM1,TRAF2,SESN2,BAX,BFAR,BCL2L1,FICD,UBXN4,DNAJB9,TMEM33,USP13,PPP1R15B,SEC16A,ATP6V0D1,TMCO1,TPP1,DNAJC18,KLHDC3,THBS1,DERL2	64	up
response to extracellular stimulus	GO:0009991	cellular response to external stimuli	1.844E-04	PMAIP1,VDR,TP53,ZFYVE1,MTMR3,SIK2,CDKN2D,PRKAG1,Fas,FES,CYP24A1,CDKN1A,SPP1,BGLAP,STAT1,SFRP1,LDLR,SIK1,ATG14,SESN3,RPS6KB1,GABARAPL1,FOXK1,OGT,LAMP2,PRKAA1,FLCN,HSPA8,HNRNPA1,WIPI2,GABARAP,PIM1,FOXO3,FOXO1,NCOA1,MAPK3,SIRT1,LARP1,ATG5,RRAGD,RRAGA,EIF4G1,INHBB,AIFM1,DCTPP1,RALB,BECN1,SESN2,ATG7,PRKD1,BCL10,NR4A2,PPARA,ADNP,FNIP1,CPEB4,BMP8A,MAPK1,KCNB1,GHSR,SGIP1,POMC,SESN1,SREBF1	64	up
response to fibroblast growth factor	GO:0071774	FGFR signalling	1.383E-02	APLN,NPTN,ESRP2,CD44,TRIM71,PTBP1,FGFR2,SHCBP1,SFRP1,CCL5,CXCL8,RAB14,FGFR3,FGF2,SPRED1,IER2,GRB2,FGFR4,HNRNPA1,SHOC2,POLR2E,MAPK3,KLB,NCBP2,RBFOX2,ESRP1,DSTYK,MAPK1,POLR2D,PRKD2,FRS2,THBS1	32	up
response to heat	GO:0009408	cellular response to external stimuli	1.433E-03	AKT1,NUP93,NUP205,RANBP2,CREBBP,NUP37,NDC1,NOS1,HSP90AA1,MAPKAPK2,HSPA8,BAG4,EIF2B2,NUP50,GSK3B,POM121C,BAG2,ATM,MAPK3,SIRT1,NUP62,IER5,NUP98,DNAJB6,RAE1,BAG3,BAG1,NUP43,MAPK1,POLR2D,NUP54,AKT1S1,THBS1,DNAJB4	34	both
response to hydroperoxide	GO:0033194	cellular response to external stimuli	3.859E-02	PRKCD,SP1,XRCC1,PRKD1,DAPK1	5	up
response to hypoxia	GO:0001666	cellular response to external stimuli	3.047E-02	MYC,TWIST1,PSMB9,NOTCH1,RORA,EP300,ADAM17,NFE2L2,TERT,SIRT1,HIF1A,ROCK2,HSP90B1,PMAIP1,SUV39H2,PDK3,GATA6,DDIT4,ZFP36L1,BBC3,MMP2,MDM2,REST,VEGFA,VHL,SMAD3,ITPR1,LMNA,NF1,AQP3,HIF3A,TP53,MDM4,TMBIM6,AK4,SRF,SLC11A2,PSMC4,ANGPT4,THBS1,PSMD3,BACH1,CREBBP,CITED2	44	both
response to increased oxygen levels	GO:0036296	oxygen levels	3.339E-02	Fas,FOXO1,ATG7,PDPN,ATP6V0D1,CCDC115	6	up
response to insulin	GO:0032868	endocrine system	3.815E-03	PKM,IGF2,AKT1,SIK2,SORT1,IGF1R,APC,PARP1,STAT1,SOS1,IRS1,RAB12,PIK3R3,RPS6KB1,RAB15,OGT,MYO5A,NUCKS1,GRB2,EPM2AIP1,KANK1,PRKCD,CPEB2,INSR,PIK3R1,GSK3B,FOXO3,FOXO1,SLC2A4,VAMP2,SIRT1,ATP6V1E1,INHBB,INSIG1,SLC39A14,ATP6V1C1,ATP6V1B2,GRB10,ATP6V0E1,ZBTB7B,ATP6V0D1,SNX5,EIF6,RAB31,RAB10	45	up
response to interleukin-12	GO:0070671	interleukin signalling	1.376E-02	JAK2,RPLP0,MIF,PDCD4,PAK2,HNRNPDL,HNRNPA2B1,CDC42,CFL1,SNRPA1,MTAP,AIP,IL10,ARF1,SOD2,PLCB1	16	up
response to ionizing radiation	GO:0010212	cellular response to external stimuli	1.152E-03	MYC,DCUN1D3,MAPK14,CLOCK,USP28,TRIM13,SIRT1,YAP1,ATM,TOPBP1,HMGA2,MDM2,CCND2,NET1,INIP,RFWD3,GADD45A,CDKN1A,NUCKS1,TP53,MRNIP,HUS1,RAD51,FANCD2,NABP2,AEN	26	both
response to ischemia	GO:0002931	cellular response to external stimuli	3.844E-02	REST,PIK3CB,CSF1,HYOU1,MEF2C,TIGAR,AIFM1,CSF1R,CPEB4,PER2	10	up
response to mechanical stimulus	GO:0009612	cellular response to external stimuli	8.727E-04	MAP3K2,BAK1,TNFRSF10B,Fas,NFKB1,FADD,STAT1,TLR4,CHEK1,USP53,SLC9A1,MAPK3,CD40,MAP3K14,MAP3K1,CTNNB1,BNIP3,CASP1,CRADD,GADD45A,TNFRSF10A,KIT,LTBR,TNFRSF1A,BCL10,CASP8,TLR3,F11R,MAP2K4,IRF1,HABP4	31	up
response to nutrient levels	GO:0031667	cellular response to external stimuli	1.663E-04	PMAIP1,VDR,TP53,ZFYVE1,MTMR3,SIK2,CDKN2D,PRKAG1,Fas,FES,CYP24A1,CDKN1A,SPP1,BGLAP,STAT1,SFRP1,LDLR,SIK1,ATG14,SESN3,RPS6KB1,GABARAPL1,FOXK1,OGT,LAMP2,PRKAA1,FLCN,HSPA8,HNRNPA1,WIPI2,GABARAP,PIM1,FOXO3,FOXO1,NCOA1,MAPK3,SIRT1,LARP1,ATG5,RRAGD,RRAGA,EIF4G1,INHBB,AIFM1,RALB,BECN1,SESN2,ATG7,PRKD1,BCL10,PPARA,FNIP1,CPEB4,BMP8A,MAPK1,KCNB1,GHSR,SGIP1,POMC,SESN1,SREBF1	61	up
response to organic cyclic compound	GO:0014070	cellular response to external stimuli	1.805E-02	CBFB,PMAIP1,VDR,STAT3,NCOR2,TNF,CDKN2D,GABRB3,MED1,REST,NPM1,SMO,STRN3,KMT2D,FES,ABL1,CYP24A1,EGFR,SPP1,BGLAP,STAT1,SFRP1,SMAD2,BRCA1,IL6,CCL5,IFIT1,CASP7,CLOCK,COLEC12,HSP90B1,IGFBP5,GABPA,PDE4D,BCL2L11,GNAL,GNB1,CARM1,PAGR1,ZCCHC3,ABHD2,HEYL,YWHAH,CLU,GSK3B,PIM1,DIAPH1,YAP1,SLC9A1,MEF2C,CFTR,CCL3,HDAC1,MAPK3,SRC,CASP3,SIRT1,AR,TGFBR2,LARP1,IFNB1,PER1,CTNNB1,SMARCA4,RAD51,AIFM1,RALB,BMP7,IL10,CASP6,CNOT2,RBFOX2,INSIG1,TLR3,LCOR,TMF1,PMEPA1,CNOT1,ZBTB7A,MAVS,MAPK1,TRPC3,SSTR2,ESR1,ARID1A,PDGFB,SSTR1,ACTB,ZNF703,THBS1	90	up
response to osmotic stress	GO:0006970	cellular response to external stimuli	3.967E-02	EPO,TNF,MYLK,DDX3X,WNK3,CAB39,ABCB1,AKR1B1,SLC12A5,LETM1,TLR3,LRRC8D,MAP7,KMO	14	up
response to oxygen levels	GO:0070482	oxygen levels	6.215E-04	MYC,TWIST1,PSMB9,NOTCH1,RORA,EP300,ADAM17,FOXO1,NFE2L2,TERT,SIRT1,HIF1A,ROCK2,HSP90B1,PMAIP1,SUV39H2,PDK3,GATA6,CPEB4,DDIT4,ZFP36L1,BBC3,MMP2,MDM2,REST,VEGFA,VHL,SMAD3,ITPR1,LMNA,NF1,AQP3,HIF3A,TP53,MDM4,TMBIM6,AK4,SRF,SLC11A2,PDPN,PSMC4,ANGPT4,THBS1,PSMD3,BACH1,CREBBP,CITED2	47	both
response to peptide	GO:1901652	cellular response to external stimuli	1.541E-03	PKM,STAT3,IGF2,TP53,JAK2,AKT1,SIK2,SORT1,IGF1R,APC,MMP13,MMP2,PARP1,ABCC1,ROCK1,NFKB1,STAT1,TLR4,SOS1,ICAM1,IRS1,RAB12,IGFBP5,PIK3R3,RPS6KB1,RAB15,OGT,MYO5A,PRKAR2A,NUCKS1,GRB2,EPM2AIP1,KANK1,PRKCD,AGER,CPEB2,INSR,PIK3R1,EIF2B2,TGFBR3,APP,GSK3B,FOXO3,FOXO1,MDM2,SLC2A4,STAT5A,VAMP2,HNF4A,SRC,SIRT1,ATP6V1E1,INHBB,RIPK2,NOD1,TREM2,NR4A2,AGTR1,INSIG1,STAT2,CREB1,RPL23,SLC39A14,ATP6V1C1,ATP6V1B2,PRNP,GRB10,ATP6V0E1,ZBTB7B,ATP6V0D1,SNX5,ERBIN,CD36,EIF6,RAB31,RAB10	76	up
response to peptide hormone	GO:0043434	endocrine system	8.275E-03	PKM,STAT3,IGF2,JAK2,AKT1,SIK2,SORT1,IGF1R,APC,PARP1,ROCK1,NFKB1,STAT1,SOS1,IRS1,RAB12,IGFBP5,PIK3R3,RPS6KB1,RAB15,OGT,MYO5A,PRKAR2A,NUCKS1,GRB2,EPM2AIP1,KANK1,PRKCD,CPEB2,INSR,PIK3R1,EIF2B2,TGFBR3,GSK3B,FOXO3,FOXO1,SLC2A4,STAT5A,VAMP2,HNF4A,SRC,SIRT1,ATP6V1E1,INHBB,NR4A2,AGTR1,INSIG1,STAT2,CREB1,SLC39A14,ATP6V1C1,ATP6V1B2,GRB10,ATP6V0E1,ZBTB7B,ATP6V0D1,SNX5,EIF6,RAB31,RAB10	60	up
response to radiation	GO:0009314	cellular response to external stimuli	1.275E-02	MYC,DCUN1D3,PARP1,MAPK14,CLOCK,BRSK1,FMR1,GNAQ,USP28,YY1,EP300,METAP1,TRIM13,CCND1,SIRT1,YAP1,AKT1,CCAR2,MMP3,MAP2K7,PPM1D,ATM,NMT2,PER2,TOPBP1,BCL2,HMGA2,RHBDD1,COL3A1,ITGB1,PER1,MMP2,MDM2,SPRTN,CCND2,PPP1CB,PPP1CC,SDE2,CHEK1,NET1,FBXL3,INIP,CRY2,RFWD3,GADD45A,CDKN1A,CPT1B,NUCKS1,NF1,TP53,MRNIP,RBM4B,HUS1,RAD51,CREBBP,SCARA3,FANCD2,UBE2B,NABP2,PPP1CA,AEN	61	both
response to starvation	GO:0042594	cellular response to external stimuli	4.559E-04	PMAIP1,TP53,ZFYVE1,MTMR3,SIK2,PRKAG1,Fas,CDKN1A,SFRP1,SIK1,ATG14,SESN3,GABARAPL1,FOXK1,LAMP2,PRKAA1,FLCN,HSPA8,HNRNPA1,WIPI2,GABARAP,FOXO3,FOXO1,MAPK3,SIRT1,LARP1,ATG5,RRAGD,RRAGA,INHBB,RALB,BECN1,SESN2,ATG7,PRKD1,PPARA,FNIP1,CPEB4,MAPK1,SESN1,SREBF1	41	up
response to sterol depletion	GO:0006991	lipid metabolism	2.731E-02	PIP4P1,FBXW7,ERLIN1,ERLIN2,INSIG1,ZBTB7B,SREBF1	7	up
response to temperature stimulus	GO:0009266	cellular response to external stimuli	1.043E-03	AKT1,NUP93,NUP205,RANBP2,CREBBP,NUP37,HSPD1,NDC1,NOS1,HSP90AA1,MAPKAPK2,HSPA8,BAG4,EIF2B2,NUP50,GSK3B,POM121C,FOXO1,BAG2,TRPV2,ATM,MAPK3,SIRT1,NUP62,IER5,NUP98,DNAJB6,RAE1,BAG3,BAG1,NUP43,MAPK1,POLR2D,NUP54,AKT1S1,THBS1,DNAJB4	37	both
response to topologically incorrect protein	GO:0035966	cellular response to external stimuli	1.005E-02	BBC3,EXTL3,EDEM1,BAK1,YOD1,HDGF,HSPD1,SRPRB,CXCL8,HSP90AA1,HSP90B1,HSPA4L,CREBRF,SRPRA,BCL2L11,CUL3,DNAJA1,HSPA8,TM7SF3,PIK3R1,KLHL15,CLU,CANX,HYOU1,PDIA6,GFPT1,TATDN2,BAG6,BAX,BAG3,BFAR,HSPA13,FICD,TOR1B,DNAJB9,TMEM33,PPP1R15B,ATP6V0D1,TPP1,DNAJC18,KLHDC3,DERL2,DNAJB4	43	up
response to transforming growth factor β	GO:0071559	TGF signalling	8.326E-05	WNT4,ZFHX3,LIMS1,PPARA,PDE3A,SOX6,EP300,ADAM17,ZNF703,DAB2,PDPK1,PARD3,SIRT1,SOX9,ROCK2,PTK2,NR3C1,FERMT2,TGFBR1,TGFBRAP1,TGFBR2,LATS2,ARRB2,ZFP36L2,MPP5,NLK,ZFP36L1,COL1A2,COL3A1,FOS,FBN1,JUN,SMAD2,SMAD3,SKI,APPL1,CRKL,RHOA,IL4,ROCK1,HSP90AB1,FOXH1,SPRED3,GIPC1,ITGA3,LPXN,SMAD9,THBS1,WNT5A,CREBBP,BMPR1A,CITED2	52	both
response to tumor cell	GO:0002347	cellular response to external stimuli	2.335E-02	FBXO38,HSPD1,HLA-A,TXNIP,CD274,HMGB1,ADAM15,CD226,PVR	9	up
response to unfolded protein	GO:0006986	cellular response to external stimuli	1.544E-02	BBC3,EXTL3,EDEM1,BAK1,YOD1,HDGF,HSPD1,SRPRB,CXCL8,HSP90AA1,HSP90B1,HSPA4L,CREBRF,SRPRA,BCL2L11,DNAJA1,HSPA8,TM7SF3,PIK3R1,CANX,HYOU1,PDIA6,GFPT1,TATDN2,BAX,BAG3,BFAR,HSPA13,FICD,TOR1B,DNAJB9,TMEM33,PPP1R15B,ATP6V0D1,TPP1,KLHDC3,DERL2,DNAJB4	38	up

response to virus	GO:0009615	viral of bacterial infection	2.397E-07	PMAIP1,ZMYND11,BCL3,TNFAIP3,BCL2,TNF,PCBP2,MAPK14,PRKRA,HMGA2,HMGA1,CXCR4,TRIM22,IFI27,IFIT5,IFIT3,FADD,ISG15,IFITM3,IFITM1,IFI44L,STAT1,IRF7,MX2,OASL,IL6,RSAD2,CCL5,IFIT1,IFI44,CXCL12,IL23R,IVNS1ABP,TARBP2,CDK6,CCL4,DDX3X,CHUK,ZCCHC3,USP15,C6orf106,CLU,POU2AF1,STMN1,LGALS8,CFL1,RRP1B,MOV10,BIRC3,IFNLR1,CCL22,PUM2,CD40,MAP3K14,HNRNPUL1,IFNB1,TRAF3,BNIP3,FOSL1,ATG7,NLRC5,BCL2L1,BIRC2,NLRP9,ARF1,APOBEC3F,STAT2,TLR3,AGBL5,DDIT4,RPS15A,MAVS,IRF1,SERINC3,RNF125,F2RL1,G3BP1,DTX3L,PPM1B	79	up
retina vasculature development in camera-type eye	GO:0061298	organogenesis	2.111E-02	BMPR2,PDGFRA,COL4A1,PDGFRB,FZD4,CYP1B1	6	down
rev-mediated nuclear export of hiv rna	REAC:R-HSA-165054	viral of bacterial infection	9.986E-03	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,RANGAP1,NUP62,RAE1,NUP43,RAN,NUP54	13	up
rho gtpase effectors	REAC:R-HSA-195258	Rho GTPase signalling	4.266E-03	KNTC1,PAK2,MAPK1,NCF1,MAPK14,HIST1H2BJ,CENPN,PRKCD,CDH1,WIPF2,PIK3C3,PDPK1,TAOK1,SCAI,RANGAP1,YWHAG,S100A9,PFN2,ROCK2,PTK2,RHOC,HIST1H2BK,INCENP,PPP2R5E,KIF2C,TUBB2A,DYNC1LI2,RHOG,CENPO,FMNL3,CDC42,ITGB1,RCC2,PPP1CB,PPP1CC,WASL,CDKN1B,CLIP1,TUBB3,CTTN,BUB1,RHOA,ROCK1,DSN1,CTNNB1,KLK2,XPO1,DYNC1H1,KNL1,DVL3,SRF,ACTG1,BIRC5,NUP85,NDEL1,YWHAE,NDE1,YWHAB,PFN1,DVL1,CENPK	61	both
rho gtpases activate formins	REAC:R-HSA-5663220	Rho GTPase signalling	4.593E-02	AURKB,PPP2CA,RANBP2,FMNL3,NUP37,CENPP,RHOA,NSL1,RCC2,KIF2C,TAOK1,PAFAH1B1,BIRC5,DYNLL2,TUBB2A,CDC42,PPP2R5C,DIAPH1,RHOB,ITGB1,RANGAP1,ERCC6L,ACTG1,CDC20,CKAP5,KIF2A,PPP1CC,NUP43,INCENP,DYNC1LI2,CLIP1,DSN1,ACTB,SKA2	34	both
rho gtpases activate ktn1	REAC:R-HSA-5625970	Rho GTPase signalling	2.727E-02	KLC2,RHOA,KIF5B,CDC42,KLC1,KTN1	6	up
rho protein signal transduction	GO:0007266	Rho GTPase signalling	2.992E-02	STARD13,RAF1,RHOV,PLEKHG5,ABL1,STARD8,RHOA,ROCK1,ROBO1,NRP1,ABL2,CUL3,FLCN,KANK1,ARHGDIA,CDC42,STMN1,RHOB,ITGB1,CFL1,MET,ARHGAP1,ARHGDIB,EPS8L2,AGTR1,F11R,PDPN,KCTD10,DLC1,F2RL1	30	both
rhythmic process	GO:0048511	endocrine system	4.624E-02	KMT2A,ZFHX3,CLOCK,GNAQ,PPARA,RORA,EP300,GFPT1,PDGFRA,CPT1A,SIRT1,EZH2,SERPINE1,ROCK2,CCAR2,PPARG,PTEN,KDM5A,PER2,SUV39H2,ID4,EREG,PER1,ID3,HUWE1,PPP1CB,PPP1CC,KLF10,FBXL3,CRY2,PPARGC1A,TP53,RBM4B,TYRO3,GSK3B,KDM2A,PPP1CA	37	down
ribonucleoprotein complex localization	GO:0071166	protein localization	4.047E-03	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,NUP50,POLDIP3,HNRNPA2B1,POM121C,YTHDC1,THOC2,RBM15B,NUP62,NCBP2,NUP98,RAE1,NUP43,RAN,POLR2D,SRSF2,NUP54,SMG1,EIF6,FYTTD1,DDX39A,PABPN1	35	up
ribonucleoprotein complex subunit organisation	GO:0071826	cell organisation	5.260E-03	EIF5,LSM4,RRP7A,RPL3,RPLP0,LUC7L3,SNRPB,RPS28,CDC73,MDN1,HSP90AA1,AGO3,DICER1,AGO2,TARBP2,SRPK1,KIF5B,CPSF7,AGO1,AGO4,SRSF1,DYRK3,RPL10,RPS5,YTHDC1,ATM,PWP2,GEMIN5,KLC1,STRAP,NOL3,WDR77,EIF2S2,GEMIN2,SNRPD1,RPL24,RPF2,POLR2D,SF3A1,RPS14,EIF6,EIF3A,COIL,BRIX1,SF1	45	up
ribonucleoside diphosphate metabolic process	GO:0009185	metabolic process	2.543E-04	PKM,STAT3,NUP93,NUP205,RANBP2,NUP37,PRKAG1,PFKM,HK2,NDC1,ENTPD5,FOXK1,OGT,PRKAA1,TPI1,CBFA2T3,INSR,NUP50,APP,POM121C,NUDT5,LDHA,GPI,NUP62,TIGAR,NUP98,CMPK1,RAE1,PPARA,NUP43,PGAM4,ZBTB7A,NUP54,EIF6	34	up
rig-i-like receptor signalling pathway	KEGG:04622	signalling pathways	2.970E-03	TNF,MAPK14,TRAF6,NFKB1,FADD,ISG15,SIKE1,IRF7,CXCL8,DDX3X,CHUK,CYLD,MAP3K7,ATG5,IFNB1,MAP3K1,TRAF3,TRAF2,CASP8,CASP10,TANK,MAVS,RNF125	23	up
ripk1-mediated regulated necrosis	REAC:R-HSA-5213460	apoptosis	2.485E-05	XIAP,TNFRSF10B,Fas,FADD,BIRC3,TNFRSF10A,TRAF2,FASLG,CASP8,BIRC2,UBB,RPS27A,UBC	13	up
rmts methylate histone arginines	REAC:R-HSA-3214858	epigenetic mechanism	2.951E-02	SMARCD2,JAK2,CCND1,CDK4,CARM1,SMARCD1,HIST1H2AC,SMARCC2,RPS2,SMARCA4,SMARCC1,HIST1H2AH,WDR77,ARID1B,ARID1A	15	up
rna export from nucleus	GO:0006405	cellular transport	1.416E-03	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,POM121C,YTHDC1,THOC2,RBM15B,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,RAE1,NUP43,RBM27,RAN,POLR2D,SRSF2,NUP54,SMG1,EIF6,FYTTD1,DDX39A,PABPN1	39	up
rna localization	GO:0006403	protein localization	2.000E-03	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,ZNF385A,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,CCT6A,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,SIDT2,POM121C,YTHDC1,ATM,THOC2,RBM15B,TGFBR2,NUP62,RBM26,CCT3,KHDRBS1,NCBP2,NUP98,CKAP5,YBX1,RAE1,NUP43,RBM27,RAN,POLR2D,SRSF2,NUP54,ARC,SMG1,EIF6,FYTTD1,DDX39A,MRPL18,PABPN1,HNRNPA3	50	up
rna secondary structure unwinding	GO:0010501	transcription and translation	2.287E-02	AGO3,AGO2,AGO1,DDX3X,AGO4	5	up
rna splicing	GO:0008380	gene expression	2.320E-04	SPEN,DHX38,PABPC1,HNRNPK,LSM4,CASC3,PPP2CA,FUS,THRAP3,PCBP2,REST,NPM1,SRRM2,FXR1,ESRP2,KHSRP,PTBP1,LUC7L3,SNRPB,PPWD1,ELAVL1,RBM23,SLC38A2,RBM38,RALY,AKAP17A,IVNS1ABP,PPIL1,SRPK1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PPIG,PLRG1,HNRNPA1,PIK3R1,U2SURP,AHNAK2,POLR2E,HNRNPA2B1,EFTUD2,YTHDC1,NOVA2,PTBP2,RRP1B,SNRPA1,RBM15B,GEMIN5,STRAP,CHERP,SF3B3,IK,AHNAK,HNRNPUL1,RBM12,KHDRBS1,SON,NCBP2,CDC5L,NUP98,YBX1,WBP11,NOL3,WDR77,RBFOX2,ESRP1,GEMIN2,SNRPD1,SMU1,GRSF1,ZBTB7A,QKI,PRPF38A,PRPF4,HABP4,RBM20,MBNL1,MBNL3,POLR2D,SF3A1,SRSF2,DYRK1A,DDX39A,SNRNP48,PABPN1,ELAVL2,RBM3,COIL,PAPOLA,HNRNPC,SF1,HNRNPA3	94	up
rna splicing, via transesterification reactions	GO:0000375	transcription and translation	4.138E-03	SPEN,DHX38,PABPC1,HNRNPK,LSM4,CASC3,FUS,THRAP3,PCBP2,REST,NPM1,SRRM2,FXR1,KHSRP,PTBP1,LUC7L3,SNRPB,PPWD1,ELAVL1,RBM23,RALY,PPIL1,SRPK1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PLRG1,HNRNPA1,U2SURP,POLR2E,HNRNPA2B1,EFTUD2,YTHDC1,NOVA2,SNRPA1,RBM15B,GEMIN5,STRAP,CHERP,SF3B3,IK,HNRNPUL1,KHDRBS1,SON,NCBP2,CDC5L,NUP98,YBX1,WBP11,NOL3,WDR77,RBFOX2,GEMIN2,SNRPD1,SMU1,ZBTB7A,QKI,PRPF38A,PRPF4,MBNL1,MBNL3,POLR2D,SF3A1,SRSF2,DDX39A,SNRNP48,PABPN1,ELAVL2,RBM3,COIL,PAPOLA,HNRNPC,SF1,HNRNPA3	76	up
rna splicing, via transesterification reactions with bulged adenosine as nucleophile	GO:0000377	transcription and translation	4.995E-03	SPEN,DHX38,PABPC1,HNRNPK,LSM4,CASC3,FUS,THRAP3,PCBP2,REST,NPM1,SRRM2,FXR1,PTBP1,LUC7L3,SNRPB,PPWD1,ELAVL1,RBM23,RALY,PPIL1,SRPK1,CPSF7,SNRPB2,RNPS1,SRSF1,HSPA8,PLRG1,HNRNPA1,U2SURP,POLR2E,HNRNPA2B1,EFTUD2,YTHDC1,NOVA2,SNRPA1,RBM15B,GEMIN5,STRAP,CHERP,SF3B3,IK,HNRNPUL1,KHDRBS1,SON,NCBP2,CDC5L,NUP98,YBX1,WBP11,NOL3,WDR77,RBFOX2,GEMIN2,SNRPD1,SMU1,ZBTB7A,QKI,PRPF38A,PRPF4,MBNL1,MBNL3,POLR2D,SF3A1,SRSF2,DDX39A,SNRNP48,PABPN1,ELAVL2,RBM3,COIL,PAPOLA,HNRNPC,SF1,HNRNPA3	75	up
rna stabilization	GO:0043489	transcription and translation	4.380E-02	PABPC1,FUS,THRAP3,MAPK14,TAF15,NSUN2,ELAVL1,RBM38,MAPKAPK2,AXIN2,E2F1,LARP1,YBX1,PAIP1,TIRAP,HNRNPC	16	up
rna transport	GO:0050658	cellular transport	2.160E-04	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,SIDT2,POM121C,YTHDC1,THOC2,RBM15B,TGFBR2,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,CKAP5,YBX1,RAE1,NUP43,RBM27,RAN,POLR2D,SRSF2,NUP54,ARC,SMG1,EIF6,FYTTD1,DDX39A,MRPL18,PABPN1,HNRNPA3	46	up
rna transport	KEGG:03013	cellular transport	2.160E-04	DHX38,SUPT6H,LTV1,CASC3,NUP93,NUP205,RANBP2,NUP37,NPM1,EIF4E,NSUN2,NDC1,RNPS1,SRSF1,HNRNPA1,NUP50,POLDIP3,HNRNPA2B1,SIDT2,POM121C,YTHDC1,THOC2,RBM15B,TGFBR2,NUP62,RBM26,KHDRBS1,NCBP2,NUP98,CKAP5,YBX1,RAE1,NUP43,RBM27,RAN,POLR2D,SRSF2,NUP54,ARC,SMG1,EIF6,FYTTD1,DDX39A,MRPL18,PABPN1,HNRNPA3	46	up
roof of mouth development	GO:0060021	organogenesis	4.002E-02	BCOR,GABRB3,SMAD4,SMAD2,SKI,WNT7A,TFAP2A,TGFBR3,LEF1,TGFBR2,SOX11,CHD7	12	up
rora activates gene expression	REAC:R-HSA-1368082	gene expression	9.277E-03	NCOA1,PPARA,RORA,EP300,CPT1A,CHD9,CARM1,TBL1XR1,CREBBP	9	down
runx1 interacts with co-factors whose precise effect on runx1 targets is not known	REAC:R-HSA-8939243	RUNX metabolism	1.052E-02	CBFB,SMARCD2,RYBP,CSNK2A1,CBX2,CBX4,PHC3,CBX6,SMARCD1,SMARCC2,SMARCA4,SMARCC1,ARID1B,ARID1A	14	up
runx2 regulates bone development	REAC:R-HSA-8941326	organogenesis	3.811E-02	CBFB,SMAD4,ABL1,BGLAP,YAP1,MAPK3,SRC,AR,SATB2,MAPK1,WWTR1	11	up

runx2 regulates genes involved in cell migration	REAC:R-HSA-8941332	cell adhesion and migration	1.818E-03	CBFB,AKT1,MMP13,ITGBL1,ITGA5,AKT3	6	up
runx2 regulates osteoblast differentiation	REAC:R-HSA-8940973	cell differentiation	1.671E-02	CBFB,ABL1,BGLAP,YAP1,MAPK3,SRC,AR,SATB2,MAPK1,WWTR1	10	up
runx3 regulates cdkn1a transcription	REAC:R-HSA-8941855	RUNX metabolism	4.447E-02	TP53,SMAD4,CDKN1A,SMAD3	4	up
runx3 regulates wnt signalling	REAC:R-HSA-8951430	Wnt signalling	4.654E-03	CCND1,MYC,LEF1,CTNNB1,TCF7,TCF7L2	6	up
s phase	REAC:R-HSA-69242	cell cycle	8.812E-03	PDS5A,AKT1,CCNE1,PSMB1,ANAPC16,LIN52,CDKN1A,CCND1,CCNA2,CDKN1B,CDK4,WEE1,ORC4,CDC25A,CDC27,AKT3,POLE4,CCNE2,GSK3B,PSMB5,CDK2,E2F1,MYC,STAG2,POLD1,MCM4,FZR1,MCM2,MCM7,FEN1,E2F5,PRIM1,ANAPC5,MCM6,MCM3,CDC23,MCM5,UBB,RPS27A,UBC,RFC2,ORC1,CABLES1	43	up
salmonella infection	KEGG:05132	viral of bacterial infection	2.299E-14	KLC2,AKT1,BCL2,TNF,BAK1,MAPK14,TNFRSF10B,PIK3CB,PODXL,EXOC7,DYNC2H1,RAF1,PIK3CD,RHOA,ARL8A,FOS,TRAF6,NFKB1,TLR2,FADD,IRAK1,MYO6,IL6,CXCL8,TLR4,CASP7,HSP90AA1,WASL,KPNA4,HSP90B1,ARL8B,ACTR3B,ACTR2,KIF5B,MAP2K3,DCTN5,CHUK,TUBB,TAB3,AKT3,AHNAK2,NCKAP1,DYNLL2,TUBB2A,CDC42,MAP3K7,KPNA1,KPNA3,RHOB,NLRP3,MYL9,MYC,ACTG1,CYTH1,LEF1,BIRC3,MAPK3,KLC1,CASP3,RRAS,AHNAK,MAP2K1,CTNNB1,NAIP,PIK3CG,CASP1,CYCS,TNFRSF10A,TRAF2,ARF6,CSE1L,BAX,RIPK2,NOD1,TNFRSF1A,CYTH3,CASP8,TCF7,BIRC2,ARF1,EXOC5,TIRAP,DYNC1LI2,CYTH2,MAP2K4,RAB5B,TCF7L2,MAPK1,ARHGEF26,FLNC,RHOH,ACTB,TAB2,PAK3,ACTR1A	95	both
secondary palate development	GO:0062009	organogenesis	2.204E-02	SMAD4,SMAD2,WNT7A,TGFBR3,LEF1,TGFBR2,SOX11,CHD7	8	up
sema3a pak dependent axon repulsion	REAC:R-HSA-399954	neuronal architecture	1.599E-02	FES,HSP90AA1,NRP1,PAK2,SEMA3A,CFL1,PLXNA3,PAK3	8	up
semaphorin interactions	REAC:R-HSA-373755	MAPK signalling	9.616E-04	ERBB2,PLXND1,FES,RHOA,ROCK1,HSP90AA1,NRP1,PAK2,GSK3B,RHOB,ITGB1,MYL9,SEMA3A,CFL1,MET,RRAS,TREM2,CDK5R1,PIP5K1C,PLXNA3,DPYSL2,MYH11,ITGA1,PAK3	24	up
senescence-associated secretory phenotype (sasp)	REAC:R-HSA-2559582	senescence	4.317E-05	CDKN2A,RPS6KA1,EHMT1,STAT3,CDKN2D,ANAPC16,FOS,NFKB1,CDKN1A,IL6,CXCL8,CCNA2,CDKN1B,CDK4,CDK6,CDC27,RPS6KA3,CDK2,FZR1,MAPK3,HIST1H2AC,CEBPB,ANAPC5,HIST1H2BJ,CDKN2C,CDC23,UBB,MAPK1,RPS27A,UBC	30	up
shc-related events triggered by igf1r	REAC:R-HSA-2428933	signalling pathways	4.447E-02	IGF2,IGF1R,SOS1,NRAS	4	up
shc1 events in egfr signalling	REAC:R-HSA-180336	EGFR signalling	4.207E-02	EGFR,SOS1,TGFA,AREG,NRAS,EREG	6	up
shigellosis	KEGG:05131	viral of bacterial infection	2.615E-14	VCL,TP53,AKT1,BCL2,TNF,MAPK14,VDAC1,PIK3CB,CD44,PIK3CD,EGFR,HK2,RHOA,ROCK1,TRAF6,NFKB1,WASF2,SQSTM1,CCL5,CXCL8,PRKCE,TLR4,WASL,ITGA5,UBE2D3,ATG14,PIK3R3,ACTR3B,UBE2V1,ACTR2,RPS6KB1,GABARAPL1,BTRC,CHUK,PRKCD,ITPR1,CRKL,PIK3R1,TAB3,WIPI2,AKT3,GABARAP,CDC42,GSK3B,MAP3K7,CRK,DIAPH1,FOXO3,NLRP3,FOXO1,MDM2,ITGB1,MYL9,ATM,ACTG1,CYTH1,MAPK3,SRC,CBX3,ATG5,RRAGD,IFNB1,RRAGA,SEPT7,PLCG1,NAIP,BNIP3,CASP1,CYCS,TRAF2,ARF6,BECN1,RBCK1,BAX,RIPK2,NOD1,TNFRSF1A,CYTH3,CAPN1,CTTN,BCL10,BCL2L1,ARF1,CYTH2,UBB,MAPK1,RPS27A,UBC,RPS6KA5,UBE2D2,AKT1S1,PLCB1,ACTB,TAB2	94	both
signal attenuation	REAC:R-HSA-74749	signalling pathways	9.795E-03	SOS1,IRS1,INSR,MAPK3,GRB10,MAPK1	6	up
signal transduction by l1	REAC:R-HSA-445144	signalling pathways	1.605E-03	EGFR,CSNK2A1,L1CAM,ITGA5,NRP1,VAV2,ITGB1,MAPK3,MAP2K1,ITGB3,MAPK1	11	up
signal transduction by p53 class mediator	GO:0072331	apoptosis	2.467E-03	CDKN2A,PMAIP1,TP53INP1,E2F7,EHMT1,BCL3,TP53,ARID3A,AKT1,BCL2,AURKB,ZNF385A,PRKAG1,RPS7,NPM1,MAPK14,TAF15,BTG2,CD44,DYRK2,TNKS1BP1,MUC1,CSNK2A1,MIF,CDKN1A,MTA2,BRCA1,MYO6,CNOT6L,RBM38,CDKN1B,CNOT4,NDRG1,CHEK1,SUPT16H,SPRED1,TMEM109,PRKAA1,SSRP1,CARM1,TAF13,CDK1,PPP2R5C,CDK2,MDM2,E2F1,HEXIM1,ATM,HDAC1,MRE11,CDC25C,SFN,MDM4,SIRT1,BAG6,CRADD,GADD45A,TP73,SNAI1,SESN2,BAX,TP53BP2,CNOT2,SOX4,USP28,AEN,AURKA,CDK5R1,CCNB1,RPL23,DDIT4,MAPKAPK5,UBB,CHEK2,CNOT1,RPF2,RFC2,JMY,DYRK1A,BRPF1,TWIST1,HIPK1	82	both
signal transduction in absence of ligand	GO:0038034	signalling pathways	3.073E-02	AKT1,BCL2,TNF,BAK1,ERBB3,Fas,MCL1,BCL2A1,GSK3B,RET,CASP3,CASP9,BAX,MOAP1,BCL2L1	15	both
signal transduction in response to dna damage	GO:0042770	cell cycle	2.530E-02	CDKN2A,PMAIP1,E2F7,BCL3,TP53,ARID3A,ZNF385A,NPM1,MAPK14,BTG2,CD44,TNKS1BP1,ABL1,MUC1,MIF,CDKN1A,BRCA1,MYO6,CNOT6L,WNT1,RBM38,CDKN1B,CNOT4,NDRG1,CHEK1,SPRED1,GRB2,CARM1,CDK1,PPP2R5C,CDK2,MDM2,E2F1,ATM,CDC25C,SFN,MDM4,FZR1,SIRT1,CDC5L,CASP9,CRADD,GADD45A,SNAI1,SESN2,BAX,CNOT2,SOX4,AURKA,CCNB1,CHEK2,CNOT1,DYRK1A,TWIST1	54	both
signal transduction involved in cell cycle checkpoint	GO:0072395	cell cycle	5.886E-10	E2F7,TP53,ARID3A,ZNF385A,BTG2,TNKS1BP1,MUC1,CDKN1A,BRCA1,CNOT6L,RBM38,CDKN1B,CNOT4,CHEK1,CARM1,CDK1,PPP2R5C,CDK2,MDM2,E2F1,ATM,CDC25C,SFN,MDM4,FZR1,CDC5L,CRADD,GADD45A,BAX,CNOT2,SOX4,AURKA,CCNB1,SOX11,CHEK2,CNOT1	36	up
signal transduction involved in dna integrity checkpoint	GO:0072401	cell cycle	1.796E-09	E2F7,TP53,ARID3A,ZNF385A,BTG2,TNKS1BP1,MUC1,CDKN1A,BRCA1,CNOT6L,RBM38,CDKN1B,CNOT4,CHEK1,CARM1,CDK1,PPP2R5C,CDK2,MDM2,E2F1,ATM,CDC25C,SFN,MDM4,FZR1,CDC5L,CRADD,GADD45A,BAX,CNOT2,SOX4,AURKA,CCNB1,CHEK2,CNOT1	35	up
signalling by cytosolic fgfr1 fusion mutants	REAC:R-HSA-1839117	FGFR signalling	4.903E-02	STAT3,GAB2,STAT1,PIK3R1,STAT5A,LRRFIP1,FGFR1OP	7	up
signalling by egfr	REAC:R-HSA-177929	EGFR signalling	2.519E-02	EGFR,SOS1,ADAM17,TGFA,PAG1,PIK3R1,CDC42,SRC,PLCG1,STAM2,AREG,NRAS,UBB,RPS27A,UBC,EREG	16	up
signalling by egfr in cancer	REAC:R-HSA-1643713	EGFR signalling	1.560E-03	EGFR,SOS1,HSP90AA1,TGFA,PIK3R1,PLCG1,AREG,NRAS,UBB,RPS27A,UBC,EREG	12	up
signalling by erbb2	REAC:R-HSA-1227986	ERB signalling	1.113E-04	ERBB2,AKT1,USP8,EGFR,RHOA,PRKCE,SOS1,HSP90AA1,PRKCD,PIK3R1,AKT3,RNF41,DIAPH1,SRC,PLCG1,NRAS,UBB,RPS27A,UBC,EREG,ERBIN	21	up
signalling by erbb2 ecd mutants	REAC:R-HSA-9665348	ERB signalling	6.616E-03	ERBB2,EGFR,SOS1,HSP90AA1,PIK3R1,PLCG1,NRAS,ERBIN	8	up
signalling by erbb2 in cancer	REAC:R-HSA-1227990	cancer	3.512E-02	ERBB2,EGFR,SOS1,HSP90AA1,PIK3R1,PLCG1,NRAS,EREG,ERBIN	9	up
signalling by erbb2 kd mutants	REAC:R-HSA-9664565	ERB signalling	2.698E-02	ERBB2,EGFR,SOS1,HSP90AA1,PIK3R1,PLCG1,NRAS,EREG,ERBIN	9	up
signalling by erbb2 tmd/jmd mutants	REAC:R-HSA-9665686	ERB signalling	3.114E-02	ERBB2,EGFR,SOS1,HSP90AA1,PLCG1,NRAS,EREG,ERBIN	8	up

signalling by erbb4	REAC:R-HSA-1236394	ERB signalling	1.625E-02	GABRB3,EGFR,SOS1,CXCL12,ADAM17,PIK3R1,YAP1,STMN1,STAT5A,SRC,NRAS,UBB,RPS27A,UBC,EREG,ESR1,NCSTN,TAB2	18	up
signalling by erythropoietin	REAC:R-HSA-9006335	signalling pathways	1.560E-03	EPOR,JAK2,EPO,PIK3CB,PIK3CD,SOS1,CRKL,PIK3R1,STAT5A,PLCG1,PIK3CG,NRAS	12	up
signalling by fgfr	REAC:R-HSA-190236	FGFR signalling	1.587E-02	PPP2CA,ESRP2,PTBP1,SOS1,FGF2,SPRED1,FGFR4,HNRNPA1,PIK3R1,POLR2E,MAPK3,KLB,PLCG1,NCBP2,RBFOX2,NRAS,ESRP1,UBB,MAPK1,RPS27A,UBC,POLR2D,FRS2	23	up
signalling by fgfr in disease	REAC:R-HSA-1226099	FGFR signalling	5.017E-03	STAT3,GAB2,FGFR2,STAT1,SOS1,FGFR3,FGF2,BAG4,FGFR4,PIK3R1,POLR2E,STAT5A,ERLIN2,PLCG1,NCBP2,LRRFIP1,NRAS,POLR2D,FGFR1OP,FRS2	20	up
signalling by fgfr1 in disease	REAC:R-HSA-5655302	FGFR signalling	3.662E-03	STAT3,GAB2,STAT1,SOS1,FGF2,BAG4,PIK3R1,STAT5A,ERLIN2,PLCG1,LRRFIP1,NRAS,FGFR1OP,FRS2	14	up
signalling by fgfr2	REAC:R-HSA-5654738	FGFR signalling	2.128E-02	PPP2CA,ESRP2,PTBP1,SOS1,FGF2,HNRNPA1,PIK3R1,POLR2E,MAPK3,PLCG1,NCBP2,RBFOX2,NRAS,ESRP1,UBB,MAPK1,RPS27A,UBC,POLR2D,FRS2	20	up
signalling by fgfr3	REAC:R-HSA-5654741	FGFR signalling	2.591E-02	PPP2CA,SOS1,FGF2,PIK3R1,MAPK3,PLCG1,NRAS,UBB,MAPK1,RPS27A,UBC,FRS2	12	up
signalling by fgfr3 fusions in cancer	REAC:R-HSA-8853334	cancer	2.727E-02	SOS1,FGFR3,PIK3R1,NRAS,FRS2	5	up
signalling by fgfr4	REAC:R-HSA-5654743	FGFR signalling	8.312E-03	PPP2CA,SOS1,FGF2,FGFR4,PIK3R1,MAPK3,KLB,PLCG1,NRAS,UBB,MAPK1,RPS27A,UBC,FRS2	14	up
signalling by fgfr4 in disease	REAC:R-HSA-5655291	FGFR signalling	9.795E-03	SOS1,FGFR4,PIK3R1,PLCG1,NRAS,FRS2	6	up
signalling by hippo	REAC:R-HSA-2028269	signalling pathways	4.686E-02	CASP3,YAP1,SAV1,LATS2,WWTR1,YWHAE,YWHAB,MOB1B	8	both
signalling by interleukins	REAC:R-HSA-449147	interleukin signalling	8.777E-12	MYC,PITPNA,PAK2,OSMR,PDCD4,MAPK1,YES1,MAPK14,IL10RB,TWIST1,IL12RB2,PSMB9,PTPN2,RORA,RPS6KA5,VIM,HMGB1,PTPN14,FOXO1,CCND1,CASP3,IL10RA,LCN2,HIF1A,NFKB1,AKT1,MMP3,UBE2V1,MAP2K7,HSP90B1,CCL22,IL1A,VCAM1,RAP1B,BCL2,RPS6KA3,IL7,IL2,MAP3K3,COL1A2,MCL1,CDC42,FOS,ITGB1,MMP2,FSCN1,JUN,VEGFA,NKIRAS2,SOCS5,SMAD3,STAT3,TCP1,CANX,SOX2,HSPA8,HNRNPA2B1,LIFR,FOXO3,TNIP2,CRKL,IL4,PELI1,SOCS3,SOD2,CDKN1A,IRAK4,CRK,MAP3K8,ICAM1,TP53,IKBKG,CD4,BIRC5,IRAK2,STAT2,PSMC4,TOLLIP,STX4,PSMD3,PTPN9,MIF	82	both
signalling by leptin	REAC:R-HSA-2586552	endocrine system	4.467E-02	STAT3,JAK2,IRS1,STAT5A,SOCS3	5	up
signalling by ligand-responsive egfr variants in cancer	REAC:R-HSA-5637815	EGFR signalling	6.489E-03	EGFR,SOS1,HSP90AA1,PIK3R1,PLCG1,NRAS,UBB,RPS27A,UBC	9	up
signalling by met	REAC:R-HSA-6806834	signalling pathways	4.727E-02	PTPN2,COL1A1,PTK2,RAP1B,EPS15,ARF6,COL1A2,COL3A1,ITGB1,COL5A2,LAMC2,LAMC1,STAT3,MET,CRKL,CRK,ITGA3,RAB4A,MUC20,SH3GL1	20	down
signalling by nodal	REAC:R-HSA-1181150	signalling pathways	1.999E-02	SMAD4,SMAD2,FURIN,SMAD3,ACVR2A,FOXO3,DAND5,PCSK6,LEFTY1	9	up
signalling by non-receptor tyrosine kinases	REAC:R-HSA-9006927	signalling pathways	4.071E-03	STAT3,ERBB2,AKT1,CCNE1,EGFR,RHOA,CCND1,CDKN1B,CDK4,CRK,CDK2,KHDRBS1,NRAS,PELP1,UBB,RPS27A,UBC,EREG,SOCS3	19	up
signalling by notch	REAC:R-HSA-157118	NOTCH signalling	4.530E-03	E2F3,NCOR2,SEL1L,TP53,AKT1,CREBBP,PLXND1,PSMB1,TNRC6B,EGFR,STAT1,LFNG,NUMB,CCND1,NOTCH2,NOTCH1,TACC3,AGO3,DTX4,FURIN,ADAM17,TNRC6A,AGO2,SMAD3,AGO1,RBPJ,AGO4,CDK8,TLE4,HEYL,B4GALT1,MIB1,TBL1XR1,PSMB5,E2F1,FABP7,MYC,JAG1,HDAC1,DLL1,MOV10,HIST1H2AC,HIST1H2BJ,YBX1,SIRT6,CREB1,UBB,RPS27A,UBC,NCSTN,RAB6A,MAMLD1	52	up
signalling by notch1	REAC:R-HSA-1980143	NOTCH signalling	3.492E-02	NCOR2,CREBBP,NUMB,NOTCH1,DTX4,ADAM17,RBPJ,CDK8,TLE4,HEYL,MIB1,TBL1XR1,MYC,JAG1,HDAC1,DLL1,UBB,RPS27A,UBC,NCSTN,MAMLD1	21	up
signalling by notch1 hd domain mutants in cancer	REAC:R-HSA-2691230	NOTCH signalling	1.052E-02	NOTCH1,ADAM17,MIB1,JAG1,DLL1,UBB,RPS27A,UBC	8	up
signalling by notch1 hd+pest domain mutants in cancer	REAC:R-HSA-2894858	NOTCH signalling	2.698E-02	NCOR2,CREBBP,NOTCH1,ADAM17,RBPJ,CDK8,HEYL,MIB1,TBL1XR1,MYC,JAG1,HDAC1,DLL1,UBB,RPS27A,UBC,NCSTN,MAMLD1	18	up
signalling by notch1 in cancer	REAC:R-HSA-2644603	NOTCH signalling	2.698E-02	NCOR2,CREBBP,NOTCH1,ADAM17,RBPJ,CDK8,HEYL,MIB1,TBL1XR1,MYC,JAG1,HDAC1,DLL1,UBB,RPS27A,UBC,NCSTN,MAMLD1	18	up
signalling by notch1 pest domain mutants in cancer	REAC:R-HSA-2644602	NOTCH signalling	2.698E-02	NCOR2,CREBBP,NOTCH1,ADAM17,RBPJ,CDK8,HEYL,MIB1,TBL1XR1,MYC,JAG1,HDAC1,DLL1,UBB,RPS27A,UBC,NCSTN,MAMLD1	18	up
signalling by notch3	REAC:R-HSA-9012852	NOTCH signalling	4.848E-03	CREBBP,PLXND1,EGFR,STAT1,NOTCH1,TACC3,RBPJ,HEYL,MIB1,FABP7,JAG1,DLL1,YBX1,UBB,RPS27A,UBC,NCSTN,MAMLD1	18	up
signalling by ntrk1 (trka)	REAC:R-HSA-187037	signalling pathways	8.371E-04	RPS6KA1,STAT3,PPP2CA,DUSP6,REST,MAPK14,PIK3CB,RHOA,FOS,SOS1,IRS1,YWHAB,AP2B1,MAPKAPK2,CRKL,PIK3R1,CRK,RPS6KA3,F3,MEF2C,AP2A1,MAPK3,AP2M1,MAP2K1,AP2A2,PLCG1,FOSL1,RALB,NRAS,CDK5R1,CLTA,CREB1,MAPK1,RPS6KA5,ARC,FRS2	36	up
signalling by ntrk3 (trkc)	REAC:R-HSA-9034015	signalling pathways	4.035E-03	NTRK3,SOS1,IRS1,PIK3R1,SRC,PLCG1,BAX,NRAS	8	up
signalling by ntrks	REAC:R-HSA-166520	signalling pathways	2.250E-04	RPS6KA1,STAT3,PPP2CA,DUSP6,REST,MAPK14,PIK3CB,NTRK3,RHOA,FOS,SOS1,IRS1,FURIN,YWHAB,AP2B1,MAPKAPK2,CRKL,PIK3R1,CRK,RPS6KA3,F3,MEF2C,AP2A1,MAPK3,SRC,AP2M1,MAP2K1,AP2A2,PLCG1,FOSL1,RALB,BAX,DOCK3,NRAS,CDK5R1,CLTA,CREB1,PCSK6,MAPK1,RPS6KA5,ARC,FRS2	42	up
signalling by nuclear receptors	REAC:R-HSA-9006931	gene expression	6.570E-04	MYC,MAPK1,NCOA1,ESR1,HIST1H2BJ,RDH11,AGO3,SP1,YY1,PCK1,ABCG1,EP300,TNRC6B,ZDHHC21,AGO4,PDPK1,POLR2D,CPT1A,CCND1,RARA,AKT1,IGF1R,PTK2,AGO1,MMP3,GNAI2,POLR2E,HIST1H2BK,NCOA3,STAG1,SCD,PDK3,BCL2,CARM1,TBL1XR1,EREG,GNB4,FOS,MMP2,JUN,PDHX,AKT2,AKT3,MYLIP,CDKN1B,UHMK1,DDX5,GREB1,KCTD6,FOXO3,SMC3,HSP90AB1,CPT1B,XPO1,SRF,EGF,CCNT1,GNAI3,CREBBP,JUND	60	both
signalling by pdgf	REAC:R-HSA-186797	PDGF signalling pathway	1.625E-02	STAT3,PIK3CB,SPP1,STAT1,SOS1,FURIN,CRKL,PIK3R1,CRK,STAT5A,SRC,PDGFRB,PDGFRA,PLCG1,NRAS,PDGFB,THBS1,COL4A1	18	up
signalling by pdgfr in disease	REAC:R-HSA-9671555	PDGF signalling pathway	9.906E-03	STAT3,PIK3CB,STAT1,SOS1,KANK1,PIK3R1,KDR,PDGFRA,NRAS	9	up

signalling by pdgfra extracellular domain mutants	REAC:R-HSA-9673770	PDGF signalling pathway	3.238E-03	STAT3,PIK3CB,STAT1,SOS1,PIK3R1,PDGFRA,NRAS	7	up
signalling by pdgfra transmembrane, juxtamembrane and kinase domain mutants	REAC:R-HSA-9673767	PDGF signalling pathway	3.238E-03	STAT3,PIK3CB,STAT1,SOS1,PIK3R1,PDGFRA,NRAS	7	up
signalling by ptk6	REAC:R-HSA-8848021	signalling pathways	4.071E-03	STAT3,ERBB2,AKT1,CCNE1,EGFR,RHOA,CCND1,CDKN1B,CDK4,CRK,CDK2,KHDRBS1,NRAS,PELP1,UBB,RPS27A,UBC,EREG,SOCS3	19	up
signalling by receptor tyrosine kinases	REAC:R-HSA-9006934	signalling pathways	2.410E-08	RRAD,KLB,PAK2,THBS2,MAPK1,ADAM12,NCF1,YES1,MAPK14,ESR1,GRAP2,PRKCD,HNRNPA1,PTPN2,COL9A2,GABRB1,EP300,MAP2K2,ADAM17,IGF1,RPS6KA5,SH2B3,MEMO1,PDGFRA,PIK3C3,PDPK1,COL1A1,POLR2D,YAP1,ROCK2,AKT1,IGF1R,PTK2,FOSL1,POLR2E,FGF19,CUL5,KIT,TIAL1,HNRNPH1,RAP1B,RPS6KA3,EPS15,ID4,ARF6,EREG,CTNND1,COL1A2,COL4A1,CDC42,COL3A1,FOS,ITGB1,SGK1,ID3,SPARC,COL6A2,PDGFRB,COL4A2,COL5A2,TIAM1,REST,AKT2,AKT3,VEGFA,LAMC2,LAMC1,STMN1,CHEK1,STAT3,RIT1,FRS2,ITPR1,PTBP1,GALNT3,MET,CRKL,RHOA,ROCK1,CTNNB1,CRK,ITGA3,SRF,EGF,ACTG1,ATP6V0D2,RAB4A,MUC20,SH3GL1,PTK6,ITCH,MEF2D,THBS1,YWHAB,NCSTN,ADCYAP1,EPS15L1,JUND	98	both
signalling by rho gtpases	REAC:R-HSA-194315	Rho GTPase signalling	1.605E-02	NF2,KLC2,S100A8,AURKB,PPP2CA,STARD13,RANBP2,FMNL3,NUP37,MAPK14,RHOV,PLEKHG5,ABL1,CENPP,STARD8,RHOA,ROCK1,WASF2,MYLK,SOS1,NSL1,WASL,RCC2,SOS2,KIF2C,CDKN1B,YWHAB,TAOK1,PAFAH1B1,ACTR2,KIF5B,VAV2,ARHGAP12,OCRL,PAK2,BIRC5,PRKCD,RACGAP1,NCKAP1,DYNLL2,YWHAQ,ARHGDIA,YWHAH,TUBB2A,CDC42,PPP2R5C,ARHGAP32,DIAPH1,TRIP10,RHOB,ITGB1,MYL9,CFTR,RANGAP1,ECT2,CFL1,VAV3,ARHGAP1,CDC25C,ERCC6L,SFN,ACTG1,CDC20,MAPK3,HIST1H2AC,KLC1,KTN1,AR,ARHGDIB,CTNNB1,HIST1H2BJ,CKAP5,GDI1,KIF2A,CTTN,PPP1CC,CYBB,NUP43,INCENP,DYNC1LI2,MAPK1,ARHGEF26,WIPF2,DLC1,CLIP1,MYH11,DSN1,DEPDC1B,RHOH,ACTB,SKA2,PAK3	92	up
signalling by scf-kit	REAC:R-HSA-1433557	signalling pathways	6.823E-03	STAT3,JAK2,GAB2,FES,GRAP2,STAT1,SOS1,PIK3R3,CHEK1,PIK3R1,STAT5A,KIT,NRAS,SH2B3,GRB10	15	up
signalling by tgf-β receptor complex	REAC:R-HSA-170834	TGF signalling	3.371E-04	NCOR2,CGN,SMAD4,PPP1CA,MTMR4,PARP1,RHOA,SMAD2,FURIN,UBE2D3,SKI,SMAD3,CCNT1,PPM1A,CCNT2,CDK8,FKBP1A,SMAD7,USP15,SMURF1,SP1,MYC,HDAC1,STRAP,E2F5,TGFBR2,TGIF2,PPP1CC,F11R,PMEPA1,UBB,RPS27A,UBC,TRIM33,WWTR1,TGIF1	36	both
signalling by tgf-β receptor complex in cancer	REAC:R-HSA-3304351	cancer	6.376E-03	SMAD4,SMAD2,SMAD3,FKBP1A,TGFBR2	5	both
signalling by tgfb family members	REAC:R-HSA-9006936	TGF signalling	4.052E-04	BMPR1B,NCOR2,CGN,SMAD4,PPP1CA,MTMR4,PARP1,RHOA,SMAD2,FURIN,UBE2D3,SKI,SMAD3,CCNT1,PPM1A,CCNT2,CDK8,ACVR2A,FKBP1A,SMAD7,USP15,SMURF1,SP1,MYC,HDAC1,STRAP,E2F5,TGFBR2,INHBB,TGIF2,PPP1CC,BMPR1A,F11R,PMEPA1,UBB,RPS27A,UBC,TRIM33,WWTR1,TGIF1	40	both
signalling by vegf	REAC:R-HSA-194138	signalling pathways	1.828E-03	SPHK1,AKT1,CDH5,MAPK14,PIK3CB,RHOA,ROCK1,WASF2,HSP90AA1,NRP1,VEGFA,VAV2,MAPKAPK2,PAK2,PRKCD,ITPR1,PIK3R1,AKT3,NCKAP1,CDC42,KDR,CRK,VAV3,ACTG1,ITGB3,PLCG1,CTNNB1,AXL,RICTOR,CYBB,NRAS,ACTB,PAK3	33	up
signalling by wnt	REAC:R-HSA-195721	Wnt signalling	1.783E-02	FZD4,XIAP,FRAT2,AKT1,PPP2CA,CREBBP,KMT2D,PSMB1,APC,FZD6,USP8,TNRC6B,CSNK2A1,RHOA,CDC73,SFRP1,SOX2,WNT2B,AGO3,DKK1,WNT1,FZD5,TNRC6A,AGO2,AP2B1,WNT7A,AGO1,GNB1,BTRC,CUL3,AMER1,CCDC88C,AGO4,ITPR1,TLE4,AXIN2,PPP2R5C,GSK3B,SMURF1,MAP3K7,GNG12,ZNRF3,PSMB5,MYC,AP2A1,HDAC1,LEF1,MOV10,HIST1H2AC,CLTB,SNX3,AP2M1,AP2A2,CTNNB1,SMARCA4,HIST1H2BJ,PPP3R1,TLE3,TCF7,SOX4,CLTA,UBB,CBY1,TCF7L2,RPS27A,UBC,KREMEN1,PLCB1	68	up
signalling by wnt in cancer	REAC:R-HSA-4791275	cancer	3.811E-02	FZD4,PPP2CA,APC,FZD6,DKK1,FZD5,AMER1,PPP2R5C,GSK3B,CTNNB1,TCF7L2,KREMEN1	12	up
signalling pathways regulating pluripotency of stem cells	KEGG:04550	signalling pathways	1.191E-04	WNT4,MYC,DUSP9,MAPK1,MAPK14,ZFHX3,APC,RIF1,BMPR2,MAP2K2,IGF1,AKT1,IGF1R,KRAS,ID4,ID3,KLF4,FZD5,REST,FZD4,AKT2,AKT3,ACVR1C,SMAD2,SMAD3,STAT3,PCGF2,SOX2,LIFR,JARID2,CTNNB1,DVL3,FZD7,SMAD9,WNT5A,BMI1,GSK3B,DVL1,BMPR1A	39	both
signalling to erks	REAC:R-HSA-187687	MAPK signalling	1.999E-02	MAPK14,SOS1,YWHAB,MAPKAPK2,CRKL,CRK,MAPK3,MAP2K1,RALB,NRAS,MAPK1,FRS2	12	up
sister chromatid segregation	GO:0000819	chromatin organisation	4.351E-03	VPS4B,PDS5A,AURKB,APC,SMC2,KPNB1,DUSP1,HORMAD2,KIF22,NSL1,TACC3,KIF2C,CHMP4B,CUL3,VPS4A,KIF23,RACGAP1,CDC27,AXIN2,FBXW7,CHMP2B,ATM,STAG2,MRE11,CDC20,FEN1,MCMBP,IK,KIF4A,NUP62,ANAPC5,NCAPG,CTNNB1,POGZ,BECN1,CDC23,CCNB1,NCAPG2,NCAPD2,RAN,NAA50,DSN1,PHF13,TOP2A	44	up
skeletal system morphogenesis	GO:0048705	organogenesis	3.997E-02	TWIST1,BMPR2,SOX6,SIX1,PDGFRA,SOX9,FOXC1,MTHFD1L,TGFBR1,TGFBR2,LRP6,SKI,HOXA9,CTNNB1,RFLNB,HOXB3,EIF4A3,ALX1,BARX2,HOXD3,TFAP2A	21	down
smac (diablo) binds to iaps	REAC:R-HSA-111463	mitochondrial activity	9.186E-05	XIAP,CASP7,CASP3,DIABLO,CASP9,CYCS,APAF1	7	up
smac, xiap-regulated apoptotic response	REAC:R-HSA-111469	apoptosis	9.186E-05	XIAP,CASP7,CASP3,DIABLO,CASP9,CYCS,APAF1	7	up
smac(diablo)-mediated dissociation of iap:caspase complexes	REAC:R-HSA-111464	caspase signalling pathway	9.186E-05	XIAP,CASP7,CASP3,DIABLO,CASP9,CYCS,APAF1	7	up
smad protein complex assembly	GO:0007183	protein metabolism	1.281E-02	SMAD4,SMAD2,SMAD3,PPM1A,FKBP1A,PMEPA1	6	up
smad protein signal transduction	GO:0060395	protein metabolism	4.573E-02	JAK2,NUP93,SMAD4,FOS,SMAD2,BMP3,SKI,SMAD3,SMAD7,INHBB,BMP7,GDF5,POU5F1,BMPR1A,SLC33A1,BMP8A,LEFTY1,WWTR1	18	up
smad2/smad3:smad4 heterotrimer regulates transcription	REAC:R-HSA-2173796	SMAD activity	1.839E-02	MYC,E2F5,SP1,SERPINE1,CCNK,CCNT2,TGIF2,WWTR1,SMAD2,SMAD3,CCNT1,TFDP2	12	both
small cell lung cancer	KEGG:05222	cancer	1.965E-11	MYC,CDK6,TRAF3,XIAP,CCND1,CASP3,NFKB1,AKT1,PTK2,PTEN,BCL2,COL4A1,ITGB1,COL4A2,AKT2,ITGA6,AKT3,LAMC2,LAMC1,CDKN1B,SKP2,GADD45A,CDKN1A,TRAF1,ITGA3,TP53,IKBKG,CKS1B,CYCS,E2F3	30	both
small gtpase mediated signal transduction	GO:0007264	Rho GTPase signalling	5.541E-06	RRAD,EPHB2,RASSF1,ABL2,MAPK14,DENND4C,GRAP2,USP28,RRAGC,NOTCH1,EPS8,FGD4,KCTD10,CDC42EP3,NUP62,IGF1,TIAM2,SPRY4,SCAI,P2RY10,HEG1,ROCK2,ARHGAP31,RHOC,RELN,ARHGEF3,CCDC88C,KRAS,FAM13A,NOTCH2,RHOG,RAP1B,G3BP2,ARF6,SHOC2,COL1A2,CDC42,COL3A1,ITGB1,CCNA2,STK19,JUN,TIAM1,STMN1,RAP2C,GPSM2,RIT1,NET1,ARHGAP12,MET,DLC1,CRKL,RHOA,ROCK1,MAPRE2,FOXM1,CDKN1A,KANK2,LZTR1,RREB1,NF1,KIAA0355,ITGA3,PLEKHG2,TP53,ARHGDIA,CGNL1,MAPKAPK5,PHACTR4,PDPN,ARHGAP11A,RRAS,PLCE1,APOC3,FAM49B,PRAG1	76	both
small interfering rna (sirna) biogenesis	REAC:R-HSA-426486	miRNA/siRNA biogenesis	1.113E-04	PRKRA,AGO3,DICER1,AGO2,TARBP2,AGO1,AGO4,TSN	8	up
small rna loading onto risc	GO:0070922	mirNA/siRNA biogenesis	6.805E-03	AGO3,DICER1,AGO2,TARBP2,AGO1,AGO4	6	up
smooth muscle cell proliferation	GO:0048659	cell proliferation	1.789E-02	AKT1,TNFAIP3,APLN,TNF,IL6R,MMP2,CDKN1A,STAT1,IL6,CCL5,DNMT1,FGF2,CDKN1B,IGFBP5,PTEN,PDCD4,ELN,MEF2C,TPM1,PDGFRB,MFN2,CTNNB1,IL10,BMPR1A,TCF7L2,EDN1,EREG,PDGFB,SOD2,THBS1	30	up

snrnp assembly	REAC:R-HSA-191859	transcription and translation	1.391E-02	NUP93,NUP205,RANBP2,NUP37,SNRPB,NDC1,NUP50,POM121C,GEMIN5,NUP62,NCBP2,RAE1,WDR77,NUP43,GEMIN2,SNRPD1,NUP54	17	up
somatic stem cell population maintenance	GO:0035019	cell proliferation	1.827E-02	STAT3,LIN28A,REST,SMAD4,SMAD2,SOX2,FGF2,KLF4,SKI,POLR2E,SALL1,MYC,NANOG,POU5F1,POLR2D	15	up
sphingolipid mediated signalling pathway	GO:0090520	lipid metabolism	2.287E-02	AKT1,PIK3CB,S1PR2,PIK3CG,S1PR1	5	up
sphingolipid metabolism	REAC:R-HSA-428157	lipid metabolism	4.491E-02	GLTP,VAPA,GM2A,KDSR,GLB1L,ARSD,SPTLC2,CERS4,PPM1L,ARSJ,SGMS1,PLPP3,SPTLC3,DEGS1,ACER3,PRKD3,ARSK,ARSA,SUMF2,ARSB,GLA,SGMS2	22	down
sphingolipid signalling pathway	KEGG:04071	lipid metabolism	1.900E-04	SPHK1,TP53,AKT1,BCL2,PPP2CA,TNF,GAB2,MAPK14,PIK3CB,SGPL1,RAF1,PIK3CD,ABCC1,RHOA,ROCK1,NFKB1,PRKCE,KRAS,PIK3R3,S1PR2,PTEN,PIK3R1,AKT3,PPP2R5C,SPTLC1,ADORA3,SGPP1,DEGS1,MAPK3,MAP2K1,TRAF2,BAX,TNFRSF1A,S1PR1,NRAS,GNAQ,MAPK1,PLCB1	38	both
sphingosine-1-phosphate receptor signalling pathway	GO:0003376	signalling pathways	2.287E-02	AKT1,PIK3CB,S1PR2,PIK3CG,S1PR1	5	up
spindle organisation	GO:0007051	cell organisation	4.442E-02	VPS4B,XIAP,AURKB,GOLGA8B,KPNB1,RHOA,TACC3,CHMP4B,MECP2,HAUS3,KIF23,BIRC5,RACGAP1,KIF3B,STMN1,CHMP2B,KIF11,STAG2,KIF4A,NUP62,TPPP,CKAP5,MAP4,RAE1,KIF2A,AURKA,CCNB1,INCENP,RNF4,TRIM36,CHEK2,SUN2,MAPRE3,RAN,SENP6,TUBGCP4,PCNT	37	up
srebp signalling pathway	GO:0032933	signalling pathways	4.808E-02	FBXW7,ERLIN1,ERLIN2,INSIG1,ZBTB7B,SREBF1	6	up
stem cell population maintenance	GO:0019827	cell proliferation	6.361E-03	STAT3,LIN28A,REST,SMAD4,HMGA2,CDC73,SMAD2,NOTCH2,ELAVL1,NOTCH1,SOX2,FGF2,KLF4,SKI,POLR2E,SALL1,MYC,JAG1,DLL1,CTNNB1,NANOG,POU5F1,KIT,CNOT2,CNOT1,POLR2D,TET1,PIWIL2	28	both
steroid biosynthesis	KEGG:00100	endocrine system	9.902E-03	LIPA,LSS,CYP24A1,LBR,MSMO1,DHCR7,CYP51A1,DHCR24,SC5D	9	up
steroid hormone mediated signalling pathway	GO:0043401	signalling pathways	9.539E-03	CBFB,NCOR2,MED1,STRN3,KMT2D,SFRP1,BRCA1,CLOCK,CARM1,PAGR1,ABHD2,HEYL,YWHAH,YAP1,HDAC1,SRC,SIRT1,AR,PER1,SMARCA4,BMP7,CNOT2,RBFOX2,TMF1,PMEPA1,CNOT1,ZBTB7A,ESR1,ARID1A	29	up
stress granule assembly	GO:0034063	cell organisation	3.298E-02	DDX3X,RPS23,PRRC2C,G3BP2,DDX6,CSDE1,ATXN2L,DYNC1H1	8	both
stress-activated mapk cascade	GO:0051403	MAPK signalling	4.128E-06	SEMA4C,SPHK1,MAP3K2,ZMYND11,MAP3K11,MAPK14,IGF1R,Fas,RASGRP1,MFHAS1,EGFR,CD40LG,DUSP1,IRAK2,TRAF6,NFKB1,IRAK1,MAP3K9,PDCD4,VEGFA,TAOK1,PAFAH1B1,UBE2V1,WNT7A,ZNF622,MAP2K3,BTRC,DNAJA1,CHUK,AGER,CRKL,CYLD,TAB3,KLHDC10,MINK1,APP,MAP4K2,MAP3K7,RASSF2,FOXO1,SEMA3A,MYC,MAPK3,MAP2K1,RAP2A,TRAF3,PER1,HMGB1,GADD45A,TRAF2,RIPK2,NOD1,LTBR,CD27,TIRAP,SASH1,MAP2K4,UBB,MAPK1,FKTN,RPS27A,UBC,F2RL1,PLCB1,TAB2,PHLPP1	66	both
stress-activated protein kinase signalling cascade	GO:0031098	protein kinase activity	1.504E-06	MYC,DUSP9,PAK2,PDCD4,MAPK1,NCF1,MAPK14,MAP3K13,DUSP1,DUSP10,TRAF3,MAP2K2,PAK5,TAOK3,HMGB1,MAP3K2,TAOK1,FOXO1,GPS1,MAP3K11,SEMA4C,NFKB1,IGF1R,ZMYND11,UBE2V1,FGF19,MAP2K7,CCDC88C,ZFP36L1,PER1,VEGFA,TNIP2,CRKL,FOXM1,GADD45A,TRAF1,MAP3K8,ERN1,IKBKG,EIF2AK2,FZD7,PYCARD,IRAK2,ITCH,SH3RF2,WNT5A,MINK1,TAOK2,PAK4	49	both
stress-induced premature senescence	GO:0090400	senescence	2.440E-02	TP53,MAPK14,CDKN1A,SIRT1,MAPKAPK5	5	both
striated muscle cell proliferation	GO:0014855	cell proliferation	1.680E-02	STAT3,SIX1,GLI1,FGFR2,ERBB4,NOTCH1,FGF2,RBPJ,TGFBR3,PIM1,MEF2C,TP73,CFLAR,BMPR1A,AKIRIN1,VGLL4	16	up
striated muscle tissue development	GO:0014706	organogenesis	7.517E-03	NEBL,SIX1,SMAD4,GLI1,FGFR2,MSC,ERBB4,LRP2,KDM6B,NOTCH1,DKK1,SIK1,FGF2,SKI,VEGFA,EFNB2,RBPJ,FKBP1A,TGFBR3,SMAD7,KLHL40,PIM1,MEF2C,ZBTB18,ITGB1,DLL1,TPM1,PDGFRB,PDGFRA,DSP,PKP2,TP73,BMP7,CFLAR,ACTC1,S1PR1,BMPR1A,CBY1,EDN1,MTPN,ACVR1,MYH11,FRS2,AKIRIN1,VGLL4,ADAMTS9,ACTA1	47	up
substrate adhesion-dependent cell spreading	GO:0034446	cell adhesion and migration	1.241E-02	NTNG2,LIMS1,NTNG1,SPRY4,PTK2,FERMT2,CDC42,FGG,RCC2,FGB,FGA,NEDD9,LAMC1,CRKL,RHOA,PARVB,CRK,RREB1,LPXN,MYADM,TYRO3,BVES,PDPN,ACTN4	24	down
sumo e3 ligases sumoylate target proteins	REAC:R-HSA-3108232	SUMOylation	5.264E-06	PARP1,TRIM27,CBX4,NCOA1,MBD1,ESR1,SUMO2,NR4A2,SATB1,PPARA,RORA,EP300,THRB,NUP62,NUP205,RANGAP1,RARA,SUZ12,RPA1,NR3C1,PPARG,INCENP,STAG1,PHC3,DNMT3A,DNMT3B,TFAP2C,TDG,MDM2,VHL,CBX2,POM121C,PCGF2,PIAS1,DDX5,MITF,NUP50,SMC3,NUP210,PPARGC1A,TP53,IKBKG,BIRC5,NUP35,NUP85,BMI1,CREBBP,AURKA	48	both
sumoylation	REAC:R-HSA-2990846	SUMOylation	2.947E-06	CDKN2A,VDR,SMC6,NCOR2,TP53,HNRNPK,AURKB,NUP93,NUP205,RANBP2,CREBBP,NUP37,NPM1,PIAS3,TDG,PARP1,NDC1,BRCA1,DNMT1,MBD1,CBX2,BIRC5,CBX4,PHC3,RNF168,NUP50,POM121C,SP3,MDM2,RANGAP1,HDAC1,STAG2,NCOA1,SENP1,AR,NUP62,SATB2,RAE1,UBA2,NR4A2,PPARA,AURKA,NUP43,INCENP,ESR1,NUP54,HERC2,CBX5,TOP2A,HNRNPC	50	both
sumoylation of chromatin organisation proteins	REAC:R-HSA-4551638	chromatin organisation	2.782E-02	CBX4,SUMO2,SATB1,NUP62,NUP205,SUZ12,PHC3,CBX2,POM121C,PCGF2,PIAS1,NUP50,NUP210,NUP35,NUP85,BMI1	16	both
sumoylation of dna damage response and repair proteins	REAC:R-HSA-3108214	SUMOylation	1.921E-02	CDKN2A,SMC6,NUP93,NUP205,RANBP2,NUP37,TDG,PARP1,NDC1,BRCA1,CBX2,CBX4,PHC3,RNF168,NUP50,POM121C,STAG2,NUP62,RAE1,NUP43,NUP54,HERC2	22	up
sumoylation of dna methylation proteins	REAC:R-HSA-4655427	SUMOylation	4.491E-02	CBX4,PHC3,DNMT3A,DNMT3B,CBX2,PCGF2,BMI1	7	down
sumoylation of dna replication proteins	REAC:R-HSA-4615885	SUMOylation	1.430E-03	AURKB,NUP93,NUP205,RANBP2,NUP37,PIAS3,NDC1,BIRC5,NUP50,POM121C,RANGAP1,NUP62,RAE1,AURKA,NUP43,INCENP,NUP54,TOP2A	18	up
sumoylation of intracellular receptors	REAC:R-HSA-4090294	SUMOylation	1.926E-02	ESR1,SUMO2,NR4A2,PPARA,RORA,THRB,RARA,NR3C1,PPARG,PIAS1	10	down
sumoylation of rna binding proteins	REAC:R-HSA-4570464	SUMOylation	9.163E-03	HNRNPK,NUP93,NUP205,RANBP2,NUP37,NDC1,CBX2,CBX4,PHC3,NUP50,POM121C,NUP62,RAE1,NUP43,NUP54,HNRNPC	16	up
sumoylation of transcription cofactors	REAC:R-HSA-3899300	SUMOylation	4.727E-02	CBX4,NCOA1,MBD1,SUMO2,EP300,PHC3,CBX2,PCGF2,PIAS1,DDX5,PPARGC1A,BMI1,CREBBP	13	down
sumoylation of ubiquitinylation proteins	REAC:R-HSA-3232142	ubiquitination	4.503E-02	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,MDM2,NUP62,RAE1,NUP43,NUP54	12	up
synthesis of pips at the plasma membrane	REAC:R-HSA-1660499	cell organisation	4.974E-03	PLEKHA8,MTMR3,PIK3CB,RAB4A,PIK3CD,PIP4K2C,RAB14,PIK3R3,PTEN,PI4K2B,OCRL,PIK3R1,PLEKHA1,MTMR2,PIK3CG,MTMR9,ARF1,PIP5K1C,PLEKHA6	19	up
t cell activation	GO:0042110	leukocyte activation	2.076E-03	CDKN2A,SLC7A1,CBFB,IRF4,STAT3,IGF2,AKT1,PRDM1,CD44,PIK3CD,RASGRP1,ABL1,HSPD1,CD40LG,FADD,GRAP2,CD80,LFNG,BTN2A2,IL6,RSAD2,CCL5,ICAM1,IL23R,HLA-A,HLA-	79	up

				G,ADAM17,CD274,VSIR,PDCD1,TNFSF9,PAG1,GRB2,PAK2,FLOT2,AGER,PIK3R1,MYB,FKBP1A,SMAD7,CDC42,SOCS5,IL6ST,NLRP3,TOX,LEF1,ZAP70,SRC,TGFBR2,CEBPB,TFRC,IFNB1,PIK3CG,HMGB1,CD24,TNFRSF21,PLA2G2D,KIT,IL10,CD70,CASP8,TCF7,SOX4,LAX1,TNFRSF13C,NKAP,DLG5,RAG1,PRNP,CHD7,IRF1,ZBTB7B,CCR6,F2RL1,RHOH,SDC4,PAK3,ATP7A,IL15		
t cell differentiation	GO:0030217	cell differentiation	3.124E-02	CDKN2A,CBFB,IRF4,STAT3,PRDM1,PIK3CD,ABL1,FADD,CD80,LFNG,IL6,RSAD2,IL23R,HLA-G,ADAM17,VSIR,TNFSF9,MYB,SMAD7,SOCS5,NLRP3,TOX,LEF1,ZAP70,TGFBR2,IFNB1,HMGB1,KIT,TCF7,SOX4,NKAP,RAG1,CHD7,IRF1,ZBTB7B,CCR6,RHOH,ATP7A	38	up
t cell mediated immune response to tumor cell	GO:0002424	cellular response to external stimuli	3.967E-02	FBXO38,HSPD1,HLA-A,HMGB1	4	up
t cell mediated immunity	GO:0002456	leukocyte activation	9.502E-03	FBXO38,HSPD1,TRAF6,FADD,IL6,RSAD2,IL23R,HLA-A,HLA-G,FZD5,AGER,SMAD7,BTN3A3,MAP3K7,NLRP3,JAG1,IFNB1,HMGB1,TRAF2,CD70,EMP2,B2M,PVR	23	up
t cell proliferation	GO:0042098	cell proliferation	1.481E-02	CDKN2A,SLC7A1,IGF2,RASGRP1,CD40LG,FADD,CD80,BTN2A2,IL6,CCL5,IL23R,HLA-A,HLA-G,CD274,VSIR,TNFSF9,AGER,IL6ST,TGFBR2,CEBPB,TFRC,PIK3CG,HMGB1,CD24,TNFRSF21,PLA2G2D,IL10,CD70,TNFRSF13C,DLG5,PRNP,IRF1,ZBTB7B,SDC4,IL15	35	up
t cell receptor signalling pathway	KEGG:04660	leukocyte activation	1.434E-03	AKT1,TNF,MAPK14,PIK3CB,RAF1,PIK3CD,RASGRP1,RHOA,CD40LG,FOS,NFKB1,GRAP2,SOS1,KRAS,SOS2,PIK3R3,CDK4,VAV2,PDCD1,GRB2,PAK2,CHUK,PIK3R1,AKT3,CDC42,GSK3B,MAP3K7,VAV3,MAPK3,ZAP70,MAP3K14,MAP2K1,PLCG1,PPP3R1,IL10,BCL10,NRAS,MAPK1,PAK3	39	both
telomere maintenance via telomere lengthening	GO:0010833	telomere	2.539E-02	AURKB,TNKS1BP1,PARP1,HSP90AA1,CCT6A,HNRNPA1,HMBOX1,HNRNPA2B1,ATM,MRE11,MAPK3,SRC,CCT3,XRN1,RAD51,SLX4,MAPKAPK5,MAPK1,TERF2,ERCC4,CTC1,HNRNPC	22	up
temperature homeostasis	GO:0001659	homeostasis	1.666E-03	IRF4,EHMT1,STAT3,PCTP,JAK2,PTGES,IP6K1,TNF,NRDC,IGF1R,APC,CXCR4,PTGS2,DECR1,KDM6B,TLR4,NOTCH1,LNPEP,ADAM17,VEGFA,OGT,FLCN,RBPJ,FOXO1,NOVA2,TRPV2,CPT2,CEBPB,ACSL1,FH,MFN2,CIDEA,SIRT6,TLE3,PER2,GRB10,ZBTB7B,THRA,CD36,ADAMTS5,IL15,FFAR4	42	up
tfap2 (ap-2) family regulates transcription of growth factors and their receptors	REAC:R-HSA-8866910	signalling pathways	2.113E-03	ERBB2,EGFR,TGFA,VEGFA,TFAP2A,YY1,KIT,ESR1	8	up
tgf-β receptor signalling activates smads	REAC:R-HSA-2173789	TGF signalling	2.485E-05	SMAD4,PPP1CA,MTMR4,SMAD2,FURIN,SMAD3,FKBP1A,SMAD7,USP15,SMURF1,STRAP,TGFBR2,PPP1CC,PMEPA1,UBB,RPS27A,UBC	17	up
tgf-β receptor signalling in emt (epithelial to mesenchymal transition)	REAC:R-HSA-2173791	TGF signalling	2.428E-03	CGN,RHOA,FKBP1A,SMURF1,TGFBR2,F11R,UBB,RPS27A,UBC	9	up
tgf-β signalling pathway	KEGG:04350	TGF signalling	1.493E-04	MYC,E2F5,MAPK1,SP1,FST,BMPR2,EP300,RGMB,TGFBR1,TGFBR2,ID4,TGIF2,ID3,FBN1,ACVR1C,SMAD2,SMAD3,RHOA,ROCK1,SMAD9,THBS1,CREBBP,BMPR1A	23	both
thyroid cancer	KEGG:05216	cancer	8.829E-06	TP53,BAK1,CDKN1A,CCDC6,CCND1,KRAS,TPM3,RET,MYC,LEF1,MAPK3,MAP2K1,CTNNB1,GADD45A,BAX,TCF7,NRAS,TCF7L2,MAPK1	19	both
thyroid hormone signalling pathway	KEGG:04919	signalling pathways	5.450E-05	WNT4,MYC,MAPK1,NCOA1,ESR1,NOTCH1,EP300,MAP2K2,THRB,PDPK1,FOXO1,CCND1,HIF1A,AKT1,NOTCH4,NCOA3,KRAS,NOTCH2,MDM2,AKT2,AKT3,ATP1A1,RCAN2,MED17,CTNNB1,TP53,MED16,ACTG1,PLCD3,PLCE1,GSK3B,CREBBP	32	both
ticam1-dependent activation of irf3/irf7	REAC:R-HSA-9013973	IRF signalling	1.059E-02	IRF7,TRAF3,TLR3,TANK,UBB,RPS27A,UBC	7	up
ticam1, rip1-mediated ikk complex recruitment	REAC:R-HSA-168927	interferon signalling	9.655E-04	TRAF6,UBE2D3,UBE2V1,CHUK,BIRC3,BIRC2,TLR3,UBB,RPS27A,UBC,UBE2D2	11	up
ticam1,traf6-dependent induction of tak1 complex	REAC:R-HSA-9014325	interferon signalling	1.023E-03	TRAF6,TAB3,MAP3K7,TLR3,UBB,RPS27A,UBC,TAB2	8	up
tissue migration	GO:0090130	cell adhesion and migration	4.995E-03	ETS1,AKT1,ANGPT2,TNF,STARD13,CDH5,PLXND1,PIK3CB,PIK3CD,PLEKHG5,ABL1,RHOA,ROCK1,PTGS2,CARD10,PRKCE,ROBO1,NOTCH1,ADAM17,FGF2,KLF4,NRP1,PIK3R3,PTEN,VEGFA,MECP2,MAP2K3,EFNB2,KANK1,AMOT,AKT3,KDR,PLPP3,RTN4,BSG,RHOB,MEF2C,SP1,LGALS8,ITGB1,STAT5A,SCARB1,MET,CORO1B,SRC,STRAP,S100A2,GPI,SIRT1,RRAS,CD40,ITGB3,PLCG1,PIK3CG,HMGB1,GADD45A,ARF6,EPHA2,KIT,PRKD1,S100P,ZEB2,ACTC1,SASH1,EDN1,MCC,PTPRG,NUS1,PRKD2,PDGFB,EMP2,THBS1,EPB41L4B,ADAMTS9,ACTA1	75	both
tissue morphogenesis	GO:0048729	organogenesis	2.535E-02	VCL,SEMA4C,FZD4,TNF,STARD13,SIX1,SMO,PODXL,PSMB1,LIF,NRARP,CD44,PIK3CD,FZD6,SMAD4,LBX2,HMGA2,FGFR2,RHOA,KDM2B,MICAL2,LRP2,STAT1,MYLK,SMAD2,KDM6B,ROBO1,NOTCH1,DKK1,PHLDB2,WNT1,ITGA5,CD151,ADAM17,FZD5,FGF2,KLF4,NRP1,PTEN,SKI,AP2B1,VEGFA,PAFAH1B1,WNT7A,ARHGAP12,TFAP2A,RBPJ,LUZP1,PRICKLE2,NKD1,ITGA2,HEYL,FKBP1A,TGFBR3,SMAD7,CDC42,KDR,SMURF1,RET,SALL1,MTHFR,PSMB5,BSG,RHOB,MEF2C,ITGB1,MYC,AP2A1,MET,DLL1,TPM1,MDM4,ACTG1,TGFBR2,AP2M1,DSP,AP2A2,GATA4,ITGB3,CTNNB1,PKP2,SNAI1,BMP7,EPHA2,CSF1R,SIRT6,BCL10,SOX4,ACTC1,S1PR1,BMPR1A,PDPN,SOX11,HOXD11,ACVR1,DLC1,AHI1,PRKD2,PLET1,ACTB,SIX3,COL4A1,MTSS1,RAB10,ATP7A,ACTA1	106	both
tnf receptor superfamily (tnfsf) members mediating non-canonical nf-kb pathway	REAC:R-HSA-5676594	Nfκ	4.100E-03	CD40LG,BIRC3,MAP3K14,TRAF3,TRAF2,LTBR,LTA,BIRC2,TNFRSF13C	9	up
tnf signalling	REAC:R-HSA-75893	signalling pathways	5.016E-06	XIAP,TNFAIP3,TNF,FADD,ADAM17,CHUK,BAG4,CYLD,TAB3,MAP3K7,SPPL2A,BIRC3,TRAF2,RBCK1,TNFRSF1A,CASP8,BIRC2,OTUD7B,UBB,RPS27A,UBC,TAB2	22	up
tnf signalling pathway	KEGG:04668	signalling pathways	2.606E-02	MAPK1,MAPK14,TRAF3,RPS6KA5,CASP3,BAG4,NFKB1,AKT1,MMP3,MAP2K7,VCAM1,FOS,JUN,AKT2,CREB5,AKT3,CASP8,SOCS3,TRAF1,MAP3K8,ICAM1,IKBKG,PGAM5,ITCH,CXCL5	25	both
tnfr1-induced nfkb signalling pathway	REAC:R-HSA-5357956	Nfκ	2.485E-05	XIAP,TNFAIP3,TNF,CHUK,CYLD,TAB3,MAP3K7,BIRC3,TRAF2,RBCK1,TNFRSF1A,BIRC2,OTUD7B,UBB,RPS27A,UBC,TAB2	17	up
tnfr1-induced proapoptotic signalling	REAC:R-HSA-5357786	apoptosis	4.035E-03	TNFAIP3,TNF,FADD,CYLD,TRAF2,TNFRSF1A,CASP8,OTUD7B	8	up
toll like receptor 10 (tlr10) cascade	REAC:R-HSA-168142	TLR signalling	2.590E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	37	up
toll like receptor 2 (tlr2) cascade	REAC:R-HSA-181438	TLR signalling	6.484E-08	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,TLR2,IRAK1,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,TIRAP,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,SFTPA1,CD36,TAB2	42	up
toll like receptor 3 (tlr3) cascade	REAC:R-HSA-168164	TLR signalling	5.151E-11	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,FADD,IRAK1,IRF7,S100A12,UBE2D3,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,BIRC3,MAPK3,MAP2K1,TRAF3,SAA1,HMGB1,RIPK2,NOD1,CASP8,BIRC2,TLR3,TANK,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,UBE2D2,TAB2	46	up
toll like receptor 4 (tlr4) cascade	REAC:R-HSA-166016	TLR signalling	5.872E-10	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,TLR2,FADD,IRAK1,IRF7,ITGB2,TLR4,S100A12,UBE2D3,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,CD180,RPS6KA3,MEF2C,BIRC3,MAPK3,MAP2K1,MAP3K1,TRAF3,SAA1,HMGB1,RIPK2,NOD1,CASP8,BIRC2,TIRAP,TANK,CREB1,MAP2K4,UBB,MAPK1,PTPN4,RPS27A,UBC,RPS6KA5,SFTPA1,UBE2D2,CD36,TAB2	54	up

toll like receptor 5 (tlr5) cascade	REAC:R-HSA-168176	TLR signalling	2.590E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	37	up
toll like receptor 7/8 (tlr7/8) cascade	REAC:R-HSA-168181	TLR signalling	2.590E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,IRF7,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	39	up
toll like receptor 9 (tlr9) cascade	REAC:R-HSA-168138	TLR signalling	8.739E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,IRF7,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	39	up
toll like receptor tlr1:tlr2 cascade	REAC:R-HSA-168179	TLR signalling	6.484E-08	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,TLR2,IRAK1,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,TIRAP,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,SFTPA1,CD36,TAB2	42	up
toll like receptor tlr6:tlr2 cascade	REAC:R-HSA-168188	TLR signalling	7.240E-08	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,TLR2,IRAK1,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,TIRAP,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,CD36,TAB2	41	up
toll-like receptor cascades	REAC:R-HSA-168898	TLR signalling	6.451E-08	RPS6KA1,S100A8,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,TLR2,FADD,IRAK1,IRF7,ITGB2,TLR4,S100A12,UBE2D3,HSP90B1,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,CD180,RPS6KA3,MEF2C,BIRC3,MAPK3,MAP2K1,MAP3K1,TRAF3,SAA1,HMGB1,RIPK2,NOD1,CASP8,BIRC2,TIRAP,TLR3,TANK,CREB1,MAP2K4,UBB,MAPK1,PTPN4,RPS27A,UBC,RPS6KA5,SFTPA1,UBE2D2,CD36,TAB2	57	up
toll-like receptor signalling pathway	GO:0002224	TLR signalling	5.504E-08	S100A8,TNFAIP3,MFHAS1,HSPD1,IRAK2,TRAF6,TLR2,FADD,IRAK1,IRF7,RSAD2,ITGB2,PRKCE,TLR4,OTUD4,UBE2D3,COLEC12,HSP90B1,MAPKAPK2,DDX3X,CHUK,TAB3,RAB11FIP2,MAP3K7,RTN4,RPS6KA3,BIRC3,CD40,MAP3K1,TRAF3,HMGB1,RIPK2,BCL10,CASP8,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,TANK,UBB,IRF1,RPS27A,UBC,CXorf21,SFTPA1,UBE2D2,F2RL1,CD36,TNIP3,TAB2	51	up
toll-like receptor signalling pathway	GO:0002224	TLR signalling	5.504E-08	S100A8,TNFAIP3,MFHAS1,HSPD1,IRAK2,TRAF6,TLR2,FADD,IRAK1,IRF7,RSAD2,ITGB2,PRKCE,TLR4,OTUD4,UBE2D3,COLEC12,HSP90B1,MAPKAPK2,DDX3X,CHUK,TAB3,RAB11FIP2,MAP3K7,RTN4,RPS6KA3,BIRC3,CD40,MAP3K1,TRAF3,HMGB1,RIPK2,BCL10,CASP8,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,TANK,UBB,IRF1,RPS27A,UBC,CXorf21,SFTPA1,UBE2D2,F2RL1,CD36,TNIP3,TAB2	51	up
toll-like receptor signalling pathway	KEGG:04620	TLR signalling	5.504E-08	S100A8,TNFAIP3,MFHAS1,HSPD1,IRAK2,TRAF6,TLR2,FADD,IRAK1,IRF7,RSAD2,ITGB2,PRKCE,TLR4,OTUD4,UBE2D3,COLEC12,HSP90B1,MAPKAPK2,DDX3X,CHUK,TAB3,RAB11FIP2,MAP3K7,RTN4,RPS6KA3,BIRC3,CD40,MAP3K1,TRAF3,HMGB1,RIPK2,BCL10,CASP8,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,TANK,UBB,IRF1,RPS27A,UBC,CXorf21,SFTPA1,UBE2D2,F2RL1,CD36,TNIP3,TAB2	51	up
toll-like receptor signalling pathway	KEGG:04620	TLR signalling	5.504E-08	S100A8,TNFAIP3,MFHAS1,HSPD1,IRAK2,TRAF6,TLR2,FADD,IRAK1,IRF7,RSAD2,ITGB2,PRKCE,TLR4,OTUD4,UBE2D3,COLEC12,HSP90B1,MAPKAPK2,DDX3X,CHUK,TAB3,RAB11FIP2,MAP3K7,RTN4,RPS6KA3,BIRC3,CD40,MAP3K1,TRAF3,HMGB1,RIPK2,BCL10,CASP8,BIRC2,LILRA2,TIRAP,GRAMD4,TLR3,TANK,UBB,IRF1,RPS27A,UBC,CXorf21,SFTPA1,UBE2D2,F2RL1,CD36,TNIP3,TAB2	51	up
tor signalling	GO:0031929	signalling pathways	4.552E-02	LIN28A,AKT1,EIF4EBP1,SESN3,RPS6KB1,PRKAA1,FLCN,SH3BP4,DYRK3,PIP4P1,ATM,SIRT1,LARP1,RRAGD,RRAGA,RICTOR,SESN2,TREM2,FNIP1,EIF4EBP2,DDIT4,SIK3,SLC38A9,MAPKAPK5,TNFAIP8L1,SMG1,AKT1S1,SESN1	28	up
toxoplasmosis	KEGG:05145	viral of bacterial infection	1.151E-02	STAT3,XIAP,JAK2,AKT1,BCL2,TNF,MAPK14,ALOX5,LAMC2,CD40LG,TRAF6,NFKB1,TLR2,IRAK1,STAT1,TGFB1,TLR4,LDLR,MAP2K3,CHUK,HSPA8,AKT3,LAMC1,MAP3K7,ITGB1,ITGA6,BIRC3,MAPK3,CASP3,CD40,PIK3CG,CASP9,CYCS,TNFRSF1A,IL10,CASP8,BCL2L1,BIRC2,MAPK1,TAB2	40	both
tp53 regulates metabolic genes	REAC:R-HSA-5628897	P53 signalling	4.957E-05	PRDX2,TP53,AKT1,COX7C,PRKAG1,TNRC6B,COX2,AGO3,TNRC6A,AGO2,SESN3,YWHAB,PTEN,LRPPRC,PRKAA1,AGO1,AGO4,AKT3,YWHAQ,YWHAH,SFN,MOV10,GPI,RRAGD,RRAGA,TIGAR,TXNRD1,CYCS,SESN2,COX20,DDIT4,SLC38A9	32	both
tp53 regulates transcription of additional cell cycle genes whose exact role in the p53 pathway remain uncertain	REAC:R-HSA-6804115	cell cycle	2.698E-02	TP53,NPM1,BTG2,TNKS1BP1,CNOT6L,CNOT4,CDC25C,CNOT2,CNOT1	9	up
tp53 regulates transcription of caspase activators and caspases	REAC:R-HSA-6803207	caspase signalling pathway	2.113E-03	TP53,ATM,CASP1,CRADD,TP73,CASP6,APAF1,CASP10	8	up
tp53 regulates transcription of cell cycle genes	REAC:R-HSA-6791312	cell cycle	3.961E-07	E2F7,TP53,ARID3A,CCNE1,ZNF385A,NPM1,BTG2,TNKS1BP1,CDKN1A,CNOT6L,CCNA2,CDKN1B,CNOT4,CARM1,CDK1,CCNE2,CDK2,E2F1,CDC25C,SFN,GADD45A,BAX,CNOT2,AURKA,CCNB1,CNOT1	26	up
tp53 regulates transcription of cell death genes	REAC:R-HSA-5633008	apoptosis	6.290E-04	PMAIP1,TP53INP1,TP53,BBC3,CREBBP,TNFRSF10B,Fas,NDRG1,BIRC5,ATM,CASP1,CRADD,TP73,TNFRSF10A,BAX,CASP6,APAF1,TP53BP2,CASP10	19	up
tp53 regulates transcription of death receptors and ligands	REAC:R-HSA-6803211	apoptosis	4.207E-02	TP53,TNFRSF10B,Fas,TP73,TNFRSF10A,TP53BP2	6	up
tp53 regulates transcription of genes involved in cytochrome c release	REAC:R-HSA-6803204	P53 signalling	1.999E-02	TP63,TP53INP1,BID,PPP1R13B,ATM,PMAIP1,BBC3,TP53,CREBBP	9	both
tp53 regulates transcription of genes involved in g1 cell cycle arrest	REAC:R-HSA-6804116	cell cycle	2.064E-05	E2F7,TP53,ARID3A,CCNE1,ZNF385A,CDKN1A,CCNA2,CDKN1B,CCNE2,CDK2,E2F1	11	up
tp53 regulates transcription of genes involved in g2 cell cycle arrest	REAC:R-HSA-6804114	cell cycle	2.526E-03	TP53,ZNF385A,CARM1,CDK1,CDC25C,SFN,GADD45A,BAX,AURKA,CCNB1	10	up
traf6 mediated induction of nfkb and map kinases upon tlr7/8 or 9 activation	REAC:R-HSA-975138	MAPK signalling	5.836E-07	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,IRAK1,TLR4,S100A12,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,MAPK3,MAP2K1,MAP3K1,SAA1,HMGB1,RIPK2,NOD1,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,TAB2	38	up
traf6 mediated irf7 activation in tlr7/8 or 9 signalling	REAC:R-HSA-975110	IRF signalling	2.644E-02	TRAF6,IRAK1,IRF7,UBE2V1,UBB,RPS27A,UBC	7	up
traf6 mediated nf-kb activation	REAC:R-HSA-933542	Nfκ	2.311E-03	NKIRAS2,TRAF6,NFKB1,S100A12,CHUK,AGER,APP,MAP3K1,SAA1,HMGB1,TRAF2,MAVS	12	up
traf6-mediated induction of tak1 complex within tlr4 complex	REAC:R-HSA-937072	TLR signalling	2.428E-03	IRAK2,TRAF6,TLR4,TAB3,MAP3K7,UBB,RPS27A,UBC,TAB2	9	up
trail signalling	REAC:R-HSA-75158	signalling pathways	4.654E-03	TNFRSF10B,FADD,TNFRSF10A,CFLAR,CASP8,CASP10	6	up
transcription elongation from rna polymerase ii promoter	GO:0006368	transcription and translation	4.040E-02	ZMYND11,SUPT6H,ADRM1,CDC73,ELP2,AFF4,SUPT16H,CCNT1,SSRP1,CCNT2,RNF168,POLR2E,HEXIM1,NELFCD,SUPT5H,NCBP2,MLLT1,ELOA,ELL2,POLR2D,ELL	21	up
transcription initiation from rna polymerase ii promoter	GO:0006367	transcription and translation	2.284E-03	ESR1,HNF4G,NR4A2,TEAD3,GTF2H5,PPARA,NOTCH1,GTF2H1,RORA,THRB,HMGB1,POLR2D,CCND1,YAP1,SOX9,RARA,POLR2E,NR3C1,PPARG,PPM1D,MECP2,NOTCH4,PTEN,NOTCH2,NR6A1,MAZ,WWTR1,ZNF45,TAF13,DR1,MED17,CDKN1A,PPARGC1A,TP53,MED16,TAF8,SRF,MED7,NR2F6,PSMC4,CREBBP,E2F3	42	both
transcriptional activity of smad2/smad3:smad4 heterotrimer	REAC:R-HSA-2173793	SMAD activity	3.151E-06	MYC,PARP1,E2F5,SP1,SERPINE1,CCNK,CCNT2,TGIF2,WWTR1,SMAD2,SMAD3,SKI,CCNT1,TFDP2,UBE2D3	15	both

transcriptional misregulation in cancer	KEGG:05202	cancer	4.566E-04	CEBPA,TP53,DUSP6,FUS,SIX1,BAK1,IGF1R,TAF15,HMGA2,NFKB1,CDKN1A,BCL2A1,IL6,CXCL8,CCND2,CCNA2,ETV7,CDKN1B,CCNT1,RUNX2,ELK4,CCNT2,REL,ZBTB16,HOXA10,TCF3,RUNX1T1,MEF2C,ZEB1,LMO2,FOXO1,SP1,MDM2,ATM,MYC,MET,HDAC1,MYCN,BIRC3,SPI1,TGFBR2,CEBPB,CD40,GADD45A,FUT8,CDKN2C,BAX,CSF1R,MLLT1,BCL2L1,BIRC2,BCL11B,PER2	53	both
transcriptional regulation by e2f6	REAC:R-HSA-8953750	gene expression	1.092E-02	RBBP4,RYBP,EPC1,EED,EZH2,SUZ12,PHC3,CHEK1,PCGF2,CBX3,TFDP2,BMI1,RAD51	13	down
transcriptional regulation by mecp2	REAC:R-HSA-8986944	signalling pathways	2.415E-04	NCOR2,GRIN2A,AURKB,GPRIN1,TNRC6B,IRAK1,LBR,SOX2,AGO3,TNRC6A,AGO2,PTEN,SLC2A3,AGO1,AGO4,TBL1XR1,MEF2C,MET,HDAC1,DLL1,MOV10,CREB1,PTPN4,TRPC3	24	up
transcriptional regulation by runx1	REAC:R-HSA-8878171	RUNX metabolism	9.773E-03	CBFB,SMARCD2,LIFR,RYBP,CREBBP,KMT2D,PSMB1,ABL1,TNRC6B,CSNK2A1,CCND1,CCND2,AGO3,TNRC6A,AGO2,CCND3,CDK6,AGO1,CBX2,AGO4,CBX4,PHC3,MYB,SETD1B,TCF3,CBX6,PSMB5,YAP1,LMO2,SMARCD1,MYL9,TAL1,HDAC1,MOV10,HIST1H2AC,SPI1,SMARCC2,SRC,SOCS4,SMARCA4,SMARCC1,HIST1H2BJ,TP73,ARID1B,UBB,RPS27A,UBC,ESR1,SOCS3,ARID1A,THBS1	51	up
transcriptional regulation by runx2	REAC:R-HSA-8878166	RUNX metabolism	2.131E-02	CBFB,AKT1,PSMB1,MMP13,SMAD4,ABL1,CDKN1A,ITGBL1,BGLAP,STAT1,CCND1,ITGA5,CDK4,CDK1,AKT3,GSK3B,SMURF1,PSMB5,YAP1,MAPK3,SRC,AR,SATB2,BAX,CCNB1,UBB,MAPK1,RPS27A,UBC,ESR1,WWTR1,TWIST1	32	up
transcriptional regulation by runx3	REAC:R-HSA-8878159	RUNX metabolism	1.441E-03	CDKN2A,CBFB,TP53,CREBBP,PSMB1,SMAD4,CDKN1A,SPP1,CCND1,NOTCH1,KRAS,SMAD3,BCL2L11,RBPJ,SMURF1,PSMB5,YAP1,FOXO3,MDM2,MYC,JAG1,LEF1,SRC,CTNNB1,TCF7,UBB,TCF7L2,RPS27A,UBC,WWTR1,MAMLD1	31	up
transcriptional regulation by the ap-2 (tfap2) family of transcription factors	REAC:R-HSA-8864260	gene expression	1.273E-03	ERBB2,CREBBP,NPM1,HSPD1,EGFR,KCTD15,CDKN1A,TGFA,VEGFA,TFAP2A,MYC,YY1,KIT,ESR1	14	both
transcriptional regulation by tp53	REAC:R-HSA-3700989	P53 signalling	3.813E-11	CDKN2A,PMAIP1,TP53INP1,E2F7,PRDX2,EHMT1,TP53,BBC3,ARID3A,AKT1,COX7C,CCNE1,AURKB,PPP2CA,ZNF385A,CREBBP,PRKAG1,NPM1,MAPK14,TNFRSF10B,TAF15,PRDM1,BTG2,Fas,DYRK2,TNKS1BP1,TNRC6B,PIP4K2C,CSNK2A1,FOS,COX2,CDKN1A,MTA2,BRCA1,CNOT6L,CCNA2,AGO3,TNRC6A,CDKN1B,AGO2,CNOT4,SESN3,YWHAB,NDRG1,PTEN,CHEK1,LRPPRC,SUPT16H,CCNT1,PRKAA1,AGO1,SSRP1,AGO4,CARM1,BIRC5,TAF13,GATAD2A,CDK1,CCNT2,AKT3,YWHAQ,YWHAH,POLR2E,CCNE2,PPP2R5C,PIP4P1,CDK2,MDM2,E2F1,ATM,HDAC1,NELFCD,SUPT5H,MRE11,CDC25C,SFN,MDM4,MOV10,GPI,RRAGD,RRAGA,TIGAR,TXNRD1,CASP1,CRADD,CYCS,GADD45A,RICTOR,TP73,TNFRSF10A,SESN2,BAX,CASP6,APAF1,TP53BP2,CASP10,CNOT2,ELOA,AURKA,CDK5R1,CCNB1,COX20,DDIT4,GATAD2B,SLC38A9,MAPKAPK5,UBB,CHEK2,CNOT1,RPS27A,UBC,RFC2,JMY,POLR2D,BRPF1,ELL,HIPK1	117	both
transcriptional regulation by ventx	REAC:R-HSA-8853884	signalling pathways	6.008E-07	CDKN2A,EHMT1,TP53,TNRC6B,ANAPC16,NFKB1,IL6,CCND1,AGO3,TNRC6A,AGO1,AGO4,CDC27,FZR1,LEF1,MOV10,CEBPB,ANAPC5,CTNNB1,CSF1R,CDC23,TCF7L2	22	up
transcriptional regulation of granulopoiesis	REAC:R-HSA-9616222	cell proliferation	2.727E-02	CBFB,STAT3,CEBPA,IL6R,CDKN1A,CDK4,MYB,CDK2,E2F1,TAL1,MYC,LEF1,HIST1H2AC,SPI1,CEBPB,HIST1H2BJ,CREB1	17	up
transcriptional regulation of pluripotent stem cells	REAC:R-HSA-452723	cell proliferation	1.240E-02	STAT3,LIN28A,SMAD4,SMAD2,SOX2,FGF2,KLF4,SALL1,NANOG,POU5F1	10	up
transcriptional regulation of white adipocyte differentiation	REAC:R-HSA-381340	cell differentiation	2.619E-03	MED28,NCOA1,PPARA,EBF1,NR2F2,PCK1,EP300,CEBPA,NFKB1,LPL,CCND3,FABP4,PPARG,NCOA3,CHD9,CARM1,TBL1XR1,KLF4,MED17,PPARGC1A,CDK19,MED16,MED7,ZNF638,CREBBP	25	both
transforming growth factor β receptor signalling pathway	GO:0007179	TGF signalling	6.822E-04	PPARA,EP300,ADAM17,ZNF703,DAB2,PDPK1,PARD3,SIRT1,PTK2,FERMT2,TGFBR1,TGFBRAP1,TGFBR2,LATS2,ARRB2,MPP5,NLK,COL1A2,COL3A1,FOS,FBN1,JUN,SMAD2,SMAD3,SKI,APPL1,RHOA,HSP90AB1,FOXH1,SPRED3,GIPC1,ITGA3,LPXN,SMAD9,THBS1,CREBBP,BMPR1A,CITED2	38	both
translational initiation	GO:0006413	transcription and translation	2.083E-03	EIF5,PABPC1,RPL29,RPS12,RPL3,EIF4EBP1,RPS7,NPM1,EIF4E,RPS3A,RPLP0,RPL35A,PPP1CA,RPS28,CCL5,AGO2,RPS6KB1,DDX3X,EIF1AX,RPL14,EIF2B2,RPL10,RPL36,RPS5,LARP1,RPL37,KHDRBS1,RPS2,NCBP2,EIF4G1,CTIF,EIF2S2,RPL9,EIF1,PAIP1,RPL23,RPL24,EIF4EBP2,RPS15A,RPL4,RPS27A,PPP1R15B,HABP4,POLR2D,RPS14,EIF3A	46	up
translocation of slc2a4 (glut4) to the plasma membrane	REAC:R-HSA-1445148	signalling pathways	4.805E-03	AKT1,PRKAG1,EXOC7,RAB4A,TBC1D1,LNPEP,RAB14,YWHAB,MYO5A,KIF3B,RALGAPB,YWHAQ,YWHAH,TUBB2A,STXBP3,SLC2A4,VAMP2,SFN,ACTG1,SNAP23,MYO1C,EXOC5,ACTB,RAB10	24	up
transmembrane receptor protein serine/threonine kinase signalling pathway	GO:0007178	protein kinase activity	6.133E-05	BMPR1B,CGN,XIAP,JAK2,NUP93,CREBBP,CDH5,SMAD4,MTMR4,FBN1,DKK3,RHOA,FOS,LRP2,SMAD2,NOTCH1,DKK1,FURIN,WNT1,UBE2D3,ADAM17,BMP3,SKI,PDCD4,SMAD3,SPRED1,CRIM1,RUNX2,PPM1A,FLCN,RBPJ,ACVR2A,TMEM100,FKBP1A,TGFBR3,SMAD7,USP15,SMURF1,MAP3K7,LATS2,VASN,MAPK3,SRC,STRAP,SIRT1,TGFBR2,PEG10,INHBB,BMP7,GDF5,CIDEA,POU5F1,PPARA,HIVEP1,BMPR1A,SLC33A1,F11R,BMP8A,SOX11,PMEPA1,DAND5,ZFYVE9,UBB,PCSK6,ZBTB7A,SPART,RPS27A,UBC,ACVR1,LEFTY1,TRIM33,WWTR1,ZNF703,THBS1	74	both
transport of mature mrna derived from an intron-containing transcript	REAC:R-HSA-159236	cellular transport	2.368E-02	DHX38,CASC3,NUP93,NUP205,RANBP2,NUP37,NDC1,RNPS1,SRSF1,NUP50,POLDIP3,POM121C,THOC2,NUP62,NCBP2,RAE1,NUP43,SRSF2,NUP54,FYTTD1,DDX39A	21	up
transport of mature mrna derived from an intronless transcript	REAC:R-HSA-159231	cellular transport	3.766E-02	NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,NUP50,POM121C,NUP62,NCBP2,RAE1,NUP43,NUP54	13	up
transport of mature mrnas derived from intronless transcripts	REAC:R-HSA-159234	cellular transport	4.467E-02	NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,NUP50,POM121C,NUP62,NCBP2,RAE1,NUP43,NUP54	13	up
transport of mature transcript to cytoplasm	REAC:R-HSA-72202	cellular transport	4.207E-02	DHX38,CASC3,NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,RNPS1,SRSF1,NUP50,POLDIP3,POM121C,THOC2,NUP62,NCBP2,RAE1,NUP43,SRSF2,NUP54,FYTTD1,DDX39A	22	up
transport of ribonucleoproteins into the host nucleus	REAC:R-HSA-168271	cellular transport	4.101E-03	NUP93,NUP205,RANBP2,NUP37,NDC1,KPNB1,NUP50,KPNA1,POM121C,NUP62,RAE1,NUP43,NUP54	13	up
transport of the slbp dependant mature mrna	REAC:R-HSA-159230	cellular transport	9.986E-03	NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,NUP50,POM121C,NUP62,NCBP2,RAE1,NUP43,NUP54	13	up
transport of the slbp independent mature mrna	REAC:R-HSA-159227	cellular transport	7.580E-03	NUP93,NUP205,RANBP2,NUP37,EIF4E,NDC1,NUP50,POM121C,NUP62,NCBP2,RAE1,NUP43,NUP54	13	up
transport of virus	GO:0046794	viral of bacterial infection	2.440E-02	NUP98,FMR1,NUP62,NUP205,RAN,NMT2,KPNA1,EPS15,TSG101,POM121C,NUP50,NUP210,XPO1,CD209,NUP35,NUP85,TPCN2	17	both
tricuspid valve development	GO:0003175	organogenesis	4.578E-02	BMPR2,TGFBR2,ZFPM1,BMPR1A	4	down
trif-dependent toll-like receptor signalling pathway	GO:0035666	TLR signalling	2.614E-05	FADD,IRF7,TLR4,UBE2D3,CHUK,BIRC3,CD40,TRAF3,CASP8,BIRC2,TLR3,TANK,UBB,RPS27A,UBC,UBE2D2	16	up
trif(ticam1)-mediated tlr4 signalling	REAC:R-HSA-937061	TLR signalling	2.098E-10	RPS6KA1,PPP2CA,DUSP6,MAPK14,NKIRAS2,FOS,IRAK2,TRAF6,NFKB1,FADD,IRAK1,IRF7,TLR4,S100A12,UBE2D3,UBE2V1,MAPKAPK2,MAP2K3,BTRC,CHUK,AGER,TAB3,APP,MAP3K7,RPS6KA3,MEF2C,BIRC3,MAPK3,MAP2K1,TRAF3,SAA1,HMGB1,RIPK2,NOD1,CASP8,BIRC2,TANK,CREB1,MAP2K4,UBB,MAPK1,RPS27A,UBC,RPS6KA5,UBE2D2,TAB2	46	up
trna transport	GO:0051031	cellular transport	6.173E-03	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,NUP62,NUP98,YBX1,RAE1,NUP43,RAN,NUP54	14	up

trna-containing ribonucleoprotein complex export from nucleus	GO:0071431	protein metabolism	8.092E-03	NUP93,NUP205,RANBP2,NUP37,NDC1,NUP50,POM121C,NUP62,NUP98,RAE1,NUP43,RAN,NUP54	13	up
tube formation	GO:0035148	organogenesis	2.036E-02	SEMA4C,SIX1,PODXL,PIK3CD,FGFR2,KDM2B,LRP2,NOTCH1,DICER1,FGF2,SKI,VEGFA,LUZP1,MTHFR,BMP7,BCL10,SOX4,SOX11,DLC1	19	both
tuberculosis	KEGG:05152	viral of bacterial infection	1.358E-03	VDR,SPHK1,JAK2,AKT1,BCL2,TNF,CREBBP,MAPK14,RAF1,CEBPG,HSPD1,RHOA,IRAK2,TRAF6,NFKB1,TLR2,FADD,IRAK1,STAT1,TGFB1,IL6,ITGB2,TLR4,LAMP2,AKT3,MAPK3,SRC,CASP3,CEBPB,IFNB1,CASP9,CYCS,BAX,RIPK2,PPP3R1,TNFRSF1A,IL10,BCL10,CASP8,APAF1,CASP10,TIRAP,CREB1,NFYB,RAB5B,RFXAP,MAPK1,ATP6V0D1	48	up
tumor necrosis factor-mediated signalling pathway	GO:0033209	signalling pathways	1.981E-02	SPHK1,TP53,JAK2,TNFAIP3,TNF,PSMB1,CD40LG,TRAF6,STAT1,ADAM17,TNFSF9,CPNE1,CHUK,BAG4,CYLD,PSMB5,FOXO3,SPPL2A,TRAIP,TNFRSF6B,BIRC3,CD40,MAP3K14,TRAF3,HIST1H2BJ,CASP1,TRAF2,RBCK1,LTBR,FASLG,TNFRSF1A,LTA,CD70,CASP8,CD27,BIRC2,TNFRSF13C,F2RL1,HIPK1	39	up
type i interferon production	GO:0032606	interferon signalling	1.575E-04	TNFAIP3,DHX33,PCBP2,CREBBP,HSPD1,NFKB1,TLR2,IRAK1,ISG15,STAT1,IRF7,TLR4,DTX4,DDX3X,CHUK,CYLD,REL,POLR2E,C6orf106,POLR3G,MRE11,YY1,POLR3E,TRAF3,CTNNB1,RIPK2,NLRC5,IL10,LRRFIP1,TIRAP,TLR3,MAVS,IRF1,RNF125,UBA7,G3BP1,PPM1B	37	up
type i interferon signalling pathway	GO:0060337	interferon signalling	4.002E-02	IRF4,IFI27,IFIT3,FADD,IRAK1,ISG15,IFITM3,IFITM1,STAT1,IRF7,MX2,OASL,RSAD2,IFIT1,HLA-A,HLA-G,HLA-C,TTLL12,IFNB1,NLRC5,STAT2,MAVS,IRF1	23	up
type ii diabetes mellitus	KEGG:04930	endocrine system	6.532E-03	PKM,TNF,PIK3CB,PIK3CD,HK2,PRKCE,IRS1,PIK3R3,PRKCD,INSR,PIK3R1,SLC2A4,MAPK3,SOCS4,MAPK1,SOCS3	16	up
tyrosine phosphorylation of stat protein	GO:0007260	phosphorylation	3.645E-02	NF2,STAT3,JAK2,EPO,PPP2CA,TNF,IL6R,LIF,ERBB4,IL6,CCL5,IL23R,FGFR3,IL6ST,CD40,CSF1R,KIT,TNFRSF1A,SH2B3,SOCS3,IL15	21	up
ubiquitin mediated proteolysis	KEGG:04120	ubiquitination	1.259E-03	XIAP,HUWE1,PIAS3,UBA6,TRAF6,BRCA1,UBE2D3,BTRC,CUL3,UBE2Q1,UBE4A,UBE3C,CUL2,ANAPC13,CDC27,UBE2Q2,SMURF1,UBE2H,FBXW7,MDM2,UBE2S,CDC20,FZR1,BIRC3,ANAPC5,BIRC6,MAP3K1,UBA2,CDC23,BIRC2,UBE2Z,UBB,TRIM37,RPS27A,UBC,UBE2D2,MGRN1,SOCS3,UBA7,HERC2	40	up
unwinding of dna	REAC:R-HSA-176974	cell cycle	4.207E-02	MCM4,MCM2,MCM7,MCM6,MCM3,MCM5	6	up
urogenital system development	GO:0001655	organogenesis	4.977E-02	ANGPT2,SIX1,ENPEP,IL6R,SMO,PODXL,LIF,FGFR2,STAT1,FGF2,VEGFA,TFAP2A,FLCN,SEC61A1,ZBTB16,RET,SALL1,MEF2C,MYC,JAG1,DLL1,PDGFRB,PDGFRA,CTNNB1,BAG6,CD24,BMP7,WDR77,AGTR1,SOX4,HOXD11,AHI1,PDGFB,HAS2,COL4A1,MTSS1	36	up
vacuolar transport	GO:0007034	cellular transport	4.445E-02	VPS4B,SCARB2,CHMP3,VPS51,SORT1,VPS37B,SNAPIN,RAB12,ATG14,VPS37A,CHMP4B,LAMP2,VPS4A,HSPA8,AP3M1,TRAK1,GGA3,CLU,SMURF1,SNX16,RHOB,CACNG8,CHMP2B,ALS2,VPS37D,BECN1,GNPTAB,KIF13A,ATP6V0D1,MGRN1,DTX3L,TMEM50B	32	up
vacuole organisation	GO:0007033	cell organisation	3.073E-02	TP53INP1,SCARB2,TMEM9,MTMR3,PIP4K2C,ATG9A,PACS2,RAB14,RAB34,SNAPIN,ATG14,RAB1B,CHMP4B,GABARAPL1,STX17,RAB23,VPS4A,TBC1D14,WIPI2,GABARAP,SMURF1,TPCN2,RAB3GAP2,ATG5,UBQLN2,MFN2,RALB,BECN1,ATG7,UBXN2B,GNPTAB,CXorf21,TPP1,FIG4,CCDC115,RAB1A	36	up
vascular endothelial growth factor receptor signalling pathway	GO:0048010	signalling pathways	1.576E-02	MAPK14,PIK3CB,RHOA,ROCK1,WASF2,HSP90AA1,ITGA5,NRP1,VEGFA,VAV2,MAPKAPK2,PAK2,PIK3R1,NCKAP1,CDC42,KDR,CRK,VAV3,SRC,ITGB3,AXL,PRKD1,CYBB,GRB10,PRKD2	25	up
vegf signalling pathway	KEGG:04370	signalling pathways	6.578E-05	SPHK1,PLA2G4F,AKT1,MAPK14,PIK3CB,RAF1,PIK3CD,PTGS2,KRAS,PIK3R3,VEGFA,MAPKAPK2,PIK3R1,AKT3,CDC42,KDR,MAPK3,SRC,MAP2K1,PLCG1,CASP9,PPP3R1,NRAS,MAPK1	24	up
vegfa-vegfr2 pathway	REAC:R-HSA-4420097	EGFR signalling	1.441E-03	SPHK1,AKT1,CDH5,MAPK14,PIK3CB,RHOA,ROCK1,WASF2,HSP90AA1,VAV2,MAPKAPK2,PAK2,PRKCD,ITPR1,PIK3R1,AKT3,NCKAP1,CDC42,KDR,CRK,VAV3,ACTG1,ITGB3,PLCG1,CTNNB1,AXL,RICTOR,CYBB,NRAS,ACTB,PAK3	31	up
vegfr2 mediated vascular permeability	REAC:R-HSA-5218920	EGFR signalling	4.503E-02	AKT1,CDH5,HSP90AA1,VAV2,PAK2,AKT3,VAV3,CTNNB1,RICTOR,PAK3	10	up
ventricular cardiac muscle tissue development	GO:0003229	organogenesis	1.039E-02	SMAD4,FGFR2,LRP2,NOTCH1,RBPJ,FKBP1A,TGFBR3,SMAD7,TPM1,DSP,PKP2,BMPR1A,ADAMTS9	13	up
ventricular compact myocardium morphogenesis	GO:0003223	organogenesis	3.967E-02	LRP2,TGFBR3,DSP,BMPR1A	4	up
ventricular septum development	GO:0003281	organogenesis	4.664E-03	SMAD4,FGFR2,ROBO1,NOTCH1,HEYL,TGFBR3,SMAD7,SALL1,MDM4,TGFBR2,GATA4,SOX4,SOX11,DAND5,ACVR1	15	up
ventricular septum morphogenesis	GO:0060412	organogenesis	1.831E-02	SMAD4,FGFR2,ROBO1,NOTCH1,HEYL,TGFBR3,SMAD7,TGFBR2,SOX4,SOX11,ACVR1	11	up
viral carcinogenesis	KEGG:05203	viral of bacterial infection	2.959E-06	CDKN2A,PMAIP1,PKM,STAT3,TP53,HNRNPK,CCNE1,BAK1,CREBBP,PIK3CB,PIK3CD,RHOA,NFKB1,CDKN1A,IRF7,CCND1,CCND2,CCNA2,HLA-A,KRAS,HLA-G,CDKN1B,HLA-C,PIK3R3,YWHAB,CDK4,CHEK1,CCND3,CDK6,MAPKAPK2,DDX3X,GRB2,RBPJ,CDK1,PIK3R1,REL,TBPL1,YWHAQ,YWHAH,CCNE2,CDC42,IL6ST,CDK2,MDM2,STAT5A,HDAC1,CDC20,MAPK3,SRC,CASP3,UBR4,TRAF3,HIST1H2BJ,TRAF2,BAX,LTBR,CASP8,NRAS,GTF2A1,CREB1,GTF2E1,MAPK1,ATP6V0D1	63	both
viral gene expression	GO:0019080	gene expression	5.899E-07	MON1B,NUP93,RPL29,RPS12,RPL3,NUP205,PCBP2,RANBP2,REST,NUP37,RPS7,RPS3A,RPLP0,RPL35A,PTBP1,HMGA2,NDC1,RPS28,IFITM3,CCL5,FURIN,TARBP2,CCL4,CCNT1,NUCKS1,CCNT2,RPL14,NUP50,POLR2E,RPL10,RPL36,POM121C,RPS5,SP1,HEXIM1,CCL3,HDAC1,NELFCD,SUPT5H,RRP1B,LEF1,NUP62,UBP1,RPL37,RPS2,NUP98,SMARCA4,RAE1,RPL9,NUP43,SPCS3,RPL23,RPL24,RPS15A,RPL4,RPS27A,POLR2D,NUP54,RPS14,EIF3A	60	up
viral genome replication	GO:0019079	viral of bacterial infection	2.988E-02	PABPC1,TNF,PCBP2,HMGA2,IFI27,IFIT5,ISG15,IFITM3,IFITM1,SLPI,OASL,RSAD2,CCL5,IFIT1,CXCL8,SETDB1,TARBP2,SRPK1,NUCKS1,DDX3X,TBC1D20,CDC42,NFIA,LARP1,IFNB1,ADARB1,PPARA,APOBEC3F,MAVS,TOP2A	30	up
viral life cycle	GO:0019058	viral of bacterial infection	1.192E-04	LARP1,TRIM27,NUP98,DDX3X,FBXL2,PDE12,VAPA,FMR1,CHMP3,ZNF502,PPARA,SPCS1,USP6NL,NUP62,APOBEC3C,NUP205,TRIM13,TRIM38,PLSCR1,DEK,ROCK2,RAN,CCNK,NMT2,KPNA1,CHMP2B,GRK2,HMGA2,EPS15,TSG101,CDC42,DDX6,POM121C,NUP50,CHMP4B,NUP210,HSP90AB1,LRSAM1,NUCKS1,RAB7A,ICAM1,XPO1,CHMP1B,TMPRSS4,EIF2AK2,CD209,CD4,SLPI,NUP35,PABPC1,APOBEC3F,ZNF639,NUP85,ITCH,TPCN2,ZC3HAV1,ILF3	57	both
viral myocarditis	KEGG:05416	viral of bacterial infection	1.467E-02	ABL1,CD40LG,CD80,ITGB2,CCND1,ICAM1,HLA-A,HLA-G,HLA-C,ABL2,ACTG1,CASP3,CD40,EIF4G1,CASP9,CYCS,CASP8,ACTB	18	up
viral process	GO:0016032	viral of bacterial infection	4.590E-03	MON1B,VPS4B,TP53,CHMP3,PABPC1,NUP93,TNF,RPL29,RPS12,RPL3,NUP205,PCBP2,RANBP2,REST,NUP37,RPS7,RPS3A,RPLP0,RPL35A,PTBP1,HMGA2,HMGA1,NDC1,RPS28,KPNB1,CXCR4,TRIM22,IFI27,IFIT5,ISG15,IFITM3,IFITM1,SLPI,STAT1,IRF7,OASL,RSAD2,CCL5,IFIT1,CXCL8,ICAM1,KPNA4,FURIN,VPS37B,DDX6,SETDB1,RAB1B,VPS37A,TARBP2,AP2B1,SRPK1,CHMP4B,CCL4,CCNT1,TRIM35,NUCKS1,DDX3X,PAK2,HCFC2,VPS4A,CCNT2,RPL14,INSR,NUP50,POLR2E,TBC1D20,CDC42,RPL10,RPL36,KPNA1,KPNA3,BSG,POM121C,RPS5,SP1,NFIA,HEXIM1,CCL3,CHMP2B,CFL1,AP2A1,HDAC1,NELFCD,SUPT5H,RRP1B,LEF1,SNX3,VPS37D,TPCN2,NUP62,AP2M1,UBP1,LARP1,RPL37,RPS2,IFNB1,AP2A2,RRAGA,ITGB3,NUP98,SMARCA4,AXL,RAE1,ATG7,ADARB1,PPARA,CASP8,BCL2L1,ARF1,RPL9,APOBEC3F,NUP43,SPCS3,RPL23,RPL24,UBB,RPS15A,RPL4,MAVS,RPS27A,IGF2R,UBC,RAN,POLR2D,NUP54,RPS14,EIF3A,PABPN1,B2M,KPNA2,RAB1A,TOP2A	132	both
viral transcription	GO:0019083	viral of bacterial infection	1.843E-06	MON1B,NUP93,RPL29,RPS12,RPL3,NUP205,RANBP2,REST,NUP37,RPS7,RPS3A,RPLP0,RPL35A,HMGA2,NDC1,RPS28,IFITM3,CCL5,TARBP2,CCL4,CCNT1,NUCKS1,CCNT2,RPL14,NUP50,POLR2E,RPL10,RPL36,POM121C,RPS5,SP1,HEXIM1,CCL3,HDAC1,NELFCD,SUPT5H,RRP1B,LEF1,NUP62,UBP1,RPL37,RPS2,NUP98,SMARCA4,RAE1,RPL9,NUP43,RPL23,RPL24,RPS15A,RPL4,RPS27A,POLR2D,NUP54,RPS14	55	up

virion assembly	GO:0019068	viral of bacterial infection	4.664E-03	VPS4B,CHMP3,VPS37B,DDX6,RAB1B,VPS37A,CHMP4B,VPS4A,TBC1D20,CHMP2B,VPS37D,UBB,RPS27A,UBC,RAB1A	15	up
vitamin metabolic process	GO:0006766	metabolic process	4.428E-02	CD320,VDR,SHMT1,PSAT1,TNF,SLC19A1,MMAB,PDZD11,CYP24A1,ABCC1,NFKB1,LRP2,SLC2A3,RFK,PNPO,CYP26B1,TKTL1,MTHFR,CYB5A,PDXK,SNAI1,RBP2,AASDHPPT,SLC25A32,SLC46A1,PCCB,PCCA,CYP4F11,MTHFD2	29	up
vldlr internalisation and degradation	REAC:R-HSA-8866427	lipid metabolism	4.207E-02	AP2B1,AP2A1,AP2M1,AP2A2,MYLIP,CLTA	6	up
vpr-mediated nuclear import of pics	REAC:R-HSA-180910	cellular transport	7.580E-03	NUP93,NUP205,RANBP2,NUP37,HMGA1,NDC1,NUP50,KPNA1,POM121C,NUP62,RAE1,NUP43,NUP54	13	up
wnt signalling pathway	KEGG:04310	Wnt signalling	3.757E-03	WNT4,SOX4,RSPO1,DDX3X,ESR1,NR4A2,APC,GNAQ,PSMB9,CPE,AGO3,TRABD2A,XIAP,KREMEN1,TNRC6B,ZNF703,DAB2,HMGXB4,AGO4,BICC1,COL1A1,GID8,TERT,ADGRA2,SOX9,NFKB1,CBY1,CCAR2,SNAI2,AGO1,FERMT2,FOXL1,PTEN,CCDC88C,CAPRIN2,CSNK1A1,LATS2,ARRB2,PLPP3,GSKIP,TBL1XR1,NLK,CTNND1,IGFBP1,CDC42,HECW1,AMFR,AMER1,WWTR1,OTULIN,CTNNBIP1,LRP6,FZD5,TIAM1,FZD4,FRAT2,TMEM237,PPP3R1,SKI,SOX2,PRICKLE1,RHOA,CTNNB1,CSNK2A1,ITGA3,CDC73,DVL3,EGF,FZD7,USP34,WNK1,SHISA2,PSMC4,MAGI2,WNT5A,TMEM170B,GSK3B,PSMD3,UBE2B,PPP1CA,PFN1,DVL1	82	both
wnt signalling pathway	GO:0016055	Wnt signalling	3.757E-03	WNT4,SOX4,RSPO1,DDX3X,ESR1,NR4A2,APC,GNAQ,PSMB9,CPE,AGO3,TRABD2A,XIAP,KREMEN1,TNRC6B,ZNF703,DAB2,HMGXB4,AGO4,BICC1,COL1A1,GID8,TERT,ADGRA2,SOX9,NFKB1,CBY1,CCAR2,SNAI2,AGO1,FERMT2,FOXL1,PTEN,CCDC88C,CAPRIN2,CSNK1A1,LATS2,ARRB2,PLPP3,GSKIP,TBL1XR1,NLK,CTNND1,IGFBP1,CDC42,HECW1,AMFR,AMER1,WWTR1,OTULIN,CTNNBIP1,LRP6,FZD5,TIAM1,FZD4,FRAT2,TMEM237,PPP3R1,SKI,SOX2,PRICKLE1,RHOA,CTNNB1,CSNK2A1,ITGA3,CDC73,DVL3,EGF,FZD7,USP34,WNK1,SHISA2,PSMC4,MAGI2,WNT5A,TMEM170B,GSK3B,PSMD3,UBE2B,PPP1CA,PFN1,DVL1	82	both
wnt signalling pathway, calcium modulating pathway	GO:0007223	Wnt signalling	3.204E-05	FZD4,FZD6,TNRC6B,AGO3,DKK1,FZD5,TNRC6A,AGO2,AGO1,GNB1,AGO4,MAP3K7,LEF1,MOV10,CTNNB1,PPP3R1,TCF7L2,PLCB1	18	up
wnt5a-dependent internalization of fzd2, fzd5 and ror2	REAC:R-HSA-5140745	Wnt signalling	1.704E-02	FZD5,AP2B1,AP2A1,CLTB,AP2M1,AP2A2,CLTA	7	up
wnt5a-dependent internalization of fzd4	REAC:R-HSA-5099900	Wnt signalling	3.715E-02	FZD4,AP2B1,AP2A1,CLTB,AP2M1,AP2A2,CLTA	7	up
wound healing	GO:0042060	diseases	1.226E-05	VCL,ERBB2,JAK2,PABPC4,TNFAIP3,TNF,PIK3CB,ERBB3,CD44,RAF1,ALOX5,EHD1,RHOA,CD40LG,MYLK,IL6,PRKCE,TLR4,PLAUR,PHLDB2,ITGA5,CD151,ADAM17,FGF2,PTEN,VEGFA,SMAD3,WNT7A,VAV2,ALOX12,DOCK11,RCOR1,PRKAR2A,GNB1,MAFK,KANK1,PRKCD,ENTPD1,ITPR1,CASK,PIK3R1,ITGA2,CDC42,KDR,STXBP3,CRK,CAPZA2,PLPP3,F3,ITGB1,MYL9,SCARB1,HDAC1,VAV3,HNF4A,TPM1,ACTG1,CORO1B,VPS45,MAPK3,SRC,PDGFRA,CAPZB,METAP1,DSP,CD40,MYOF,IFNB1,GATA4,ITGB3,MFN2,AXL,PIK3CG,SAA1,DGKZ,FUT10,CFLAR,GGCX,SH2B3,GATA6,F11R,PDPN,AKAP10,GNAQ,DCBLD2,MAPK1,EDN1,IRF1,ENPP4,TRPC3,EREG,F2RL1,CD36,UBASH3B,PDGFB,CBX5,PLET1,CSRP1,CYP4F11,TRIM72,ACTB,THBS1,DGKB,DGKI,LMAN1,EPB41L4B	106	up
yersinia infection	KEGG:05135	viral of bacterial infection	6.143E-09	RPS6KA1,AKT1,TNF,MAPK14,PIK3CB,PIK3CD,RHOA,FOS,ROCK1,TRAF6,NFKB1,IRAK1,WASF2,IL6,CXCL8,TLR4,WASL,ITGA5,PIK3R3,ACTR3B,ACTR2,VAV2,MAP2K3,CHUK,CRKL,PIK3R1,AKT3,CDC42,GSK3B,MAP3K7,CRK,RPS6KA3,NLRP3,ITGB1,VAV3,ACTG1,MAPK3,ZAP70,SRC,MAP2K1,IFNB1,PLCG1,CASP1,TRAF2,ARF6,IL10,MAP2K4,GNAQ,PIP5K1C,MAPK1,WIPF2,ACTB,TAB2	53	both

*for pathways enriched by both gene lists, the P values represents the lower P value of both genes list

Supplementary Table 3: Pathway enrichment analysis of the six significantly dysregulated miRNAs in the blood for targeted genes highly expressed in the brain						
database code	pathway name	P value (FDR)	genes intersection	cluster	mirnas	# mirnas
GO:1905710	positive regulation of membrane permeability	0.005	GSK3B,SLC25A5,YWHAE,BLOC1S2	cellular architecture	hsa-miR-26a-5p	1
REAC:R-HSA-975110	TRAF6 mediated IRF7 activation in TLR7/8 or 9 signaling	0.006	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0006476	protein deacetylation	0.006	RCOR1,PHB,SFPQ,MTA3	protein synthesis	hsa-miR-26a-5p	1
GO:0090559	regulation of membrane permeability	0.006	GSK3B,SLC25A5,YWHAE,BLOC1S2	cellular architecture	hsa-miR-26a-5p	1
REAC:R-HSA-9006925	Intracellular signaling by second messengers	0.007	GSK3B,RPS27A,TNRC6B,RCOR1,MDM2,PPP2R5D,MTA3,PRKX	cellular signaling	hsa-miR-146a-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-9006925	Intracellular signaling by second messengers	0.007	GSK3B,RPS27A,TNRC6B,RCOR1,MDM2,PPP2R5D,MTA3,PRKX	cellular signaling	hsa-miR-146a-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
GO:0098732	macromolecule deacylation	0.007	RCOR1,PHB,SFPQ,MTA3	protein synthesis	hsa-miR-26a-5p	1
GO:1905214	regulation of RNA binding	0.009	CDK9,NUCKS1	transcription and splicing	hsa-miR-26a-5p	1
REAC:R-HSA-1257604	PIP3 activates AKT signaling	0.009	GSK3B,RPS27A,TNRC6B,RCOR1,MDM2,PPP2R5D,MTA3	tyrosine kinase signaling	hsa-miR-26a-5p	1
REAC:R-HSA-212165	Epigenetic regulation of gene expression	0.009	GSK3B,UBTF,TDG,MTA3,POLR2E	epigenetic changes	hsa-miR-26a-5p	1
REAC:R-HSA-3700989	Transcriptional Regulation by TP53	0.009	CCNE1,RPS27A,YWHAE,TNRC6B,MDM2,CDK9,POLR2E,COX5A	transcription and splicing	hsa-miR-26a-5p, hsa-miR-29c-3p	2
GO:0016032	viral process	0.013	RPS27A,DDB1,PDE12,PHB,CDK9,POLR2E,NUCKS1	viral processes	hsa-miR-26a-5p	1
GO:0031570	DNA integrity checkpoint	0.014	MDM2,CNOT4,CDC5L,CNOT2	cell cycle	hsa-miR-363-3p	1
GO:0044783	G1 DNA damage checkpoint	0.015	MDM2,CNOT4,CNOT2	cell cycle	hsa-miR-363-3p	1
REAC:R-HSA-198323	AKT phosphorylates targets in the cytosol	0.017	AKT3,MDM2	cellular signaling	hsa-miR-26a-5p, hsa-miR-29c-3p	2
REAC:R-HSA-6804759	Regulation of TP53 Activity through Association with Co-factors	0.017	PPP1R13B,AKT3	cellular signaling	hsa-miR-29c-3p	1
GO:0006283	transcription-coupled nucleotide-excision repair	0.021	RPS27A,DDB1,POLR2E	cell cycle	hsa-miR-26a-5p	1
GO:0090305	nucleic acid phosphodiester bond hydrolysis	0.021	RPS27A,DDB1,PDE12,CPSF2	cell cycle	hsa-miR-26a-5p	1
GO:0019058	viral life cycle	0.023	RPS27A,DDB1,PDE12,PHB,NUCKS1	viral processes	hsa-miR-26a-5p	1
REAC:R-HSA-8849470	PTK6 Regulates Cell Cycle	0.024	CCNE1	cell cycle	hsa-miR-144-5p	1
GO:0046677	response to antibiotic	0.026	MDM2,RPL23	response to external stimuli	hsa-miR-363-3p	1
REAC:R-HSA-166166	MyD88-independent TLR4 cascade	0.026	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1

REAC:R-HSA-168138	Toll Like Receptor 9 (TLR9) Cascade	0.026	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
REAC:R-HSA-168164	Toll Like Receptor 3 (TLR3) Cascade	0.026	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
REAC:R-HSA-168181	Toll Like Receptor 7/8 (TLR7/8) Cascade	0.026	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
REAC:R-HSA-9006925	Intracellular signaling by second messengers	0.026	IRAK1,MTA2,PRKCE	cellular signaling	hsa-miR-146a-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-9006925	Intracellular signaling by second messengers	0.026	IRAK1,MTA2,PRKCE	cellular signaling	hsa-miR-146a-5p, hsa-miR-146a-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-937061	TRIF(TICAM1)-mediated TLR4 signaling	0.026	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0000956	nuclear-transcribed mRNA catabolic process	0.027	CNOT4,CNOT2,RPL23,RPL24	cell cycle	hsa-miR-363-3p	1
GO:0002221	pattern recognition receptor signaling pathway	0.029	IRAK1,IRF7,PRKCE	cellular signaling	hsa-miR-146a-5p	1
GO:0002224	toll-like receptor signaling pathway	0.029	IRAK1,IRF7,PRKCE	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0002755	MyD88-dependent toll-like receptor signaling pathway	0.029	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0002756	MyD88-independent toll-like receptor signaling pathway	0.029	IRF7,PRKCE	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0034142	toll-like receptor 4 signaling pathway	0.029	IRAK1,PRKCE	toll like receptor signaling pathway	hsa-miR-146a-5p	1
REAC:R-HSA-166016	Toll Like Receptor 4 (TLR4) Cascade	0.030	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0051702	biological process involved in interaction with symbiont	0.031	DDB1,PHB,NUCKS1	cellular signaling	hsa-miR-26a-5p	1
REAC:R-HSA-110357	Displacement of DNA glycosylase by APEX1	0.033	MBD4	cell cycle	hsa-miR-146a-5p	1
REAC:R-HSA-168898	Toll-like Receptor Cascades	0.033	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
REAC:R-HSA-3134963	DEx/H-box helicases activate type I IFN and inflammatory cytokines production	0.033	IRF7	cytokine	hsa-miR-146a-5p	1
REAC:R-HSA-3304351	Signaling by TGF-beta Receptor Complex in Cancer	0.033	SMAD2	cytokine	hsa-miR-146a-5p	1
REAC:R-HSA-2559585	Oncogene Induced Senescence	0.033	RPS27A,TNRC6B,MDM2	senescence	hsa-miR-26a-5p	1
GO:0019080	viral gene expression	0.033	RPS27A,CDK9,POLR2E,NUCKS1	viral processes	hsa-miR-26a-5p	1
GO:0070911	global genome nucleotide-excision repair	0.033	RPS27A,DDB1	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-114452	Activation of BH3-only proteins	0.034	PPP1R13B,AKT3	apoptosis and senescence	hsa-miR-29c-3p	1

REAC:R-HSA-2173796	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	0.034	CCNT2,WWTR1	transcription and splicing	hsa-miR-29c-3p	1
REAC:R-HSA-3700989	Transcriptional Regulation by TP53	0.034	PPP1R13B,AKT3,CCNT2,MDM2	transcription and splicing	hsa-miR-26a-5p, hsa-miR-29c-3p	2
REAC:R-HSA-5633007	Regulation of TP53 Activity	0.034	PPP1R13B,AKT3,MDM2	apoptosis and senescence	hsa-miR-29c-3p	1
REAC:R-HSA-5674400	Constitutive Signaling by AKT1 E17K in Cancer	0.034	AKT3,MDM2	signaling activity	hsa-miR-29c-3p	1
REAC:R-HSA-6804757	Regulation of TP53 Degradation	0.034	AKT3,MDM2	apoptosis and senescence	hsa-miR-29c-3p	1
REAC:R-HSA-6806003	Regulation of TP53 Expression and Degradation	0.034	AKT3,MDM2	apoptosis and senescence	hsa-miR-29c-3p	1
REAC:R-HSA-1538133	G0 and Early G1	0.034	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-1638091	Heparan sulfate/heparin (HS-GAG) metabolism	0.034	HS3ST1	hormone and metabolites	hsa-miR-144-5p	1
REAC:R-HSA-2022928	HS-GAG biosynthesis	0.034	HS3ST1	hormone and metabolites	hsa-miR-144-5p	1
REAC:R-HSA-2559586	DNA Damage/Telomere Stress Induced Senescence	0.034	CCNE1	apoptosis and senescence	hsa-miR-144-5p	1
REAC:R-HSA-390471	Association of TriC/CCT with target proteins during biosynthesis	0.034	CCNE1	protein synthesis	hsa-miR-144-5p	1
REAC:R-HSA-6791312	TP53 Regulates Transcription of Cell Cycle Genes	0.034	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-6804116	TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest	0.034	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-69017	CDK-mediated phosphorylation and removal of Cdc6	0.034	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-69205	G1/S-Specific Transcription	0.034	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-69563	p53-Dependent G1 DNA Damage Response	0.034	CCNE1	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69563	p53-Dependent G1 DNA Damage Response	0.034	CCNE1	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69580	p53-Dependent G1/S DNA damage checkpoint	0.034	CCNE1	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69580	p53-Dependent G1/S DNA damage checkpoint	0.034	CCNE1	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69615	G1/S DNA Damage Checkpoints	0.034	CCNE1	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4

REAC:R-HSA-69615	G1/S DNA Damage Checkpoints	0.034	CCNE1	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-8848021	Signaling by PTK6	0.034	CCNE1	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-8848021	Signaling by PTK6	0.034	CCNE1	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-9006927	Signaling by Non-Receptor Tyrosine Kinases	0.034	CCNE1	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-9006927	Signaling by Non-Receptor Tyrosine Kinases	0.034	CCNE1	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
GO:0016311	dephosphorylation	0.036	GSK3B,YWHAE,PTPN13,PPP2R5D,MTMR12	cellular signaling	hsa-miR-26a-5p	1
REAC:R-HSA-69202	Cyclin E associated events during G1/S transition	0.036	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-69656	Cyclin A:Cdk2-associated events at S phase entry	0.036	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-69052	Switching of origins to a post-replicative state	0.037	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-390466	Chaperonin-mediated protein folding	0.037	CCNE1	protein synthesis	hsa-miR-144-5p	1
REAC:R-HSA-112382	Formation of RNA Pol II elongation complex	0.037	RTF1,CDK9,POLR2E	transcription and splicing	hsa-miR-26a-5p	1
REAC:R-HSA-198323	AKT phosphorylates targets in the cytosol	0.037	GSK3B,MDM2	cellular signaling	hsa-miR-26a-5p, hsa-miR-29c-3p	2
REAC:R-HSA-4839735	Signaling by AXIN mutants	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-4839743	Signaling by CTNNB1 phospho-site mutants	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-4839744	Signaling by APC mutants	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-4839748	Signaling by AMER1 mutants	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5339716	Signaling by GSK3beta mutants	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5358747	S33 mutants of beta-catenin aren't phosphorylated	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5358749	S37 mutants of beta-catenin aren't phosphorylated	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5358751	S45 mutants of beta-catenin aren't phosphorylated	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5358752	T41 mutants of beta-catenin aren't phosphorylated	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1

REAC:R-HSA-5467337	APC truncation mutants have impaired AXIN binding	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5467340	AXIN missense mutants destabilize the destruction complex	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-5467348	Truncations of AMER1 destabilize the destruction complex	0.037	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-6781823	Formation of TC-NER Pre-Incision Complex	0.037	RPS27A,DDB1,POLR2E	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-73762	RNA Polymerase I Transcription Initiation	0.037	UBTF,MTA3,POLR2E	transcription and splicing	hsa-miR-26a-5p	1
REAC:R-HSA-75955	RNA Polymerase II Transcription Elongation	0.037	RTF1,CDK9,POLR2E	transcription and splicing	hsa-miR-26a-5p	1
REAC:R-HSA-8848021	Signaling by PTK6	0.037	CCNE1,RPS27A,SFPQ	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-8848021	Signaling by PTK6	0.037	CCNE1,RPS27A,SFPQ	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-9006927	Signaling by Non-Receptor Tyrosine Kinases	0.037	CCNE1,RPS27A,SFPQ	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-9006927	Signaling by Non-Receptor Tyrosine Kinases	0.037	CCNE1,RPS27A,SFPQ	tyrosine kinase signaling	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-391251	Protein folding	0.037	CCNE1	protein synthesis	hsa-miR-144-5p	1
REAC:R-HSA-2468052	Establishment of Sister Chromatid Cohesion	0.038	STAG1,PDS5A	cell cycle	hsa-miR-128-3p	1
REAC:R-HSA-2470946	Cohesin Loading onto Chromatin	0.038	STAG1,PDS5A	cell cycle	hsa-miR-128-3p	1
REAC:R-HSA-2555396	Mitotic Metaphase and Anaphase	0.038	STAG1,LMNB1,KPNB1,PDS5A,TNPO1	cell cycle	hsa-miR-128-3p	1
REAC:R-HSA-447115	Interleukin-12 family signaling	0.038	LMNB1,HNRNPF,CANX	cytokine	hsa-miR-128-3p	1
REAC:R-HSA-68882	Mitotic Anaphase	0.038	STAG1,LMNB1,KPNB1,PDS5A,TNPO1	cell cycle	hsa-miR-128-3p	1
REAC:R-HSA-68884	Mitotic Telophase/Cytokinesis	0.038	STAG1,PDS5A	cell cycle	hsa-miR-128-3p	1
GO:0044788	modulation by host of viral process	0.039	PHB,NUCKS1	viral processes	hsa-miR-26a-5p	1
GO:0072331	signal transduction by p53 class mediator	0.040	MDM2,CNOT4,CNOT2,RPL23	cell cycle	hsa-miR-363-3p	1
GO:0097168	mesenchymal stem cell proliferation	0.041	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-1630316	Glycosaminoglycan metabolism	0.041	HS3ST1	hormone and metabolites	hsa-miR-144-5p	1
REAC:R-HSA-69206	G1/S Transition	0.041	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-69306	DNA Replication	0.041	CCNE1	cell cycle	hsa-miR-144-5p	1

REAC:R-HSA-196299	Beta-catenin phosphorylation cascade	0.041	GSK3B,PPP2R5D	Wnt/beta-catenin signaling pathway	hsa-miR-26a-5p	1
REAC:R-HSA-6782135	Dual incision in TC-NER	0.041	RPS27A,DDB1,POLR2E	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-6782210	Gap-filling DNA repair synthesis and ligation in TC-NER	0.041	RPS27A,DDB1,POLR2E	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-6807070	PTEN Regulation	0.041	RPS27A,TNRC6B,RCOR1,MTA3	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-69563	p53-Dependent G1 DNA Damage Response	0.041	CCNE1,RPS27A,MDM2	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69563	p53-Dependent G1 DNA Damage Response	0.041	CCNE1,RPS27A,MDM2	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69580	p53-Dependent G1/S DNA damage checkpoint	0.041	CCNE1,RPS27A,MDM2	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69580	p53-Dependent G1/S DNA damage checkpoint	0.041	CCNE1,RPS27A,MDM2	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
GO:0032606	type I interferon production	0.041	IRAK1,IRF7	cytokine	hsa-miR-146a-5p	1
REAC:R-HSA-5663202	Diseases of signal transduction by growth factor receptors and second messengers	0.041	GSK3B,RPS27A,PHB,MDM2,PPP2R5D,POLR2E	diseases	hsa-miR-26a-5p	1
REAC:R-HSA-69615	G1/S DNA Damage Checkpoints	0.041	CCNE1,RPS27A,MDM2	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-69615	G1/S DNA Damage Checkpoints	0.041	CCNE1,RPS27A,MDM2	cell cycle	hsa-miR-144-5p, hsa-miR-144-5p, hsa-miR-26a-5p, hsa-miR-26a-5p	4
REAC:R-HSA-5250913	Positive epigenetic regulation of rRNA expression	0.041	GSK3B,MTA3,POLR2E	epigenetic changes	hsa-miR-26a-5p	1
GO:0000377	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	0.041	HNRNPU,SFPQ,POLR2E,HNRNPA0,CPSF2	transcription and splicing	hsa-miR-26a-5p	1
GO:0006289	nucleotide-excision repair	0.041	RPS27A,DDB1,POLR2E	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-6804760	Regulation of TP53 Activity through Methylation	0.041	RPS27A,MDM2	epigenetic changes	hsa-miR-26a-5p	1
GO:0000375	RNA splicing, via transesterification reactions	0.042	HNRNPU,SFPQ,POLR2E,HNRNPA0,CPSF2	transcription and splicing	hsa-miR-26a-5p	1
KEGG:04110	Cell cycle	0.043	GSK3B,CCNE1,YWHAE,MDM2	cell cycle	hsa-miR-26a-5p	1
KEGG:04120	Ubiquitin mediated proteolysis	0.043	UBA2,RPS27A,DDB1,MDM2	protein synthesis	hsa-miR-26a-5p	1
REAC:R-HSA-109606	Intrinsic Pathway for Apoptosis	0.044	PPP1R13B,AKT3	apoptosis and senescence	hsa-miR-29c-3p	1
REAC:R-HSA-202131	Metabolism of nitric oxide: NOS3 activation and regulation	0.044	WASL,DDAH1	cellular signaling	hsa-miR-128-3p	1

GO:0031109	microtubule polymerization or depolymerization	0.044	ZNF207,BLOC1S2,TUBGCP5	cellular architecture	hsa-miR-26a-5p	1
GO:0044843	cell cycle G1/S phase transition	0.044	MDM2,CNOT4,CNOT2,FBXW7	cell cycle	hsa-miR-363-3p	1
REAC:R-HSA-453279	Mitotic G1 phase and G1/S transition	0.044	CCNE1	cell cycle	hsa-miR-144-5p	1
REAC:R-HSA-2995383	Initiation of Nuclear Envelope (NE) Reformation	0.045	LMNB1,KPNB1	cell cycle	hsa-miR-128-3p	1
REAC:R-HSA-2559583	Cellular Senescence	0.045	CCNE1	senescence	hsa-miR-144-5p, hsa-miR-26a-5p	2
REAC:R-HSA-69242	S Phase	0.045	CCNE1	cell cycle	hsa-miR-144-5p	1
KEGG:04064	NF-kappa B signaling pathway	0.046	IRAK1,CARD10	NF kappa beta signaling pathway	hsa-miR-146a-5p	1
KEGG:04620	Toll-like receptor signaling pathway	0.046	IRAK1,IRF7	toll like receptor signaling pathway	hsa-miR-146a-5p	1
KEGG:04933	AGE-RAGE signaling pathway in diabetic complications	0.046	SMAD2,PRKCE	signaling activity	hsa-miR-146a-5p	1
KEGG:05142	Chagas disease	0.046	IRAK1,SMAD2	diseases	hsa-miR-146a-5p	1
REAC:R-HSA-73854	RNA Polymerase I Promoter Clearance	0.047	UBTF,MTA3,POLR2E	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-73864	RNA Polymerase I Transcription	0.047	UBTF,MTA3,POLR2E	cell cycle	hsa-miR-26a-5p	1
REAC:R-HSA-2559583	Cellular Senescence	0.047	CCNE1,RPS27A,TNRC6B,MDM2	senescence	hsa-miR-144-5p, hsa-miR-26a-5p	2
REAC:R-HSA-1502540	Signaling by Activin	0.048	SMAD2	hormones	hsa-miR-146a-5p	1
REAC:R-HSA-209543	p75NTR recruits signalling complexes	0.048	IRAK1	cellular signaling	hsa-miR-146a-5p	1
REAC:R-HSA-209560	NF-kB is activated and signals survival	0.048	IRAK1	nF kappa beta signaling pathway	hsa-miR-146a-5p	1
REAC:R-HSA-9013973	TICAM1-dependent activation of IRF3/IRF7	0.048	IRF7	cellular signaling	hsa-miR-146a-5p	1
REAC:R-HSA-918233	TRAF3-dependent IRF activation pathway	0.048	IRF7	cellular signaling	hsa-miR-146a-5p	1
REAC:R-HSA-975144	IRAK1 recruits IKK complex upon TLR7/8 or 9 stimulation	0.048	IRAK1	toll like receptor signaling pathway	hsa-miR-146a-5p	1
GO:0034504	protein localization to nucleus	0.048	GSK3B,HNRNPU,YWHAE,MDM2	cellular architecture	hsa-miR-26a-5p	1
REAC:R-HSA-6781827	Transcription-Coupled Nucleotide Excision Repair (TC-NER)	0.048	RPS27A,DDB1,POLR2E	transcription and splicing	hsa-miR-26a-5p	1
REAC:R-HSA-2995410	Nuclear Envelope (NE) Reassembly	0.050	LMNB1,KPNB1,TNPO1	cell cycle	hsa-miR-128-3p	1
GO:0006296	nucleotide-excision repair, DNA incision, 5'-to lesion	0.050	RPS27A,DDB1	cell cycle	hsa-miR-26a-5p	1