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Defining the Role of Rare Genetic Variants that Drive Risk and Pathogenesis of Alzheimer's Disease

by

Matthew James Rosene

A dissertation presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

May 2022
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Matthew James Rosene

Washington University in St. Louis

May 2022

Dedicated to my family.
You had faith in me when I had none in myself.

ABSRACT OF THE DISSERTATION

Defining the role of rare genetic variants that drive risk and pathogenesis of Alzheimer's disease

By

Matthew James Rosene

Doctor of Philosophy in Biology and Biomedical Sciences

Molecular Cell Biology

Washington University in Saint Louis, 2022

Celeste M. Karch, Chair

Alzheimer's disease (AD) is the leading cause of dementia and is pathologically defined by the aggregation of extracellular amyloid plaques and intracellular neurofibrillary tangles. Rare heritable mutations within the genes for *amyloid precursor protein* (*APP*) and *presenilin 1* (*PSEN1*), and *presenilin 2* (*PSEN2*) cause early onset AD and account for approximately 1% of AD cases. While the majority of AD cases are late-onset (LOAD), which is defined by a markedly more complex genetic architecture that is comprised of many genetic risk factors that influence AD through multiple cellular pathways. The advent of deep sequencing analyses have allowed for the identification of novel risk factors and genetic variants. By identifying these genetic risk factors, characterizing their cellular and molecular function, and then identifying the roles they play influencing AD risk, this knowledge may be leveraged for the development of more effective therapeutics. In this dissertation, I look more deeply into three risk factors: *LMNA*, *RAB10,* and *PLD3*. Through a combination of computational analysis and

functional/biochemical assays, I attain a deeper understanding of the roles of these genes as they affect AD pathogenesis.

The first of these genes, *LMNA*, encodes a nuclear lamin protein that is associated with the accelerated aging condition Hutchinson-Guilford Progeria Syndrome (HGPS). In this condition, a mutation in *LMNA* leads to the production of progerin, which is unable to be processed by ZMPSTE24 and constitutively incorporates into the nuclear membrane, causing nucleoskeletal dysfunction. In AD, some of these same nucleoskeletal deficiencies have also been observed. Through mRNA expression analysis of laser-captured microdissected neurons, we observe a significant elevation of *LMNA* expression coupled with a reduction of *ZMPSTE24* expression in diseased brains, resulting in more immature, unprocessed prelamin A. When we induced progerin expression in iPSC-derived cortical neurons, we observed disruption in pathways associated with the oxidative stress response as well as the lysosome, which has been associated with AD pathology in the literature.

Further genomic analyses in increasingly larger datasets has led to the identification of genetic variants that protect against AD. One study by our group identified a rare SNP in the 3'-untranslated region (3'-UTR) of *RAB10* (rs142787485). As a Rab GTPase, RAB10 plays a role in the endo-lysosomal network (ELN), a central pathway to the processing of APP and the production of Aβ. In AD brains, we observe increased levels of *RAB10* mRNA and RAB10 protein expression. Overexpressing RAB10 in N2A695 cells increases the ratio of extracellular Aβ42/40, which is associated with increased pathogenicity. Furthermore, when investigating the rs142787485 SNP, the location of this SNP is predicted to interfere with the binding of multiple miRNAs. However, these predictions still need to be validated through functional and biochemical assays.

In our efforts to better understand AD genetics, there remain challenges posed by genes that remain uncharacterized in terms of their function. One such gene is *PLD3*, a member of the phospholipase D family, but lacks any confirmed phospholipase activity or substrate. Whole exome sequencing of families densely affected by LOAD uncovered the rare variant in PLD3 p.V232M. Further deep sequencing uncovered additional variants associated with increased disease risk. In our work we find that one particular synonymous variant, p.A442A, activates a cryptic splice site, resulting in the reduced expression of exon 11. Furthermore, studies of AD patients show that *PLD3* is reduced in the neurons of AD brains. When we look at loss of *Pld3* in amyloid model mice, we observe significantly decreased Aβ turnover and altered plaque pathology which we further attribute to reduced microglial plaques, mirroring what has been observed in *Trem2*-deficient amyloid mice. Together, these studies illustrate the critical role of nuclear and ELN function in AD risk and resilience.

Chapter 1: Introduction and Overview

1.1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disease defined clinically by progressive memory decline [1]. AD currently affects more than 44 million people worldwide, and this number is expected to rapidly increase as the population ages (http://www.alz.co.uk). Neuropathologically, AD is characterized by neuronal loss and the accumulation of amyloid plaques and neurofibrillary tangles in the brain, much of which occurs many years before the onset of clinical symptoms [2]. While clinical diagnosis of AD is challenging because it is dependent primarily on observations of family members and caregivers, changes in protein analytes in plasma and cerebrospinal fluid (CSF) and brain imaging, although not widely used in clinical practice, may facilitate AD diagnosis [2]. AD can broadly be defined as early-onset, occurring prior to age 65, or the much more common late-onset, occurring after age 65 (>96.5% of total cases).

1.2 Pathology of AD

AD is clinically characterized by extracellular amyloid plaques and intracellular neurofibrillary tau tangles, both of which occur in sequential order of each other and are requisite for the development of AD [3]. Extracellular amyloid accumulation is characterized by the aggregation of pathogenic amyloid-β (Aβ), a peptide generated through the sequential cleavage of the amyloid precursor protein (APP) by β-secretase and γ-secretase within endo-lysosomal compartments within neurons. Aβ was first isolated from the cerebral amyloidosis of both AD and Down Syndrome patients [4]. While ranging in length from 38-43 amino acids in length, the largest proportion of Aβ peptides are the 40 amino acid long Aβ40 peptide and the 42 amino acid

long Aβ42 peptide to a much lesser degree. Upon its release from the presynaptic neuron, Aβ can be endocytosed by post-synaptic neurons for lysosomal degradation, engulfed by glial cells for lysosomal degradation, or transcytosed across the blood-brain barrier (BBB) and cleared through the cerebrovascular system. Aβ that is not cleared can aggregate into the amyloid plaques, with the Aβ42 being especially aggregate prone due to increased hydrophobicity of the extra two amino acids. In the timeline of AD pathology and disease progression, accumulation of amyloid plaques is the first occurring pathology in AD, starting ~20 years before the initial onset of cognitive decline [5]. This paradigm, along with discovery of the first mutations within the genes *APP*, *PSEN1*, and *PSEN2* is what ultimately led to the formulation of the amyloid cascade hypothesis [6-8]. While this hypothesis has been called into question over the years, it still stands that amyloid has an important role to play in AD disease pathogenesis and disease progression.

1.3 Reconciling the Genetic Architecture of AD with Pathology

The genetics of early-onset AD (EOAD) are relatively well understood. Autosomal dominant mutations occurring in *APP*, *PSEN1*, or *PSEN2* give rise to a subset of EOAD cases. More than 200 pathogenic mutations have been reported worldwide (https://www.alzforum.org/mutations) [9]. Clinically, EOAD mutation carriers exhibit disease onset prior to 65 years of age [10]. Neuropathologically, EOAD and late-onset AD (LOAD) are indistinguishable [11]. Unfortunately, the genetics of LOAD is more complex (Figure 1.1) [12].

Among individuals with LOAD, there is strong evidence for genetic heritability of disease [13-17]. The single largest genetic risk factor for LOAD is *APOE* [18]. APOE plays critical roles in cholesterol transport, neuroplasticity, and inflammation [19]. APOE regulates Aβ metabolism directly through binding and clearance of Aβ [20] and indirectly via the LRP1 receptor [21]. Moreover APOE influences tau-mediated neurodegeneration [22]. Two different

APOE alleles, ε4 and ε2, affect risk for AD. Risk for developing AD is 3-fold higher in individuals carrying one copy of the *ε4* allele and 12-fold higher in individuals carrying two copies of *APOE ε4* [23]. Conversely, *APOE ε2* confers resilience to AD, while the *ε3* allele is considered neutral risk [23].

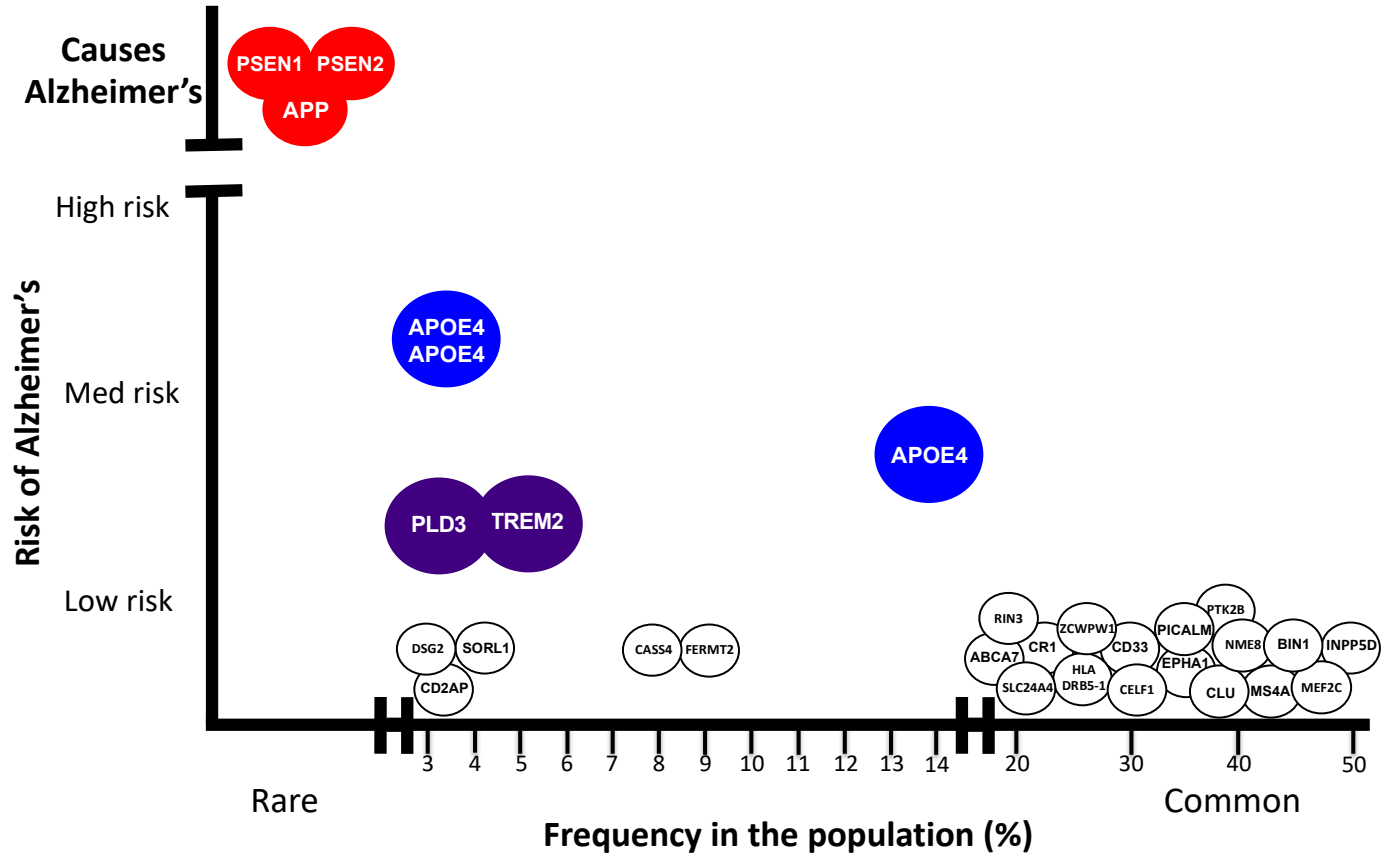

Figure 1.1: The complex genetic architecture of AD. While EOAD has been solely attributed to mutations in the APP metabolism genes *PSEN1/2* and *APP*, LOAD is influenced a broader range of factors that have different cellular functions and exert their own unique influence on AD risk.

Genetic variants that influence risk for AD can be broadly classified into two groups: common and rare. The majority of common variants (minor allele frequency (MAF) >5%) were identified using genome-wide association studies (GWAS).[15] With the exception of variants in

APOE, all other common variants have small effect sizes on AD risk (odds ratios=1.08-1.22, 0.73-0.94) [15]. While GWAS variants provide insights into disease processes, none of the common risk variants for AD that have been identified by GWAS have clear functional effects and efforts to identify functional variants in the regions of GWAS variants have largely been unsuccessful.

The advent of next-generation sequencing has enabled the sequencing of whole exomes and genomes, resulting in progressively larger AD datasets and providing insights into the contribution of low frequency (MAF 1-5%) and rare variants (MAF<1%) to the genetic architecture of AD. Using a variety of study designs, multiple rare variants have been identified that affect risk for AD [15, 24-27]. Rare variants typically have much larger effect sizes on disease risk than common variants identified by GWAS. Rare variants are also more likely to occur in coding or regulatory regions and thus are more likely to be functional. Thus, rare variants represent effective therapeutic targets.

Finally, alternative study designs can provide additional insights into the genetics of AD. For example, the use of quantitative endophenotypes (eg, CSF levels protein analytes such as Aβ and tau [28-30]; mitochondrial copy number [31]; metabolic efficiency [32, 33]; measurements of progressive brain atrophy [34]; among others), and the analysis of mitochondrial genomic variation [35] have expanded our understanding of the genetic architecture underlying disease onset and disease course.

1.4 Using the Genetics of AD to Identify Therapeutic Targets

Genes and pathways that regulate AD pathogenesis may represent viable targets for treating disease. For example, therapies targeting the removal of Aβ or inhibition of Aβ

production are currently in clinical trials. These strategies are based on our understanding of the mechanisms by which rare mutations in *APP*, *PSEN1* and *PSEN2* drive AD pathogenesis in EOAD and focus on inhibition of the deposition of Aβ in the brain. Similarly, targeting APOE function has been investigated for its therapeutic capacity [36-38]. AD risk genes implicated in immune function, endocytosis, and lipid biology represent novel avenues of therapeutic development. Unfortunately, to date, more than 90% of all clinical trials have failed. Given the expected increase in disease incidence, developing effective therapeutics is imperative and is highly dependent on better understanding the mechanisms that drive disease. For the remainder of this dissertation, I discuss the role of three genes that have been shown to alter AD risk, *LMNA*, *RAB10*, and *PLD3*, how they influence AD pathology and mechanisms, and their potential as therapeutic targets (Figure 1.2).

1.4 *LMNA* and Nucleoskeletal Integrity in AD

LMNA, HGPS, and premature aging

In order to gain a deeper understanding of neurodegenerative disease mechanisms, we must look to analogous diseases when parallels present themselves. In Hutchinson-Guilford Progeria Syndrome (HGPS), mutations in the *LMNA* gene, which codes type-A lamins (lamin A and lamin C), results in altered splicing of the *LMNA* mRNA, yielding the truncated *LMNAΔ150* and its protein product progerin. Unable to be cleaved by the zinc metallopeptidase and become defarnesylated, the constitutively farnesylated acts in a dominant negative nature by permanently anchoring into the nuclear membrane and disrupting normal lamina functions and disrupting nucleoskeletal morphology and integrity [39]. Downstream, these defects in nucleoskeletal morphology have broader detrimental effects for the cell both within the nucleus (chromatin disorganization, genomic instability and DNA damage, and abnormal gene expression) as well as

outside the nucleus (mitochondrial dysfunction, oxidative stress, and loss of proteostasis) [40-43], all of which have been also reported within AD.

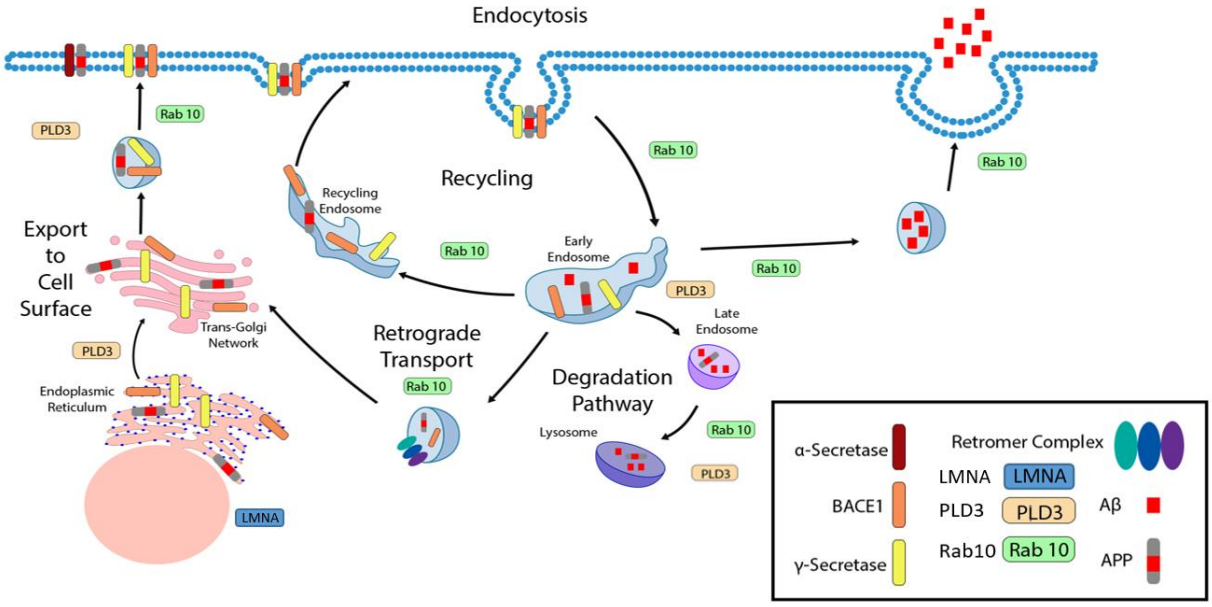

Figure 1.2: Cellular Functions of *RAB10, PLD3,* and *LMNA*. Image adapted from Tavana et al [44].

Laminopathies

The nuclear lamina refers to the structural meshwork that exists within the inner surface of the nuclear membrane, giving nuclei its shape. Comprising of both A-type (lamins A, C, AΔ10, and C2) and B-type (lamin B) lamins, expression of the nuclear lamina comes from the *LMNA* and *LMNB* genes. However, besides providing structure to the nucleus, research has also shown that the nuclear lamina serves important roles in the organization of heterochromatin, transcriptional regulation, and nuclear pore positioning and function [39, 45]. This broad range of roles means that dysfunctional lamins can have far-reaching consequences beyond the nucleus. Indeed, mutations in the lamin genes, in particular *LMNA*, have been linked to several serious diseases termed as laminopathies [46].

Of the known laminopathies, the most notable is Hutchinson Guilford Progeria Syndrome (HGPS), a markedly serious laminopathy that results in severe premature aging in children, resulting in death by roughly age 13. With ~90% of cases being caused by a the G608G (GGC>GGT) mutation that activates a cryptic splicing site within *LMNA* to yield significantly elevated levels of progerin, a truncated form of prelamin A that is normally found to increase in the skin and liver of normal individuals with age [40, 47-49]. Unlike mature Lamin A, the missing 607-656 amino acids contain the cleavage site for ZMPSTE24, the zinc metalloproteinase that defarnesylates prelamin A [47, 50]. Unable to be further processed into mature Lamin A, progerin constitutively congregates at the inner nuclear membrane in a dominant-negative manner, leading to nuclear blebbing [40, 47]. Furthermore, the missing 50 amino acids in progerin are also necessary for the binding of Lamin A to the histone modifications of heterochromatin, resulting in a loss of organization of the peripheral chromatin in the nucleus [51, 52].

Laminopathy in AD

Interestingly, many of the same nuclear defects observed in laminopathies are also observed in AD. In a cohort of collected AD brains, Frost et al., observed tubular invagination in 60% of the neuronal nuclei analyzed, a level 3-fold higher than what was observed in age-matched control brains [40]. Furthermore, a link was proposed that tauopathies may exert an effect on nucleoskeletal integrity by increasing the levels of over-stabilized filamentous actin, which interacts with the nuclear lamina through the LINC (LInker of Nucleoskeleton and Cytoskeleton) complex [40, 53, 54]. When considering the role of nuclear lamina in the organization of peripheral heterochromatin, a link between tauopathies and heterochromatin disorganization can also be reasonably postulated. Additional evidence also shows that tau can

interact with the nuclear pore complex in a manner that can alter nuclear export/import. Based on these presented findings, it becomes apparent that there is a connection between AD and nuclear and Lamin dysfunction. In **Chapter 2**, I further delve into this relationship and the role of *LMNA* in AD and neurodegeneration.

1.5 *RAB10*: The protective endo-lysosomal factor

The protective RAB10 variant in AD

Common and rare variants have been identified that reduce the risk for AD.[9] Those with the strongest protective effect include *APOEε2* and *APP*-A673T [55, 56]. Thus, genes and pathways involved in increasing AD risk may also confer resilience to disease. In order to identify additional genetic variants that confer resilience to AD, there is a need to develop novel study designs that focus on those individuals carrying protective factors for AD. In one such case, family pedigrees were identified with a statistical excess of AD mortality (ie, families with a higher number of AD deaths than expected relative to similarly sized pedigrees; termed high risk pedigrees). Within these high-risk pedigrees, elderly individuals with genetic risk for AD (i.e., *APOEε4* carriers) but who had escaped AD were evaluated using whole genome sequencing. Ridge et al. identified a rare variant (rs142787485) in the 3'-UTR of *RAB10* that confers resilience to AD [17]. In a cell model of *APP* metabolism, silencing of *Rab10* expression leads to a significant decrease in Aβ42 and the Aβ42/40 ratio, consistent with prior reports.[17, 57] Interestingly, independent of the *RAB10* SNP, individuals with a neuropathologic diagnosis of AD exhibited significantly higher levels of *RAB10* compared with neuropathology-free controls.[17] Thus, genetic and molecular evidence support a role for *RAB10* in AD pathogenesis. While not much work has been published to closely examine this role, in **Chapter**

3, I will discuss some of the proposed mechanisms through which RAB10 may contribute to AD and how the rs142787485 SNP contributes to this.

1.7 *PLD3*: A mysterious protein promoting Aβ clearance

Discovery of rare variants in PLD3

Through whole exome sequencing of families densely affected by LOAD, a rare genetic variant located within the seventh exon, V232M, was identified in the gene for phospholipase D3 (*PLD3*) and perfectly segregated with disease in two different families. Further deep sequencing of additional unrelated cohorts of AD and control patients further uncovered additional variants that were also significantly associated with disease risk, notably the M6R and A442A variants that were also associated with an increase in disease. Looking beyond variants, PLD3 is found to accumulate on the amyloid plaques of diseased brains [58]. When analyzing at RNA expression in the brain, it was found that AD brains displayed significantly reduced expression when compared to age-matched controls, with biochemical assays using *in vitro* systems implicating this altered expression to result in an alteration of APP metabolism [15].

A protein without a known function

PLD3 is a member of the phospholipase D family, which has seven known members. PLD family members are defined by the presence of two HKD "catalytic domains" [59]. However, of the seven known isoforms, the knockout of *PLD1* and *PLD2* together is sufficient to completely abrogate phospholipase activity [60-62]. To date, *PLD3* has no known substrate or confirmed function. However, some of the published literature have begun to shed some light on its role. On a macroscopic level, *PLD3* has been implicated in myotube formation [63] and, in tumors, is a marker of senescence and plays a role in HIF1α-dependent lipid metabolism [64, 65]. At the cellular level, *PLD3* has been shown to play a wide range of roles in the endo-

lysosomal network (ELN). Within the endosome, *PLD3* has been proposed to be an endonuclease in immune cells for microbic DNA to generate short oligos for presentation to Tlr9 in mice [66]. In addition, within neurons, PLD3 colocalizes with APP in endolysosomal compartments and also has been postulated to play a role in retromer transport from the endosome, where β- and γ-secretases are rich in concentration, to the Golgi, where their concentration is much lower [67-70]. Finally, evidence both from our group as well as others have been pointed to a role for PLD3 in the lysosome. The *PLD3* promoter contains a CLEAR motif, suggesting that it is a member of the CLEAR network, a family of lysosomal enzymes regulated by TFEB, the master lysosomal transcription factor [71]. Furthermore, PLD3 not only carries a mannose-6-phosphate tag to direct it to the lysosome without being degraded and colocalizes with Lamp2 [72-74], but evidence has also demonstrated that PLD3 is trafficked to the lysosome via the endosome and requires ubiquitination of its N-terminus [66]. While the role of PLD3 in the lysosome is not fully understood, lysosomes in *Pld3*-deficient mouse neurons are increased in size and density, implying a buildup of undigested cargo [75]. Recently, it was reported that within the lysosome, PLD3 exhibits display phospholipase activity [76]. In chapters four and five of this dissertation, all of this will be further discussed and elaborated on at length.

As stated above, the genetics of LOAD is remarkably complex and, while much progress has been made, many factors still yet remain to be identified, and even more are yet to be functionally characterized. However, by better shining a light on the many genes that can influence AD risk, we stand to gain a deeper understand the pathways and mechanisms that drive disease and, by extension, we can better develop therapeutics to slow disease progression or treat the symptoms that result. For the remainder of this dissertation, I will outline and discuss my work on my own efforts to do this very thing for *LMNA*, *RAB10*, and *PLD3*.

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Chapter 2: *LMNA*-mediated nucleoskeleton dysregulation in Alzheimer's disease

2.1 Abstract

Nucleoskeleton dysfunction has been implicated in Alzheimer disease (AD). Tubular invaginations of the nuclear envelope observed in AD brains are consistent with the accumulation of farnesylated prelamin A (encoded by the *LMNA* gene) that occurs in Hutchinson-Gilford Progeria Syndrome, a premature aging disorder caused by *LMNA* mutations. Proper function of the nuclear membrane is required for neuronal survival and for maintenance of genetic architecture. To determine whether dysregulated *LMNA* expression and prelamin A processing are responsible for nucleoskeleton dysfunction in AD, we performed differential gene expression and network analyses in human AD and age-matched control brains. In AD brains, we observed a significant increase in *LMNA* and a significant decrease in *ZMPSTE24*, which encodes the zinc metallopeptidase protein that defarnesylates prelamin A. We replicated these findings in laser capture microdissected neurons from AD brains, suggesting that the effect is neuronally driven. Thus, high levels of *LMNA* paired with low levels of *ZMPSTE24* could result in the accumulation of farnesylated prelamin A and tubular invaginations in the nuclear membrane. *LMNA*-associated networks were also differentially expressed in AD brains. Genes within the dysregulated *LMNA* network were enriched in lysosomal and chromatin remodeling pathways. We propose that β-amyloid and tau accumulation disrupts prelamin A processing and downstream changes in the nuclear membrane. Alterations in the nucleoskeleton induce genomic instability, loss of proteostasis, and cellular senescence, which may accelerate AD pathogenesis.

2.2 Introduction

Alzheimer disease (AD) is a neurodegenerative disorder characterized by extensive neuronal loss and accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles. Nucleoskeleton dysfunction has also been reported in AD brains [1, 2]. Dysfunction of this kind can cause genomic instability, loss of proteostasis, epigenetic changes, mitochondrial dysfunction, deregulated nutrient sensing and cellular senescence [1, 3-5], all of which have been described in AD [2, 6, 7]. The precise mechanism by which nucleoskeleton dysfunction occurs in AD remains unclear. Thus, identifying the molecular and protein triggers that drive these defects could allow us to target and modify critical phenotypes in AD.

Genetic and cell-based evidence point to a critical role of lamin A in proper nuclear membrane function. Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare premature aging disorder. HGPS is caused by mutations in *LMNA*, the gene that encodes A-type lamins (lamin A and lamin C), activating a cryptic splice site that gives rise to a truncated transcript termed *LMNAΔ150* and its protein product progerin [8, 9]. Under normal conditions, immature lamin A protein (prelamin A) is post-translationally modified at the nuclear membrane by farnesylation, cleavage, carboxyl methylation and excision of the farnesylated residue by the zinc metallopeptidase ZMPSTE24 [10-12]. The *LMNAΔ150* transcript, however, lacks the ZMPSTE24 binding site, leading to accumulation of progerin, a shorter protein with retained farnesyl modification, in the nuclear membrane and subsequent nuclear shape abnormalities, chromatin disorganization, damage to DNA and abnormal gene expression [13-15]. These progerin-induced phenotypes mimic several aspects of normal aging [16, 17]. Deficiency in

ZMPSTE24 function, which results in build-up of farnesylated prelamin A in the nuclear membrane, also causes nuclear distortion and a premature aging phenotype [18-20]. Notably, progerin builds up in the nuclear envelope even in normal cells with aging due to sporadic use of the cryptic splice site, which prevents defarnesylation (Figure 2.1) [9, 16].

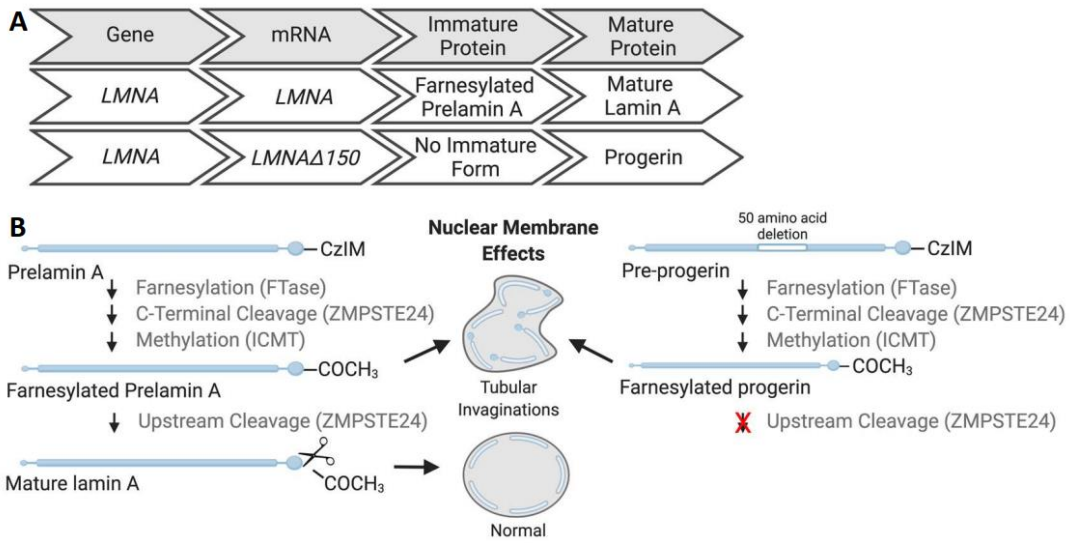

Figure 2.1: Model of lamin A processing. A. Schematic of lamin A and progerin processing. B. After translation, immature prelamin A is farnesylated, then cleaved by ZMPSTE24 to remove the farnesyl residue and yield mature lamin A. Farnesylated prelamin A or progerin are unable to properly incorporate into the nuclear lamina but are retained in the nuclear membrane resulting in tubular invaginations.

The changes observed in nuclear envelope morphology in AD brains are consistent with the build-up of farnesylated prelamin A or progerin, which could indicate an AD-associated change in the regulation of lamin A expression and processing [1, 2]. Here, we show that AD pathology is associated with disrupted *LMNA* and *ZMPSTE24* expression, which, in turn, brings about changes in lamin A protein levels and subsequently alters molecular networks associated with proteostasis and chromosome remodeling. Thus, nucleoskeleton defects caused by altered

lamin A processing may contribute to downstream pathways that promote neurodegeneration and AD pathogenesis.

2.3 Materials and Methods

Human Subjects

The Washington University IRB reviewed the Charles F. and Joanne Knight Alzheimer Disease Research Center (Knight ADRC) Neuropathology Cores (from whom the brains were obtained) operating protocol as well as this specific study and determined it was exempt from approval. In the state of Missouri, individuals can give prospective consent for autopsy. Our participants provide this consent by signing the hospital's autopsy form. If the participant does not provide future consent before death the DPOA or next of kin provide it after death. All data were analyzed anonymously.

Laser Capture Microdissected Neurons

The GSE5281 dataset was obtained from laser capture microdissected neurons from AD and control brains (Table 2.1) [21]. Brain samples from individuals of European descent that were collected from Washington University, Duke University, and Sun Health Research Institute were included in the study. Samples were obtained from the entorhinal cortex, hippocampus, medial temporal gyrus, posterior cingulate, superior frontal gyrus, and primary visual cortex and were clinically and neuropathologically confirmed AD (N=33) or controls (N=14). RNA expression was measured using an Affymetrix GeneChip for gene expression. To analyze RNA expression, the log transformed expression values were analyzed with brain region, age, and gender as covariates as previously described [22].

Mount Sinai Brain Bank

Mount Sinai Brain Bank (MSBB) RNA sequencing (RNAseq) study was accessed from the Accelerating Medicines Partnership – Alzheimer's Disease (AMP-AD) portal (syn8690199; accessed December 2017). We examined gene expression in the parahippocampal gyrus (PHG; BA36) of brains with a neuropathologic diagnosis of AD (N=135) and neuropathology free, age matched controls (N=85; Table 2.1). RNAseq was performed using the Illumina HiSeq 2500 System with an average of 38.7 million reads per sample [23, 24]. The gene count data generated from RNAseq analysis was imported into RStudio, an integrated development environment that supports R, a programming language for statistical computations. Differential gene expression analysis was performed using the package *DESeq2* with covariates including age at death, post-mortem interval, sex, and RNA integrity number.

Mayo Clinic Brain Bank

Mayo Clinic Brain Bank (Mayo) RNAseq study was accessed from the AMP-AD portal (syn6090813). We examined gene expression in the temporal cortex of brains with neuropathologic diagnosis of AD (N=82), pathologic aging (N=29), and elderly control brains that lacked a diagnosis of neurodegenerative disease (N=80; Table 2.1). Pathologic aging is defined as the presence of amyloid plaques (CERAD neuritic and cortical plaque densities of 2 or more) without neurofibrillary tangles (Braak NFT stage of less than 3 and no other co-morbid pathology) [25]. These brains were part of the Mayo Clinic RNAseq cohort, as described previously [25]. RNAseq was performed using Illumina HiSeq 2000, 101-base-pair, paired-end sequencing at the Mayo Clinic Genomic Core Facility. After applying quality control steps, raw read counts were normalized according to conditional quantile normalization (CQN) using the

Bioconductor package. Differential gene expression comparing AD to controls used a "Simple Model." In this model, multi-variable linear regression analyses were conducted in R, using CQN normalized gene expression measures and including age-at-death, gender, RNA integrity number (RIN), brain tissue source, and flowcell as biological and technical covariates.

Frontotemporal Lobar Dementia-tau (FTLD-tau) Brains

Insular cortex from autopsy-confirmed, FTLD-tau with a causative mutation at *MAPT* p.R406W (N=2) and age-matched, cognitively normal control brains (N=2) were obtained from the Knight ADRC (Table 2.1) [26]. RNAseq paired end reads were generated using Illumina HiSeq 4000 with a mean coverage of 80 million reads per sample. FastQC was applied to the data to evaluate sequencing quality [27]. Data were aligned to GRCh37 primary assembly using STAR (ver 2.5.2b) [28]. Reads alignment were further evaluated by applying Picard CollectRnaSeqMetrics (ver 2.8.2) to examine reads distribution on the genome [29]. The gene count data generated from RNAseq analysis was imported into RStudio. Differential gene expression analysis was performed using the package *DESeq2* with covariates including age at death, post-mortem interval, sex, and RNA integrity number as previously described [30].

Table 2.1: Study demographics

Dataset	Brain Region	N	Male (%)	Mean Age at Death	AD	PA	FTLD-MAPT	Control
MSBB	PHG*	220	36	83.3	135	0	0	85
GSE5281	EC, HPC, MTG, PC, SFG, PVC**	47	53.2	79.9	33	0	0	14
Mayo [25]	Temporal Cortex	191	50.2	80.2	82	29	0	80
Knight ADRC [26]	Insular Cortex	4	50	69.5	0	0	2	2

*****PHG, Parahippocampal Gyrus. **, EC, Entorhinal Cortex; HPC, Hippocampus; MTG, Medial Temporal Gyrus; PC, Posterior Cingulate; SFG, Superior Frontal Gyrus; PVC, Primary Visual Cortex. AD, Alzheimer's disease. PA, pathological aging. FTLD-tau, frontotemporal lobar dementia with tau inclusions.

Developmental expression of LMNA and ZMPSTE24

Developmental gene expression for *LMNA* and *ZMPSTE24* were evaluated using a spatial and temporal microarray expression data set focusing on the prenatal brain [31]. These exon-level expression data originate from 25 areas and 9 layers (fetal mitotic and post-mitotic zones) of the human brain sampled in 40 clinically normal postmortem brains of diverse ethnicity that span 32 consecutive periods of neurodevelopment and adulthood from 8 post-conception weeks (PCW) to 40 years (for additional details see http://www.brainspan.org/). We downloaded expression values, calculated using z-score normalization. Using line and bar plots we visualized patterns of gene expression, across region and over time (from 8 PCW to 40 years of age). Using a repeated measure analysis of variance (ANOVA), we evaluated whether gene expression patterns over time showed statistically significant differences between brain regions.

Network Analysis

LMNA-associated gene networks were defined as those genes that were significantly differentially expressed in response to forced progerin expression (GEO: GSE52431) [5]. Briefly, these expression profiles were generated in a prior study of Parkinson disease models by differentiating human induced pluripotent cells (iPSC) into dopaminergic (mDA) neurons using a modified Dual-SMAD protocol [5]. RNAseq was performed in 70-day iPSC-derived mDA neurons expressing nuclear-GFP or progerin-GFP [5].

Briefly, paired-end reads were generated on an Illumina HiSeq2000. Reads were mapped to the human genome (Hg19) using STAR 2.3.0e [28] using default mapping parameters, and read counts were assessed using HTSeq. Differentially expressed genes were identified with limma voom in R. A low read count filter was used such that all samples were required to contain non-zero read counts for a gene to be assessed. Differentially expressed genes were identified using a fold change cut off of +/- 2 and a Bonferroni adjusted p-value of 0.05.

Forced progerin expression in iPSC-derived mDA neurons resulted in 113 up-regulated and 1,318 down-regulated genes (FDR<0.05; Supplemental Table 2.1) [5]. We used these genes to construct a *LMNA* network in the Mayo and MSBB-PHG datasets. In the Mayo dataset (Table 2.1), 1,273 genes were identified. In the MSBB dataset (Table 2.1; PHG), 693 genes were identified. Subsequent analyses were then focused on those genes that were differentially expressed in the same direction across all three datasets: iPSC-derived mDA, Mayo, and MSBB.

Pathway Analysis

To identify enrichments in gene ontology associated with the genes within the *LMNA* network, we used the Consensus Path Database (CPDB). Gene ontology analyses were performed using CPDB (Release 31; http://cpdb.molgen.mpg.de/)[32, 33]. CPDB compares gene ontology terms between background and candidate gene sets using the hypergeometric test and generates p-values that are corrected for multiple testing using FDR. We used the default background gene set, which includes 18,043 genes. Biological, cellular and molecular gene ontology terms were included in a single analysis.

GWAS

Single Nucleotide Polymorphisms (SNPs) within 10kb of *LMNA* and *ZMPSTE24* were identified using NCBI. To determine whether these SNPs were associated with AD risk, we used the International Genomics of Alzheimer's Project (IGAP), a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 SNPs to meta-analyze four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's Disease Initiative–EADI the Alzheimer Disease Genetics Consortium–ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium–CHARGE The Genetic and Environmental Risk in AD consortium–GERAD).

Lamin A and ZMPSTE24 protein analyses in human AD brains

Parietal lobes from autopsy-confirmed AD (CDR 3; N = 3) and age-matched, cognitively normal control (CDR 0; N = 3) brains were obtained from the Knight ADRC. Brains were homogenized in RIPA lysis buffer (50mM Tris pH 7.6, 2.5mM EDTA, 150mM NaCl, 0.5% SDS, 1.0% Triton X-100, 0.5% sodium deoxycholate, protease inhibitor cocktail) on ice by sonication and centrifuged at 14,000g for 10 minutes at 4°C as previously described [34]. The resulting supernatants were analyzed for total protein levels by bicinchoninic acid assay (Thermo Fisher). Standard SDS-PAGE was performed with 10µg of protein for each sample using NuPAGE Novex 4-12% Bis-Tris Protein Gels (Thermo Fisher) in NuPAGE MOPS SDS Running Buffer (Thermo Fisher). Samples were boiled for 5 min in Laemmli sample buffer prior to electrophoresis [35]. Proteins were subsequently transferred onto Immobilon-P polyvinylidene fluoride (PVDF) Membrane, 0.45µm (Millipore) in Tris-Glycine buffer with 20% methanol. Immunoblots were stained with Ponceau S solution (0.1 % (w/v) in 5% acetic acid) to evaluate total protein. Immunoblots were probed with antibodies to lamin A/C (Santa Cruz sc-376248

1:200), or lamin B2 (Abcam ab8983 1:500). Primary antibodies were detected with goat anti-mouse IgG (H+L) HRP secondary antibody (KPL 074-1806 1:6000). Immunoblots were exposed with Pierce ECL Western Blotting Substrate (Thermo Fisher) on a G:BOX Gel Documentation System (Syngene). Band intensities were quantified using GeneTools software (Syngene) manual band quantification. Band intensities were normalized to quantified levels of Ponceau S staining and then expressed relative to the average band intensity of control samples.

2.4 Results

LMNA and ZMPSTE24 are dysregulated in AD brains

To determine whether *LMNA* expression is altered in AD, we analyzed publicly available transcriptomic data generated from a large collection of neuropathologically defined AD and control brains (MSBB). In the parahippocampal gyrus of AD brains, a region affected early in disease pathogenesis, we observed a significant increase in *LMNA* expression and a significant reduction in *ZMPSTE24* (Figure 2.2A). To begin to understand the contribution of AD pathology to lamin A processing, we examined the correlation between *LMNA* and *ZMPSTE24* with plaque and tangle load in human brains. *LMNA* was significantly positively correlated with plaque load and tau Braak stage in the parahippocampal gyrus (Figure 2.2A). Conversely, *ZMPSTE24* was marginally negatively correlated with plaque load, but not statistically significant (Figure 2.2A). In control brains, *LMNA* and *ZMPSTE24* are expressed at similar levels across the cortex (Appendix 1).

When interpreting gene expression data in tissue homogenates from brains with neurodegenerative disease, changes in gene expression may be driven by the cellular composition of the tissue (e.g. extensive neuronal loss) [36]. To replicate our findings and to

begin to understand the cell-type specific impact of *LMNA* and *ZMPSTE24* expression in AD, we examined a publicly available dataset containing RNA expression data from laser capture microdissected neurons from AD and age-matched, control brains (Figure 2.2B) [21]. Consistent with our findings in tissue homogenates from MSBB, we found that *LMNA* was significantly elevated (Figure 2.2C; $p=9.79\times10^{-4}$) and *ZMPSTE24* was significant reduced (Figure 2.2D; $p=1.0\times10^{-3}$) in neurons isolated from AD brains compared with neurons isolated from neuropathology free control brains. These findings suggest that the impact of AD on *LMNA* and *ZMPSTE4* occurs in neurons.

A

	DISEASE STATUS		PLAQUE LOAD		BRAAK STAGE	
Gene	Log2 Fold Change	p value	Log2 Fold Change	p value	Log2 Fold Change	p value
LMNA	0.103	0.0140	0.005	0.0012	0.054	0.0125
ZMPSTE24	-0.062	0.0143	-0.0017	0.0821	-0.004	0.7320

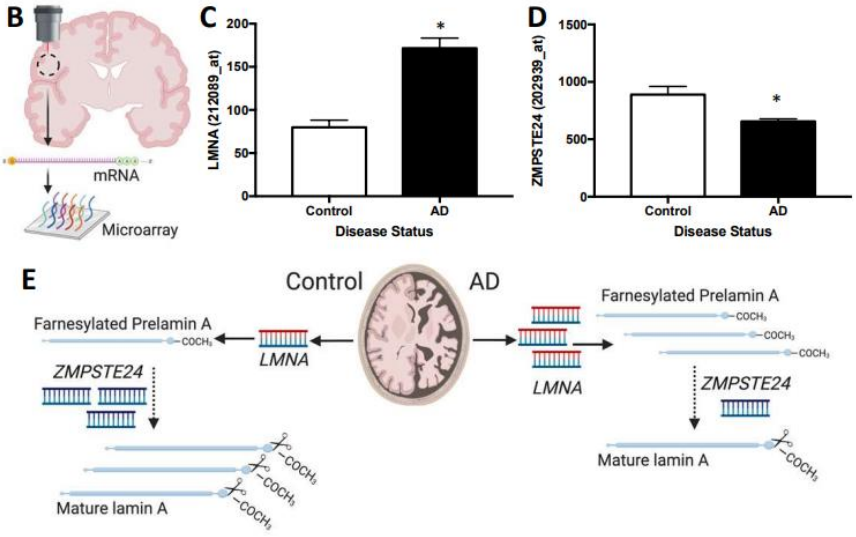

Figure 2.2: *LMNA* and *ZMPSTE24* expression are altered in AD brains. A. *LMNA* and *ZMPSTE24* gene expression are associated with disease status, plaque load (amyloid), and Braak Stage (tau) in brain homogenates from AD and control brains. Parahippocampal gyrus (BA36; MSBB). B-D. *LMNA* and *ZMPSTE24* expression are altered in neurons isolated from AD brains. B. RNA expression was evaluated in laser capture microdissected

neurons isolated from AD and control brains (GSE4281). C-D. Graphs of mean expression (AU) ± SEM. C. *LMNA* expression is significantly elevated in AD neurons. $p=9.79\times10^{-4}$. D. *ZMPSTE24* expression is significantly reduced in AD neurons. $p=1.0\times10^{-3}$. E. In AD brains, increased *LMNA* expression coupled with decreased *ZMPSTE24* may result in an accumulation of immature, farnesylated prelamin A. * <0.05.

To determine whether amyloid plaques are sufficient to trigger dysregulation of *LMNA* progressing, we examined *LMNA* and *ZMPSTE24* expression in the temporal cortices of brains with pathologic aging [37]. Pathologic aging is defined as the presence of amyloid plaques (CERAD neuritic and cortical plaque densities of 2 or more) with minimal neurofibrillary tangle burden (Braak NFT stage of less than 3 and no other co-morbid pathology) [25]. Interestingly, we found that *LMNA* was significantly reduced in brains with pathologic aging (p=0.01), while *ZMPSTE24* levels were unchanged (p=0.69; Table 2.2). Thus, these findings suggest that the observed effects of *LMNA* and *ZMPSTE24* are not solely β-amyloid dependent.

Table 2.2: *LMNA* and *ZMPSTE24* expression in brains with Pathology Aging (amyloid plaques) and FTLD-tau (tau tangles)

	Pathologic Aging		**FTLD-Tau**	
Gene	**Fold Change (Log2)**	**p value**	**Fold Change (Log2)**	**p value**
LMNA	-0.40	0.0126	1.25	7.60E-03
ZMPSTE24	0.03	0.6970	-0.92	1.51E-04

To determine whether tau aggregation is sufficient to alter lamin A processing, we measured *LMNA* and *ZMPSTE24* expression in FTLD-tau brains [30]. In brains with FTLD-tau caused by autosomal dominant mutations in *MAPT* p.R406W, we observed a significant increase

in *LMNA* ($p=7.6\times10^{-3}$) and a significant decrease in *ZMPSTE24* expression ($p=1.51\times10^{-4}$; Table 2.2).

Prelamin A accumulates in AD brains

We predict that the molecular phenotypes of increased *LMNA* and decreased *ZMPSTE24* that we observed in AD brains result in lamin A dysregulation at the protein level (Figure 2.2E). To test whether our molecular observations lead to a change in the total levels of mature lamin A protein, we measured lamin A in tissue homogenates from AD and control brains (Figure 2.4). Lamin A protein levels were significantly lower in AD brains compared with control brains (Figure 2.4). Of the two protein products that *LMNA* encodes, lamin A requires sequential processing to produce a mature form of the protein that can be normally incorporated into the nuclear lamina, while lamin C does not. As a control, we evaluated lamin C and lamin B2 protein levels and found that these nuclear proteins were unchanged across the brain samples (Figure 2.4). Together, these findings point to a specific effect on lamin A processing in AD brains (Figure 2.4) and as a result, altered ratios of lamins which can change the mechanophenotype of the nuclear membrane [38].

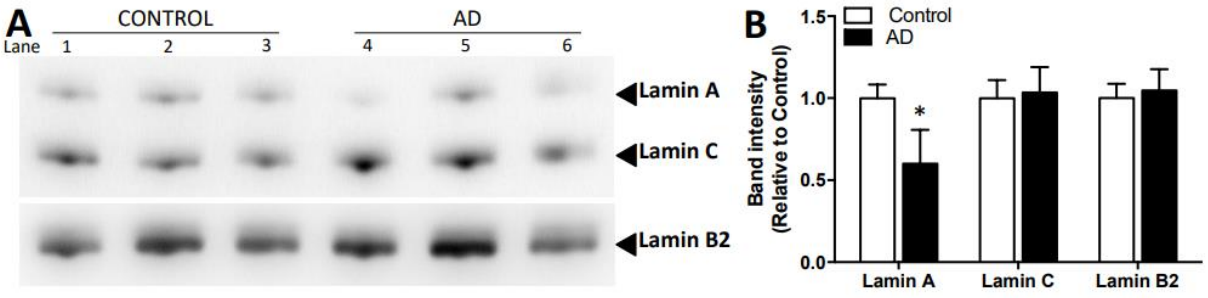

Figure 2.3: Lamin A protein levels are altered in AD brains. Autopsy confirmed AD (CDR 3;N=3) and control (CDR 0; N=3) parietal brain tissue were analyzed by SDS-PAGE and immunoblotting. A. Immunoblotting of

human control and AD brain tissue with antibodies specific to mature lamin A, lamin C, and lamin B2. B. Quantification of immunoblots. Graph represents mean ± SEM. *, $p<0.05$.

The LMNA network is dysregulated in AD brains

We next sought to determine whether genes associated with *LMNA* were dysregulated in AD brains. To do this, we constructed a supervised *LMNA* network using publicly available data from a stem cell model in which a mutant form of *LMNA*, progerin, was expressed in iPSC-derived mDA neurons (Figure 2.5A) [5]. Forced progerin expression resulted in 113 upregulated genes and 1,318 downregulated genes compared to iPSC-derived mDA neurons expressing GFP (FDR<0.05; Appendix 1) [5]. Importantly, forced progerin expression resulted in a significant increase in *LMNA* ($\beta=9.38$; $p=1.33\times10^{-5}$; 82y mDA neurons; Appendix 1).

To determine whether genes that are altered in response to progerin expression were also differentially expressed in AD, we next extracted these 1,431 genes from two publicly available transcriptomics datasets of AD and control brains (MSBB and Mayo Clinic). In the MSBB dataset (PHG), 74 genes were significantly differentially expressed between AD and control brains in the same direction as the iPSC-derived mDA neurons (FDR<0.05; Appendix 2). In the Mayo Clinic dataset (temporal cortex), 239 genes were significantly differentially expressed between AD and control brains in the same direction as the iPSC-derived mDA neurons (FDR<0.05; Appendix 2). In total, 53 genes were differentially expressed in AD brains in the same direction in Mayo Clinic and MSBB datasets and in iPSC-derived mDA neurons (Figure 2.5B; Table 2.3; Appendix 2).

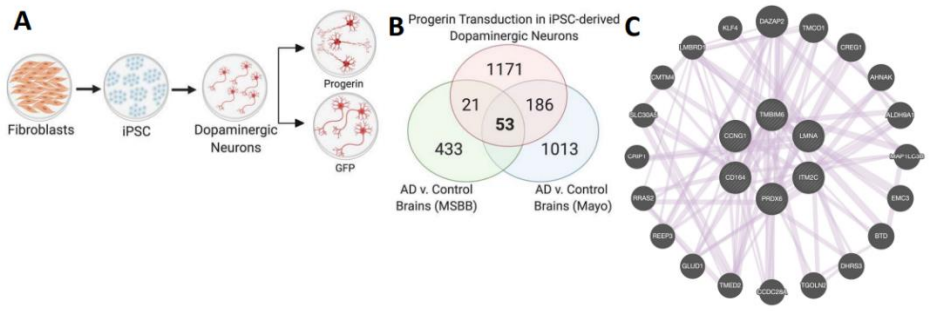

Figure 2.4: *LMNA*-associated genes are disrupted in AD brains. A. *LMNA* networks were defined as those genes altered by expression of progerin in human iPSC-derived dopaminergic neurons [5]. B. Overlap in genes altered by progerin expression *in vitro* and differentially expressed (FDR<0.05) in the same direction in AD versus control brains from two independent datasets (MSBB and Mayo). C. Relatedness of genes significantly elevated in the presence of progerin and in AD brains. Purple lines indicate prior evidence of co-expression.

The six genes that were significantly upregulated in response to progerin treatment and elevated in AD brains (Table 2.3) were highly co-expressed with one another (Figure 2.5C) and were enriched in pathways associated with lysosomal function and apoptotic signaling (Table 2.4). Genes that were downregulated in response to progerin treatment and reduced in AD brains were enriched in pathways associated with chromatin remodeling and nuclear division (Table 2.4). Together, these studies suggest that dysregulation of lamin A processing may be central to the chromatin and lysosomal abnormalities that are characteristic in AD.

Table 2.3: LMNA Network Genes are dysregulated in AD brains

Gene	MSBB		Mayo	
	Fold Change (Log2)	**FDR**	**Fold Change (Log2)**	**FDR**
PRDX6	0.32	1.13E-04	0.58	6.12E-05
LMNA	0.42	4.69E-04	0.34	4.41E-02
CD164	0.25	3.14E-03	0.39	4.08E-05

TMBIM6	0.18	1.07E-02	0.46	2.69E-06
CCNG1	0.23	1.47E-02	0.53	7.07E-06
ITM2C	0.21	1.65E-02	0.62	3.45E-04
HTR4	-0.39	3.43E-05	-0.66	1.08E-02
BCL11A	-0.38	4.13E-05	-0.67	3.60E-03
OTOGL	-0.58	4.13E-05	-0.59	1.12E-02
BMPER	-0.37	5.66E-05	-0.57	5.16E-03
CACNA2D3	-0.33	1.01E-04	-0.44	2.48E-02
CNIH3	-0.26	1.71E-04	-0.73	1.97E-04
FRMPD4	-0.39	2.64E-04	-0.72	8.21E-03
ANO3	-0.52	8.51E-04	-1.11	1.33E-03
LRRC2	-0.37	1.36E-03	-0.86	3.59E-04
MYOZ3	-0.35	1.37E-03	-0.89	5.69E-05
CLSPN	-0.40	1.41E-03	-0.60	2.19E-02
CCDC158	-0.31	1.48E-03	-0.35	2.52E-02
TRPA1	-0.47	1.71E-03	-0.61	1.25E-02
TNIP3	-0.66	2.21E-03	-0.71	2.67E-02
NRXN3	-0.32	2.25E-03	-0.95	2.09E-06
SLC26A4	-0.37	3.26E-03	-0.57	7.53E-03
TOM1L1	-0.22	3.64E-03	-0.40	9.14E-06
GRHL1	-0.27	4.92E-03	-0.62	1.64E-04
TPX2	-0.30	5.51E-03	-0.56	3.36E-04
TNFRSF11A	-0.25	5.59E-03	-0.69	2.42E-04
SATB2	-0.25	5.89E-03	-0.39	2.60E-02
TPTE2P1	-0.27	6.20E-03	-0.68	2.33E-05
ACRV1	-0.41	7.24E-03	-0.68	1.08E-03
MACROD2	-0.26	7.32E-03	-0.69	2.59E-05
CASQ1	-0.34	8.07E-03	-0.60	4.73E-03
SLC12A1	-0.41	9.10E-03	-0.86	7.36E-05
EXTL1	-0.28	1.12E-02	-0.41	3.65E-02
MIR137HG	-0.35	1.20E-02	-0.48	3.79E-02

RTKN2	-0.42	1.25E-02	-0.95	1.59E-04
ABCA10	-0.28	1.32E-02	-0.48	3.68E-04
EFNA5	-0.27	1.67E-02	-0.45	1.07E-02
IGF1	-0.34	1.67E-02	-1.10	2.40E-04
DGKH	-0.17	1.68E-02	-0.32	4.24E-03
P2RX5	-0.30	2.12E-02	-0.55	3.45E-03
PPARGC1B	-0.15	2.16E-02	-0.28	2.83E-02
C3orf49	-0.18	2.23E-02	-0.34	4.81E-02
TIAM2	-0.20	2.27E-02	-0.37	6.11E-03
PXDNL	-0.23	2.59E-02	-0.37	3.78E-02
USP43	-0.21	2.59E-02	-0.38	1.54E-02
GRB7	-0.49	2.62E-02	-0.90	4.39E-03
MOV10L1	-0.25	2.67E-02	-0.42	3.11E-03
KIAA1456	-0.22	2.95E-02	-0.51	4.62E-03
FMN1	-0.26	3.04E-02	-0.47	2.28E-02
NME9	-0.13	3.07E-02	-0.36	6.74E-05
PRR16	-0.23	3.17E-02	-0.63	8.99E-05
DMKN	-0.26	3.71E-02	-0.58	2.84E-04
BMP3	-0.33	3.83E-02	-0.76	6.72E-03

Table 2.4: *LMNA* network genes disrupted in AD are enriched in lysosomal, nuclear, and apoptotic pathways

GO Term	Pathway Name	FDR	Genes	Direction
GO:0005764	lysosome	9.92E-03	*ITM2C*, *PRDX6*, *CD164*	Up
GO:2001233	apoptotic signaling	1.43E-04	*LMNA*, *ITM2C*, TMBIM6	Up
GO:0000280	nuclear division	8.19E-03	*BMP3*, *EXTL1*, *PPARGC1B*, *IGF1*, *FMN1*, *SATB2*	Down
GO:0000793	condensed chromosome	1.69E-03	CASQ1, SLC12A1, P2RX5, SLC26A4, TRPA1, CACNA2D3, CNIH3, ANO3	Down

Genetic association with AD risk

Candidate gene studies have previously implicated *LMNA* in AD risk [39-41]. To determine whether common variants in *LMNA* or *ZMPSTE24* contribute to AD risk, we extracted all SNPs in the 10kb region around *LMNA* and *ZMPSTE24*, and we then determined whether these SNPs were associated with risk for AD in IGAP Stage 1 [42]. We identified 133 SNPs near*LMNA* and present in the IGAP Stage 1 dataset; however, no SNPs were significantly associated with AD risk (Appendix 3). Past candidate gene studies implicated rs505058 near *LMNA* in AD risk; however, in IGAP Stage 1, rs505058 was not associated with AD risk (p=0.3578). Similarly, of the 52 SNPs near *ZMPSTE24* and present in the IGAP Stage 1 dataset, we failed to observe any SNPs significantly associated with AD risk (Appendix 3). Together, these findings suggest that the observed dysregulation of lamin A processing occurs at the protein rather than the genetic level, which is consistent with previously observed sporadic use of the cryptic splice site [9, 16].

2.5 Discussion

AD is defined neuropathologically by the presence of amyloid plaques and neurofibrillary tangles. However, the underlying cellular and molecular mechanisms connecting disease pathology to neurodegeneration and cognitive decline are still not clearly understood. In our study, we demonstrate an association between lamin A-mediated nucleoskeletal dysfunction and AD. We also provide evidence demonstrating that lamin A misprocessing may influence other well-established AD-related pathways.

Nuclear membrane integrity is largely dependent on the highly controlled processing of lamin A. The *LMNA* transcript is translated into immature prelamin A, which is post-translationally modified with a farnesyl group. The zinc metallopeptidase ZMPSTE24 then cleaves this farnesyl group, producing mature lamin A [9, 43]. Interestingly, we observe an imbalance in the key components of this pathway with the elevation of *LMNA* and a reduction in *ZMPSTE24* expression. Together, this can cause a reduction of mature lamin A protein in the brain, leading to an accumulation of nuclear, immature prelamin A which constitutively interacts with and induces irregularities in the nuclear membrane [44].

Genomic integrity and global gene expression are linked to nuclear membrane integrity. In *Drosophila* and mouse models of tauopathy, defects in nuclear morphology were associated with oxidative stress, DNA damage, and loss of heterochromatin [1, 2]. Heterochromatin regulates gene expression. Global relaxation of heterochromatin can lead to aberrant gene expression [45], which has been described in AD. We aimed to more clearly define genes that are downstream of lamin A dysfunction and also change during AD pathology. Importantly,

genes upregulated due to altered lamin A processing and in AD brains are enriched for lysosomal function. The nucleus plays a critical role in lysosomal function. Nutrient sensing between the lysosome and the nucleus control energy metabolism [4]. Lysosomal biogenesis is regulated through transcription factor EB (TFEB) translocation from the cytosol to nucleus in a calcium-dependent manner [46]. Nuclear calcium is a potent regulator of gene transcription, and nuclear defects can significantly alter this signaling pathway. Moreover, nuclear calcium plays a central role in acquired neuroprotection by promoting the build-up of a neuroprotective "shield" through the induction of synaptic activity and by guarding against excitotoxic damage and classical apoptosis [47-50]. In addition, many calcium regulated genes are implicated in the protection of hippocampal and cortical neurons [47, 49-51]. Together, these findings suggest that dysregulation of lamin A processing may be upstream of the well-described lysosomal dysfunction during AD pathogenesis.

Growing evidence points to some mechanistic link between nuclear defects and AD. In a recent study, as many as 60% of nuclei from AD brains display nuclear invaginations [1]. Our data further builds on this by suggesting that the association between nuclear defects and AD is driven by accumulation of pathological tau. This association is consistent with previous reports that also show lamin-mediated nucleoskeletal dysfunction in *Drosophila* and mouse models of tauopathy. Specifically, *Drosophila* expressing tau^{R406W} exhibit nuclear deformities along with a decrease in mature lamin protein [1, 52]. Tau-transgenic mice and *Drosophila* display a senescent-like phenotype along with other nuclear defects such as abnormal morphology, dysfunctional nuclear pores, loss of heterochromatin, and changes in gene expression [1, 2, 6, 53]. These defects may occur by altered actin and microtubule dynamics in the cytoskeleton. Both fibrillar-actin (F-actin) and microtubules interact with the nuclear lamina through the

nuclear-envelope-spanning linker of nucleoskeleton and cytoskeleton (LINC) complex such that changes to the cytoskeleton also disrupt the nuclear lamina [1, 44]. In iPSC-derived neurons from *MAPT* mutation carriers, microtubule and actin-mediated deformation of the nucleus is observed with microtubule filaments invading the nucleus through the tubular invaginations [54]. Thus in model systems and human brain tissue, tau-induced alterations in the actin and microtubule cytoskeleton lead to nuclear invaginations containing mislocalized nuclear pores, disrupting nucleocytoplasmic transport [1, 44, 54-56]. Thus, the lamin A processing defects we describe could be driven by tau pathology.

Here, we leveraged data from progerin-transduced iPSC-derived neurons in order to define those genes that change upon disrupted lamin A processing [5]. Miller and colleagues demonstrated that progerin expression was sufficient to capture aging and disease-associated phenotypes that were absent in the naïve cells [5]. This was an important breakthrough in overcoming the relative immaturity of neuronal cultures derived from iPSC [57]. Yet, an important question remained: does altered lamin A processing truly model diseases related to aging? We identified a number of genes that were differentially expressed in this iPSC model due to progerin expression that were also differentially expressed in AD brains in a similar manner. Additionally, these genes were enriched in pathways previously implicated in AD, such as lysosomal dysfunction, apoptosis, and nuclear function. Additionally, another gene of interest that we identified was *SLC30A5*, which codes for a zinc transporter [58, 59]. Zinc transporters have been previously implicated as potential therapeutic targets due to both differential expression in AD as well as brain zinc dyshomeostasis also being linked to AD progression [60]. The effect on *SLC30A5* expression in AD is currently unknown [60], but considering that we find this gene to be altered after forced progerin expression, this finding implies the possibility

that this zinc transporter may have a regulatory role on ZMPSTE24 function and subsequently on *LMNA* processing. Taken together, these results support the notion that forced *LMNA* expression could be used to model aging *in vitro*.

While our study provides evidence for the association of dysfunction of lamin A processing with AD, there remain some important questions. While the mutation known to cause progerin expression in HGPS, *LMNAΔ150,* results in disrupted nuclear integrity in the hippocampal neurons of transgenic mice, neurodegeneration is not observed in HGPS patients [61-63]. It has been proposed that a microRNA miR-9 represses *LMNA* expression in the brain [44, 61-63]. However, we and others demonstrate that *LMNA* transcripts and lamin A protein levels are highly abundant in human brain tissue [64]. HGPS patients may succumb to cardiovascular disease prior to demonstrating neurological effects [44]. Alternatively, given progerin-associated toxicity is increased in the presence of wild-type lamin A [65], it is conceivable that specific inter-lamin interactions might occur in AD patients and result in greater neurotoxicity. Indeed, lamin A may be just one of the lamins that contributes to nuclear defects in AD. Interestingly, it has been demonstrated that lamin B-mediated dysfunction occurs in both tau-transgenic *Drosophila* and mice as well in AD brains [1, 44, 61]. Changes in the relative levels and processing of individual lamins are known to contribute to abnormal nuclear structure and function [44]. Progerin disrupts the normal homotypic biding of A-type and B-type lamins leading to abnormal A-B heteropolymers [18]. Further, changes in the ratio of A and B lamins can significantly alter the mechanical properties and stiffness of the nuclear membrane, leading to alterations in several downstream functions including heterochromatin organization and cell signaling [66]. Moreover, failure to assemble an appropriate nuclear lamina can signal apoptosis [67]. Abnormal nuclear morphology and altered trafficking between the nucleus and cytoplasm

has also been described in Huntington's disease, amyotrophic lateral sclerosis, and FTLD [68-71]. Hence our observations of increased expression of *LMNA* and potential deficits in processing through reduced *ZMPSTE24* in affected AD brain tissue are consistent with alterations in the structure of the nuclear envelope and nuclear lamina and far-reaching effects on gene expression, cell signaling and behavior.

Conclusions

Here, we show that *LMNA* and *ZMPSTE24* expression are disrupted in AD, which leads to changes in lamin A protein levels and alters molecular networks associated with proteostasis and chromosome remodeling. Thus, nucleoskeleton defects induced by lamin A processing abnormalities may contribute to downstream pathways that promote neurodegeneration and AD pathogenesis. Together, these findings provide compelling evidence for new therapeutic avenues.

2.6 References

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Chapter 3: RAB10: a protective factor in AD

3.1 Abstract

Research into Alzheimer's disease (AD) has revealed a complex genetic architecture that comprises a multitude of genes across many different pathways. Furthermore, each of these differing risk factors exert different affects on AD risk. In a 2017 study by our group, a rare SNP in the 3'-untranslated region (3'-UTR) of *RAB10* was found to confer AD resilience in individuals who would normally be at higher risk of disease. A Rab GTPase, *RAB10* regulates subcellular trafficking within the endo-lysosomal network (ELN) a pathway central to APP metabolism. We find that, in AD, RAB10 protein is elevated, which is shown in *in vitro* models to alter the Aβ42/40 ratio in a manner that promotes protein aggregation and plaque formation. While the rare SNP, rs142787485, appears to have no influence on mRNA expression as a whole or on an allele specific level, we hypothesize that it instead affects post-transcriptional gene expression through the interference of miRNAs, with at least 5 miRNAs that bind at the SNP site and all of which are differentially expressed in AD. While this remains to be replicated *in vitro*, these findings, along with what has been published in the literature, presents interesting opportunities to the field of AD medicine for potential therapeutics against disease.

3.2 Introduction

Understanding the genetic architecture of AD can provide critical insights into genes and pathways that drive disease risk, and this has been a major focus of genetic studies in the AD field. However, genetic architecture may also include variants, genes and pathways that confer resilience to AD. While understanding variants that increase risk allow us to better understand disease mechanisms, understanding protective variants also allow us to better understand successful aging without dementia [1]. In addition, due to the complex nature of AD genetics, successful therapeutics of many individual cases of LOAD may very well require a deep understanding of both risk and protective variants.

This is further demonstrated by a case study of an individual from the largest autosomal dominant AD (ADAD) kindred who carried the *PSEN1* E280A variant but remained cognitively normal until developing mild cognitive impairment (MCI) at well into her seventies, 30 years beyond her estimated age at onset [2]. Whole exome sequencing showed that, while this individual did indeed carry the *PSEN1* mutation, she also carried two copies of the rare *APOE3* R136S variant, known as the Christchurch mutation (*APOE3ch*), which was identified in select patients with hyperlipoproteinemia type III (HLP-III) [2, 3]. These findings serve to demonstrate how a protective variant can counteract a disease-driving mutation, resulting in a normal aging phenotype.

RAB10 is a member of the RAB family of small GTPases, which are key regulators of vesicular trafficking. RAB proteins are cyclically controlled. RAB activation requires a GDP-GTP exchange that is facilitated by RAB guanine nucleotide exchange factors [4]. This requires

phosphorylation at Thr73, which is mediated by Leucine-rich repeat kinase 2 (*LRRK2*), a protein kinase associated with Parkinson's disease [5, 6]. Unlike most of the other RAB proteins, which have relatively specific roles within intracellular transport, RAB10 is relatively unique because it carries out a wide variety of functions and has multiple subcellular localizations [7].

Rab10 plays essential functional roles in development: mice are embryonic lethal when both alleles are deleted [8]. In addition, RAB10 plays a role in maintenance and regulation of endoplasmic reticulum (ER) morphology [9-11]. When RAB10 is mutated or constitutively inactive (e.g. GDP-locked), the ER contains more cisternae, suggesting that RAB10 plays a critical role in maintaining and/or generating tubule extension and fusion in the ER [10]. RAB10 function has also been linked to neuronal morphology and polarization, playing a critical role in axonal development and dendrite arborization [12, 13]. During neuronal development, RAB10 associates with plasmalemmal precursor vesicles, which are linked to kinesin 1 via c-Jun N-terminal protein kinase-interacting protein 1 [14]. Together this complex mediates anterograde transport of RAB10-positive vesicles to axonal tips, promoting axonal growth [14]. Thus, RAB10 function is critical for proper neuronal function.

RAB10 has been linked to many roles involved in intracellular transport (Figure 3.1). RAB10 plays a role in endocytic recycling. In *C. elegans*, rab10 is required for AMPA-type glutamate receptor recycling in postsynaptic membranes [15]. RAB10 is likely functional upstream of RME-1/EHD, a protein involved in recycling endosome tubulization and endosome function [16-18]. RAB10 is expressed at the interface of early endosomes and recycling endosomes. These structures are morphologically defective in *rab-10* mutant *C. elegans* models [16, 18]. RAB10 is required for endosomal recruitment of CNT-1 [19]. This likely contributes to biogenesis and/or maintenance of recycling endosome compartments. RAB10 could also play a

role in promoting the maturation of early endosomes to recycling endosome. RAB10 is also involved in protein degradation. RAB10 and RAB3A are essential for lysosomal exocytosis and plasma membrane repair [20, 21]. RAB10-mediated lysosomal secretion is also found to play a role in the cellular response to stressed lysosomes [5]. RAB10 associates with lipid droplets [22]. Complexes of RAB10-EHBP1-EHD2 promote autophagic engulfment and degradation of lipid droplets [23]. Thus, these functional roles for RAB10 in recycling and degradation make it an interesting candidate protein in AD pathogenesis.

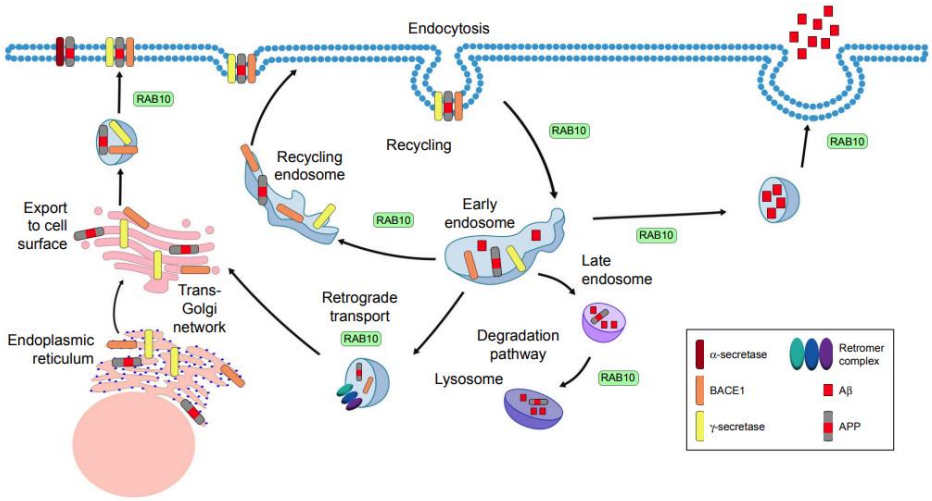

Figure 3.1: Diagram of APP trafficking and the role of RAB10 in these intracellular transport pathways.

RAB10 is involved in transport of proteins from the early endosome to the Trans-Golgi Network (TGN), where it may also function in the retromer pathway [24]. The retromer complex consists of Vps26, Vps35, Vps29, SNX1, SNX2, SNX5, and SNX6 [25]. The retromer complex regulates transport of protein cargo from endosomes to the TGN by the retrograde pathway or to the cell surface through the recycling pathway [26].

In order to form the amyloid plaques that define a primary component of AD pathology, the transmembrane APP must first be processed into Aβ peptides. APP is thought to be retrieved

from the cell surface and trafficked to the early endosomes where it is initially cleaved by β-site APP-cleaving enzyme 1 (BACE1) to generate a C-terminal fragment (β-CTF) [27, 28]. The β-CTF fragments are then trafficked via retromer-dependent transport to the TGN, which facilitates further cleavage by γ-secretase to produce Aβ40 [29]. The retromer complex and its receptors can transport APP and BACE1 from endosomes to the TGN, ultimately regulating production of Aβ [26]. The retromer complex sorts APP and BACE, either through direct or indirect binding to the transmembrane adaptor protein SORLA [30]. Interestingly, common variants in the gene that encodes SORLA have been associated with AD risk [31]. Thus, genes that are involved in retromer function may influence AD pathogenesis and represent promising therapeutic targets.

Retromer complex dysfunction promotes APP accumulation in neurons and Aβ production. In addition, the retromer also appears to have a differential effect on Aβ isoforms, with evidence that retromer dysfunction alters Aβ40 secretion, which results in increasing the Aβ42/40 ratio [32]. In mouse models, reduction of a single component within the retromer complex, Vps26, is sufficient to increase soluble Aβ and APP [33]. Stabilization of the retromer in human induced pluripotent stem cell-derived neurons using the pharmacological chaperone R33 has been shown to significantly reduce the phosphorylation of Tau in a manner that correlated with, but ultimately independent of, Aβ production [34].

In 2017, our group sought to identify genes that conferred resilience upon otherwise high-risk individuals. To this end, we selected individuals who were at least 75 years of age, cognitively normal, and carried at least one copy of *APOE ε4*, a genotype that carries a significantly elevated risk of AD [35]. These individuals were determined to be "AD resilient". Through this analysis, a genetic SNP in the 3'-untranslated region (3'-UTR) of *RAB10*, rs142787485 that was linked to AD resilience [35].

An RNAi screen of RABs that modify APP processing revealed that the silencing of *RAB10* reduces Aβ without altering sAPPβ levels [36]. The LRRK2-RAB10 signaling pathway also causes an overproduction of Aβ [6]. In this chapter I describe the link we discovered between *RAB10* and sporadic AD as well as some of the working hypotheses we have regarding how the rs142787485 ameliorates AD risk.

3.3 Materials and Methods

Patient Consent

Brains were collected post-mortem following written informed consent from the donor. The Washington University School of Medicine Institutional Review Board and Ethics Committee approved the informed consent (IRB 201104178, 201306108). The consent allows for the use of tissue by all parties, commercial and academic, for research but not for human therapy.

Protein extraction and Western blot of human brain tissue

Small sections of tissue were cut from the parietal lobe of frozen brain cross sections donated by AD patients and cognitively normal individuals. 10 volumes of lysis buffer (50 mM Tris, 150 mM NaCl, 2 mM EDTA, 0.01% NP40, and 0.5% Triton X100, 1:100 protease inhibitor) were added to the tissue samples based on weight (to 0.1 g tissue, add 1 mL of lysis buffer) before the samples were sonicated 3 times for 30 seconds each. Samples were then pelleted at 14,000xg at 4°C for 10 minutes before the supernatant was collected. Protein concentration was assayed through a BCA and 20 ug of protein was run on a 4-12% bis-tris gel (10-well) (Invitrogen) in MOPS buffer (Life Technologies). The protein was then transferred to a 0.45 µm PVDF membrane activated in methanol using 1x tris-glycine buffer supplemented with

20% methanol. Membranes were then probed with α-pRAB10 (ab230261 [MJF-R21]; 1:200) or α-RAB10 (ab237703 [MJF-R23]; 1:1000) at 4°C overnight. Blots were then washed and probed with goat-anti-rabbit secondary antibody (Seracare; 1:5000.) for 2 hours. Bands were visualized with either Lumigen (Lumigen) for pRAB10 or SuperSignal™ West Pico PLUS (Thermo Scientific).

Preparation of cDNA

Tissue samples cut from human brains were dissolved in Qiazol lysis reagent (Qiagen) and mRNA was extracted with a phenol/chloroform extraction. The concentration of the mRNA was assayed and converted to complementary DNA (cDNA) through a reverse transcription PCR using the High Capacity cDNA Reverse Transcription kit (Thermofisher Scientific).

qPCR

For the standard Taqman assays, 10 ng of cDNA is loaded with and run using the PerfeCTa FastMix II qPCR master mix (QuantaBiosciences) and Low Rox (QuantaBiosciences). RAB10 was targeted using the Hs00794658_m1 TaqMan assay (Thermofisher Scientific). The qPCR was run using the QuantStudio 12k Flex Real-Time PCR thermocycler (ThermoFisher) using the Comparative CT method and the standard default cycling settings.

To assess whether rs142787485 had any allele specific effects on *RAB10* expression, cDNA from the parietal lobe of eight individual heterozygous carriers of the rs142787485 SNP were obtained and analyzed with a Kompetitive allele specific PCR (KASP) (LGC Genomics). Differential Ct (dCt) was obtained by comparing Ct values for both alleles from each sample. Three technical replicates were used for each individual and the dCts were averaged. Genomic

DNA (gDNA) from each individual was also used as an internal control. Differential expression across the minor and WT alleles were analyzed through Student's t-test.

miRNA analyses

To identify potential miRNA binding sites affected by rs142787485, the SNP was entered into the miRSNP database. From the six miRNAs given in the readout, only has-miR-378h was excluded since its affinity was only predicted to decrease in the context of the rs142787485 SNP. The remaining five miRNAs were then cross-referenced with the TargetScan database to identify the type of interaction and miRDB to identify the binding site in the 3'-UTR. To examine the relative expression of these different miRNAs in the context of AD by looking at four different online datasets: GSE16759 (parietal lobe tissue from AD [n=4] and control brains [n=4]) [37], GSE63501 (RNAseq from AD brains [n=6], tangle-prominent demented brains [n=3], and control brains [n=7]) [38], GSE46131 (temporal neocortex gray matter tissue from AD brains [n=5], demented with Lewy Bodies brains [n=4], hippocampal sclerosis of aging brains [n=4], frontotemporal lobar demented brains [n=5], and non-demented brains [n=2]) [39], and GSE48552 (prefrontal cortex tissues from late stage AD brains [n=6] and early stage AD/control brains [n=6]) [40].

3.4 Results

RAB10 is elevated in sporadic AD

Due to its role in subcellular vesicle transport, RAB10 is expressed in all cell types in the brain. However, in brains affected by LOAD, there was a significant increase in the level of expressed Rab10 protein (Figure 3.2A and 3.2B).

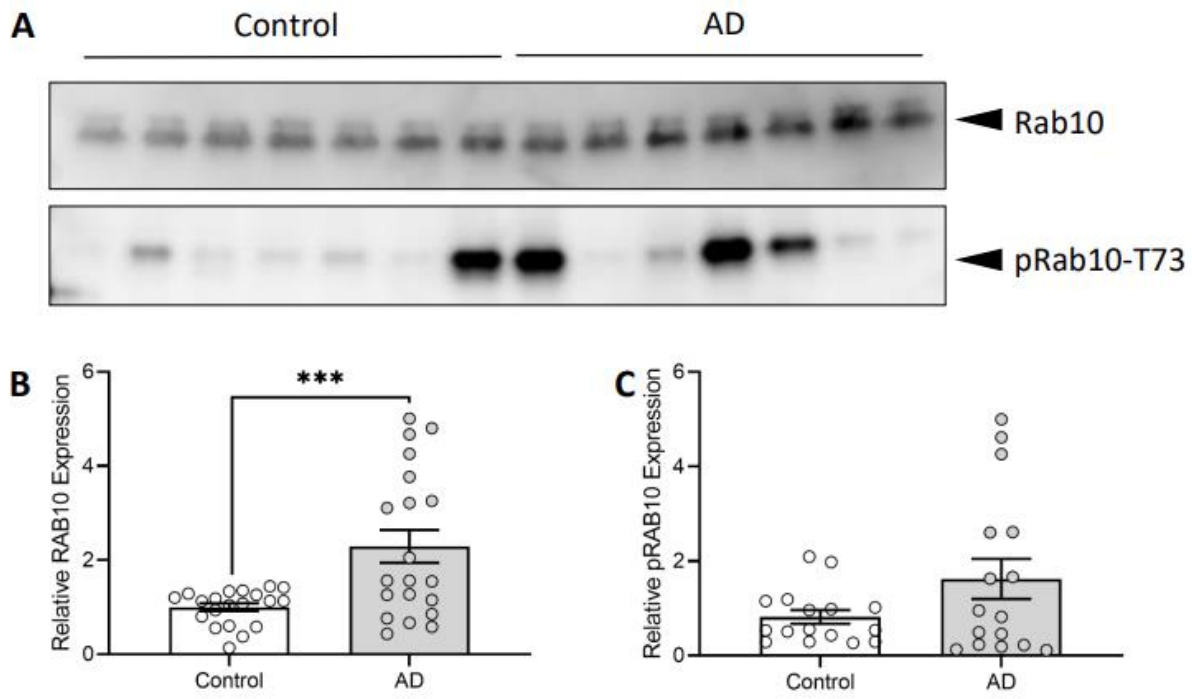

Figure 3.2: RAB10 protein expression is elevated in AD brains. A. representative Western blot of parietal brain tissue from case control and AD patients. B and C. Quantification of (A) for relative RAB10 protein expression (B) and RAB10 phosphorylation (C). Graphs display standard error of mean. ***, $p<0.0005$. Analyzed by Student's two-tailed t-test.

Rab10 cycles between its inactive, GDP-bound role and its active, GTP-bound role. When inactive, Rab10 is bound by guanine dissociation inhibitors (GDIs). GDIs extract inactive Rab proteins from their target membranes and bind them in the cytosol. However, upon phosphorylation by leucine rich repeat kinase 2 (LRRK2), a genetic risk factor for Parkinson's Disease, GDI is dissociated from Rab10 and is able to be inserted into the target membrane where it can be activated with the addition of a GTP by a guanine exchange factors (GEFs) [41]. However, beyond Parkinson's, this phosphorylation event may represent a pathological feature in the brains of AD patients [6]. Immunoblotting of parietal brain tissue shows marginal elevation of Rab10 phosphorylation (Figure 3.2A and 3.2C; $p=0.0822$). pRab10-Thr73 was

observed to co-localize with neurofibrillary tangles in AD brains as well as with granulovascular degeneration, neuropil threads, and dystrophic neurons [6]. Double immunofluorescence staining of these structures further revealed positive staining for phosphorylated tau. However, this co-localization of pRab10-Thr73 and phosphorylated tau was not complete, with some instances showing neuropil threads or dystrophic neurons containing only phosphorylated tau or pRab10-Thr73. Interestingly, dystrophic neurons near amyloid plaques stained positive for pRab10-Thr73, while the amyloid plaques themselves were negative for pRab10 [6]. Total Rab10 staining, however, did not differ between AD and control brains [6]. Thus, while pRab10-Thr73 is associated with AD pathology, it remains unclear whether this represents excess activation or aberrant function of Rab10.

Rs142787485 SNP is not differentially expressed

Among AD resilient individuals, a rare SNP in the *RAB10* 3'-UTR was found to be significantly associated with a decreased risk of LOAD (OR=0.69 [0.47-0.99]; p=0.028; MAF [controls/cases]=0.045/0.031), in the presence of at least a single copy of the harmful *APOE4* isoform [35]. Existing outside the coding exons of the mRNA transcript, rs142787485 has no effect on the amino acid coding of the final protein. Indeed, data also shows that there is no difference in relative expression of *RAB10* mRNA in the context of the rs142787485 variant (Figure 3.3A and 3.3B).

Rs142787485 may alter miRNA-mediated post-transcriptional regulation of RAB10

Alternatively, the 3'-UTR is a common binding site for many different protein complexes and molecules that regulate post-transcriptional expression, with a notable example being micro

RNAs (miRNAs). MiRNAs are endogenous peptides of non-coding RNAs, spanning roughly 20-22 nucleotides in length. In molecular biology, miRNAs serve a key role in post-transcriptional regulation by mainly inhibiting translation of protein from the mRNA or outright facilitating the degradation of the transcripts [42]. For some time, miRNAs have mostly been researched in the context of cancer, but a growing number of studies has also begun to implicate these miRNAs in AD, with the field showing much promise for both the future development of therapeutics as well as for another type of diagnostic biomarker [43]. By looking at miRNA expression in AD patients, it was in fact observed that many miRNAs that targeted genes associated with Aβ production were differentially expressed, such as miR-29a/b and miR-107, which both target the β-secretase BACE1 [44, 45].

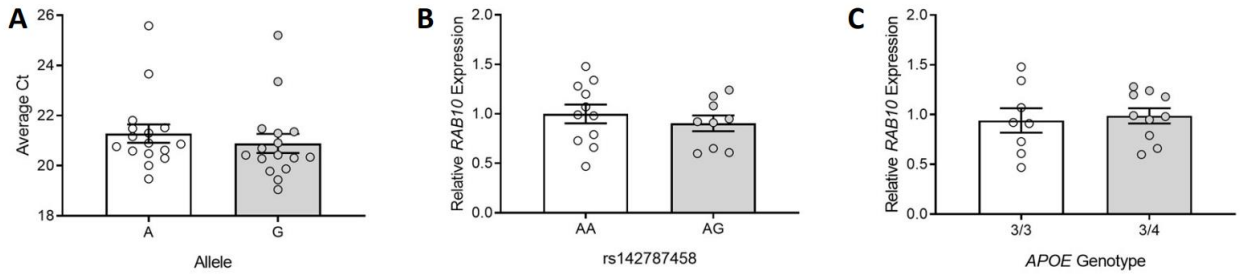

Figure 3.3: *RAB10* expression is not changed in the context of either the rs142787485 or the *APOE* genotype. A. Allele specific expression in the both the wildtype *RAB10* allele (A) and the SNP allele (G) in rs142787485. B. Relative expression of *RAB10* between wildtype (AA) and single allele carriers (AG) for the rs142787485 SNP. C. Relative *RAB10* between individuals with either the neutral *APOE3/3* genotype of the higher pathogenic *APOE3/4* genotype. Graphs display standard error of mean. Analyzed by Student's two-tailed t-test.

The location of the rs142787485 SNP in the 3'-UTR of the *RAB10* gene led us to question whether miRNA-mediated regulation may be affected. To investigate this, the rs142787485 SNP was plugged into the online tool miRSNP [46], which identifies miRNA binding sites that correlate with particular SNPs and predicts the effect of the SNP on binding affinity using a

variety of different algorithms. This includes generating a raking of miRNA target sites at SNP loci using a machine learning method, miRSVR, which trains a regression model for the features of the binding duplex, the local context features, and the global context features to generate a down-regulation score [47]. Using this tool, six miRNAs were predicted to be affected by the rs142787485 SNP (hsa-miR-369-3p, hsa-miR-374a-5p, hsa-miR-374b-5p, hsa-miR-374c-5p, hsa-miR-378h, and hsa-miR-655). For five of the six miRNAs, the protective *RAB10* SNP is predicted to prevent, or break, the interaction between the miRNA and the *RAB10* transcript, while the interaction between the sixth miRNA (hsa-miR-378h), is only predicted to decrease in affinity [46].

Furthermore, miRNAs have been implicated in multiple instances to play a role in neurodegeneration. As discussed earlier in Chapter 2, *LMNA* is regulated by miR-9 [48], while in AD, APP is targeted by multiple miRNAs that are blocked by identified genetic variants [49]. For *RAB10*, two of the predicted variants, hsa-miR-369-3p and hsa-miR-655, were both identified to be downregulated in AD along with *RAB10* [37-40, 50] (Table 3.1). Therefore, one hypothesis is that rs142787485 is providing protection against AD by disrupting the binding affinity of select miRNAs. Of course, there are some limitations with this hypothesis. Using the Mayo Clinic Brain Bank, it is shown that *RAB10* is upregulated in AD which is associated with an increase in the Aβ42/40 ratio in the brain, which is more likely to result in toxic plaque formation [35]. Therefore, it seems unlikely that a protective SNP would reduce disease risk by interfering with the binding of miRNA that serve to keep expression down. However, until further experimental work is done, more will have yet to be seen. In addition to miRNAs, the 3'-UTR also serves as a binding site for proteins that also carry out post-transcriptional regulation. These RNA binding proteins (RBPs) bind the 3'-UTR and recruit various effectors [51].

Therefore, there is a possibility that rs142787485 also influences *RAB10* expression through differential binding of RBPs to the 3'-UTR. However, further research is required to further explore this.

Table 3.1: Relative expression of various *RAB10*-targeting miRNAs across different studies.

miRNA	Family	Genome Context	miRNA Sequence (Seed Sequence; SNP site underlined)	Interaction Type	Conserved Species	GSE16759	GSE63501	GSE46131	GSE48552
hsa-miR-369-3p	miR-154	chr14: 101065598-101065667 [+]	AAUAAUACAUGGUUGA UCUUU (**GUAUUAUA**)	8mer	Conserved among human, chimp, rhesus, squirrel, mouse, rat, rabbit, pig, cow, cat, dog, brown bat, elephant, opossum	↓	↑*	–	↓
hsa-miR-655-3p	miR-154	chr14: 101049550-101049646 [+]	AUAAUACAUGGUUAAC CUCUUU (**UGUAUUA**)	7mer-m8	Conserved among human, chimp, rhesus, squirrel, mouse, rat, rabbit, pig, cow, cat, dog, brown bat, elephant, opossum	↓	–	–	↑
hsa-miR-374a-5p	miR-374	chrX: 74287286-74287357 [-]	UUAUAAUACAACCUGA UAAGUG (**UAUUAUA**)	7mer-m8	Conserved among human, chimp, rhesus, squirrel, mouse, rat, rabbit, pig, cow, cat, dog, brown bat, elephant, opossum				
hsa-miR-374b-5p	miR-374	chrX: 74218547-74218618 [-]	AUAUAAUACAACCUGC UAAGUG (**UAUUAUA**)	7mer-m8	Conserved among human, chimp, rhesus, squirrel, mouse, rat, rabbit, pig, cow, cat, dog, brown bat, elephant, opossum	↓	–	–	↑
hsa-miR-374c-5p	miR-374	chrX: 74218549-74218618 [+]	AUAAUACAACCUGCUAA GUGCU (**UGUAUUA**)	7mer-m8	Conserved among human, chimp, rhesus, squirrel, mouse, rat, rabbit, pig, cow, cat, dog, brown bat, elephant, opossum				

*Insignificant

3.5 Discussion

In a 2012 study, a coding variant for *APP* (A673T) was identified from whole genome sequencing data from 1,795 Icelanders [52]. Since then, more variants have been discovered across many different genes, including, but not limited to, *APOE*, *SORL1*, *ABCA1*, and *MS4A* [1].

Novel genes and pathways that contribute to the pathogenesis of AD provide insights into strategies to prevent or treat the disease. The amyloid hypothesis, which proposes that the accumulation of Aβ triggers the cascade of events that lead to AD, has been the focus of AD therapeutic development for decades. The development of anti-Aβ therapeutics remains the primary approach to treating AD based on our current understanding of the earliest features of this disease [53]. In this review, we emphasize the importance of RAB10 in the processing of

APP and the production of Aβ. The function of RAB10 in intracellular trafficking and evidence that a reduction of *Rab10* results in a reduction of the Aβ42/40 ratio makes inhibition of RAB10 a potential therapeutic avenue.

There are several existing strategies for therapeutic inhibition of a gene product. Potential technologies for targeting of RAB10 are small molecules, antibodies, and antisense oligodeoxynucleotide technologies. For each of these approaches the challenge of delivery across the blood brain barrier (BBB) is a significant one [54]. A molecule with high lipid solubility and molecular mass less than 400Da generally can diffuse across the BBB. These criteria limit the classes of small molecules that can be considered as potential therapeutic molecules for AD. Generally, the BBB does not permit the crossing of many antibodies to achieve an adequate therapeutic concentration without severe peripheral consequences. Several approaches have been developed to deliver antibodies to the brain. Bispecific antibodies have been developed that leverage the Transferrin receptor to successfully increase BBB penetration [55, 56]. In addition, antibody analogs that can cross the BBB are in development (Patent #EP3309171). However, even if successful across the BBB could be achieved, the targeting of intracellular proteins by these antibodies also poses a significant challenge. Antisense oligonucleotides do not readily cross the BBB [57]. However, at present, intrathecal bolus injection is an effective method for ensuring distribution in neurons and glial cells in the brain [58].

Approaches to the development and delivery of small molecule therapeutics are mature and the path, and pitfalls, are well established. Small molecules are effective enzyme inhibitors, receptor ligands, or allosteric modulators. The nature of small molecule activity can make it difficult to find the balance between efficacy and side effects when treating humans [54]. Despite these challenges, small molecule drug development has seen many successes and greater than

90% of existing therapeutics use small molecules. Small GTPases similar to RAB10 have been successfully targeted using small molecules in the past. One important use is the development of molecules to block oncogenic properties of the RAS protein to treat cancer [59]. Recent discoveries about the structure of small GTPases and advances in targeting strategies have further increased efforts to use these important proteins as therapeutic targets [60]. Targeting approaches, including interference with nucleotide binding, inactivation by irreversible covalent modification, inhibition of GTPase-GEF interactions, inhibition of GTPase-Effector interactions, and stabilization of GTPase-Protein Complexes have been successful and are reviewed by Cromm et. Al. 2015 [60]. While challenges regarding specificity and crossing the blood brain barrier remain, these advances create some optimism about the use of small molecules to inhibit RAB10 and impact AD pathology.

Antibodies function in extra- and intracellular immunity to recognize foreign or abnormal agents and target them for destruction with very high specificity. The production of monoclonal antibodies (mAb) has resulted in their use for the treatment of a wide range of human diseases [55]. There are currently >60 approved mAbs for human therapy and >50 in late-stage clinical trials [61].

Rnase H-dependent antisense oligonucleotides technology is a popular method for knockdown in cell culture. It offers specific and efficient knockdown and is a powerful tool for functional studies of genes with unknown function [62]. Antisense technology has challenges such as site specificity, toxicity at high concentrations, and the difficulty of targeting specific cell-types. However, it is a mature technology and antisense oligonucleotides offer a means to manipulate specific steps in mRNA processing, for example splicing [53]. As discussed previously, *in vitro* reduction of *Rab10/RAB10* expression using shRNA and RNAi has been

successful [36]. Expansion of antisense oligodeoxynucleotide from *in vitro* to *in vivo* represents a promising therapeutic avenue given recent successes with Spinal muscular atrophy and Huntington's disease [63, 64].

As the field of AD genetics has progressed, it has become increasingly clear that critical work needs to be done to understand not only the variants that increase disease risk, but also the variants that confer resilience to disease. Not only will such important work shed increasing light on the cellular and molecular mechanisms for how the brain combats AD, but will also assist researchers in developing more effective novel therapeutics to treat AD as well as other devastating forms of dementia and neurodegeneration.

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Chapter 4: Phospholipase D3 contributes to Alzheimer's disease risk via disruption of Aβ clearance and microglia response to amyloid plaques

4.1 Abstract

Alzheimer's disease (AD) is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain. AD is also the result of complex genetic architecture that can be leveraged to understand pathways central to disease processes. We have previously identified coding variants in the *phospholipase D3* (*PLD3*) gene that double the late-onset AD risk. However, the mechanism by which PLD3 impacts AD risk is unknown. One AD risk variant, *PLD3* p.A442A, disrupts a splicing enhancer-binding site and reduces *PLD3* splicing in human brains. Using differentiated induced pluripotent stem cells from a *PLD3* p.A442A carrier and CRISPR-reverted, isogenic control, we show that *PLD3* p.A442A cortical neurons exhibit a *PLD3* splicing defect and a significant increase in Aβ42 and Aβ40, both of which are corrected upon reversion of the risk allele in isogenic control neurons. Thus, *PLD3* p.A442A is sufficient to alter *PLD3* splicing and Aβ metabolism. While the normal function of PLD3 is poorly understood, *PLD3* is highly expressed in neurons and brain regions most susceptible to amyloid pathology. *PLD3* expression is significantly lower in AD brains than controls, suggesting that PLD3 may play a role in sporadic AD. Thus, we sought to determine whether PLD3 contributes to Aβ accumulation in AD. In a mouse model of amyloid accumulation, loss of *Pld3* increases interstitial fluid (ISF) Aβ and reduces Aβ turnover. AAV-mediated overexpression of *PLD3* in the hippocampus decreased ISF Aβ levels and accelerated Aβ turnover. To determine whether PLD3-mediated reduction of ISF Aβ impacts amyloid accumulation, we measured amyloid plaque abundance and size after significant Aβ deposition. We found that in the absence of *Pld3*, amyloid plaques were less compact and more diffuse. Additionally, we observed reduced recruitment of microglia to amyloid plaques in the absence of

Pld3. PLD3 may impact amyloid accumulation and AD risk through disrupted microglia function as *PLD3* is enriched in disease associated microglia in human brains. Together, our findings demonstrate that PLD3 regulates Aβ clearance through cell-autonomous and non-cell-autonomous pathways in a manner that likely contributes to AD risk.

4.2 Introduction

Alzheimer's disease (AD) is pathologically defined by neuronal loss and the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain. Genetic, biochemical, and neuropathologic data suggest that Aβ aggregation is central to initiating AD pathogenesis [1]. Rare mutations in *APP*, *PSEN1*, and *PSEN2* cause dominantly inherited AD. Late-onset AD (LOAD) also has a strong genetic component [2]. Identifying novel loci that affect LOAD risk is critical to our understanding of the underlying etiology of AD and novel therapeutic pathways.

The genetic architecture that underlies LOAD is complex [2]. Large-scale genomic studies have led to the identification of novel genes and risk loci that contribute to AD [2, 3]. Whole exome sequencing of densely affected LOAD families has revealed a rare genetic variant within *PLD3* (p.V232M) that perfectly segregated with disease in two independent families and doubled AD risk in seven independent case-control series (4,998 AD cases/6,356 controls; OR=2.10, $p=2.93\times10^{-5}$) [4]. Gene-based analyses indicated that multiple variants in *PLD3* increase AD risk in European (EA) and African American (AA) populations (e.g.: p.M6R, p.V232M, p.A442A; EA: OR=2.75, $p=1.44x10^{-11}$; AA: OR=5.48, $p=1.40x10^{-3}$) [4].

PLD3 is a non-classical member of the phospholipase D (PLD) family of enzymes, with no known function [5-7]. *PLD3* is expressed in pyramidal neurons within the brain, and in AD brains, PLD3 co-localizes with amyloid plaques [8, 9]. Common variants in *PLD3* are associated with CSF Aβ levels, an AD biomarker [10]. *In vitro*, *PLD3* expression is correlated with extracellular Aβ levels: *Pld3* silencing is associated with increased Aβ levels, and *PLD3*

overexpression is associated with reduced Aβ levels [4]. Thus, PLD3 may play a broader role in LOAD.

Here, we sought to define the contribution of *PLD3* risk variants to AD-related phenotypes in human stem cell models and the role of PLD3 in amyloid pathology in mouse models. We found that a *PLD3* risk variant is sufficient to increase Aβ levels in stem cell-derived neurons. In animal models of amyloid accumulation, *Pld3* silencing reduces Aβ turnover and alters the composition of amyloid plaques. In the absence of *Pld3*, microglia recruitment to plaques is attenuated. Together, this study suggests that PLD3 contributes AD pathogenesis via Aβ clearance through cell-autonomous and non-cell-autonomous pathways.

4.3 Materials and Methods

Patient Consent

Skin biopsies were collected following written informed consent from the donor. The Washington University School of Medicine Institutional Review Board and Ethics Committee approved the informed consent (IRB 201104178, 201306108). The consent allows for the use of tissue by all parties, commercial and academic, for research but not for human therapy.

Dermal Fibroblast Isolation

Dermal fibroblasts were isolated from skin biopsies obtained from the Knight Alzheimer Disease Research Center (ADRC) research participants. Briefly, skin biopsies were collected by surgical punch and stored in Fibroblast Growth Media (Lonza). To isolate dermal fibroblasts from a skin biopsy, the biopsies were rinsed with PBS and cut lengthwise with dissecting scissors. The resulting tissue sections were then plated into a dry 24-well tissue culture-treated

plate (approximately 6-12 sections). After removing excess PBS from the wells, 300ul of fibroblast growth media (Lonza) was carefully added and tissue was incubated at 37°C and 5% CO_2. After 24 hours, tissue was supplemented with 1mL fibroblast growth media and media changes were repeated every 3-4 days. Fibroblast cells migrated from the tissue within two weeks of culture. Dermal fibroblasts were maintained in fibroblast growth media (Lonza) supplemented with penicillin/streptomycin.

iPSC Generation, Characterization, and Maintenance

Human fibroblasts (F13504) were transduced with non-integrating Sendai virus carrying the four factors required for reprogramming: OCT3/4, SOX2, KLF4, and cMYC [11, 12]. Cells showing morphological evidence of reprogramming were selected by manual dissection.

Human iPSCs were cultured using feeder-free conditions (Matrigel, BD Biosciences, Franklin Lakes, NJ, USA). Human iPSCs were thawed (1-2 x 10^6 cells/mL), diluted in DMEM/F12, and centrifuged at 750 rpm for 3 minutes. The resulting iPSC pellet was then diluted in mTeSR1 supplemented with Rock inhibitor (Y-27632; 10μM final). IPSC were subsequently cultured in 37°C, 5% CO_2 with daily medium changes (mTesR1, STEMCELL Technologies, Vancouver, BC, CA).

All iPSC lines were characterized using standard methods [11]. Each line was analyzed for pluripotency markers (OCT4A, SOX2, SSEA4, TRA1-80) by immunocytochemistry (ICC) (Invitrogen A24881) and quantitative PCR (qPCR); for chromosomal abnormalities by karyotyping; and for *PLD3* variant status by Sanger sequencing (Supplemental Figure 4.1).

Genome editing

We used CRISPR/Cas9 to generate isogenic control lines for the *PLD3* p.A442A iPSC as previously described [13]. The p3s-Cas9HC Cas9 expression plasmid (Addgene 43945) and CRISPR reagents (Addgene plasmid 43860) were used [14]. Guide RNAs were designed to overlap with the allele to be modified and have at least 3bp of mismatch to any other gene in the human genome. The activity of the guide was validated using a mismatch detection assay to determine non-homologous end-joining efficiency in K562 cells. A correctly edited clone and an unmodified clone were identified, expanded and characterized as described above for karyotyping and pluripotency markers. Sanger sequencing was performed for the on-target and predicted off-target sites.

Cortical neuron differentiation

IPSCs were differentiated into neuronal cells using a two-step approach as previously described [13]. IPSCs were plated at a density of 65,000 cells per well in neural induction media (STEMCELL Technologies) in a 96-well v-bottom plate to form highly uniform neural aggregates and, after five days, transferred onto culture plates. The resulting neural rosettes were then isolated by enzymatic selection (Neural Rosette Selection Reagent; STEMCELL Technologies) and cultured as neural progenitor cells (NPCs). NPCs were differentiated in planar culture in neuronal maturation medium (neurobasal medium supplemented with B27, GDNF, BDNF, cAMP). Neurons typically arise within one week after plating, identified using immunocytochemistry for β-tubulin III (Tuj1). The cells continued to mature and were analyzed at six weeks.

Immunocytochemistry

IPSC-derived neurons were grown on PLO/laminin-coated 8-well chamber slides (Millipore). Culture media was aspirated, and cells were then washed and fixed with 4% paraformaldehyde (Sigma). After several washes, cells were permeabilized with 0.1% Triton X-100 in PBS. Cells were then blocked in 0.1% bovine serum albumin (BSA; Sigma) and treated with primary (Tuj1) and secondary antibodies diluted in 0.1% BSA. Immunostained cells were then imaged (Nikon Eclipse 80i fluorescent microscope).

Transcriptomics and Digital Deconvolution

RNA was extracted from iPSC-derived neurons from *PLD3* p.A442A vs. the isogenic controls using Tissue Lyser LT and RNeasy Mini Kit (Qiagen, Hilden, Germany). RNA-seq paired-end reads with read lengths of 2 × 150 bp were generated using Illumina HiSeq 4000 with a mean coverage of 80 million reads per sample. FastQC was applied to perform quality control and aligned to human GRCh37 primary assembly using Star (ver 2.5.2b). We applied Salmon transcript expression quantification (ver 0.7.2) to infer the gene expression. To estimate the relative proportion of major brain cell types in the dish, digital deconvolution was performed as previously described using a reference marker panel [15].

PLD3 Splicing Assay

RNA was extracted from cell lysates with an Rneasy kit (Qiagen) according to the manufacturer's protocol. Extracted RNA (10ug) was converted to cDNA by PCR using the High-Capacity cDNA Reverse Transcriptase kit (ABI). SYBR-green primers were designed using Primer Express software, Version 3 (ABI). Real-time PCR assays were used to quantify *PLD3* exon 7 (forward primer: GCAGCTCCATCCCATCAACT; reverse: CTTGGTTGTAGCGGGTGTCA), exon 8 (forward primer: CTCAACGTGGTGGACAATGC;

reverse: AGTGGGCAGGTAGTTCATGACA), exon 9 (forward primer: ACGAGCGTGGCGTCAAG; reverse: CATGGATGGCTCCGAGTGT), exon 10 (forward primer: GGTCCCCGCGGATGA; reverse: GGTTGACACGGGCATATGG) and exon 11 (forward primer: GCTGCTGGTGACGCAGAAT; reverse: AGTCCCAGTCCCTCAGGAAAA). Each qPCR analysis included technical replicates and biological triplicates. Real-time data were analyzed using the comparative Ct method. Only samples with a standard error of <15% were analyzed. The Ct values for exon 11 were normalized with the Ct value for exons 7-10. The relative exon 11 levels for the iPSC-derived neurons from *PLD3* p.A442A vs. the isogenic control were compared using a Tukey's t-test.

Aβ Measurements

Conditioned medium was collected from neurons after six weeks in culture and centrifuged at 3,000xg at 4°C for 10 minutes to remove cell debris. The levels of Aβ42 and Aβ40 were measured in cell culture media by sandwich ELISA as described by the manufacturer (Life Technologies). To account for variability in transfection efficiency between experiments, ELISA values were obtained (pg/mL) and corrected for total intracellular protein (ug/mL). Statistical difference was measured using an unpaired Student's t-test.

PLD3 expression in AD and neuropathology free human brains

Laser microdissected neurons from AD and control brains were previously reported and deposited as GSE5281 [38]. Brain samples were analyzed from 47 individuals of European descent clinically and neuropathologically confirmed AD cases or controls. The 33 AD samples were 54.5% female with a mean age of 79.9 years (range 73–86.8) and an average postmortem interval (PMI) of 2.5 hours. The 14 control brains were 28.6% female with a mean age of 79.8

years (range 70.1–88.9). Samples were obtained from the entorhinal cortex, hippocampus, medial temporal gyrus, posterior cingulate, superior frontal gyrus, and primary visual cortex. RNA expression was measured using an Affymetrix GeneChip for gene expression. The log-transformed expression values were analyzed with brain region, age, and sex as covariates to analyze RNA expression.

Gene expression was analyzed in a second, independent, publicly available dataset of the temporal cortex of 76 control and 80 AD brains (syn6090813). Differential gene expression comparing controls v. AD was performed using a "Simple Model", multi-variable linear regression analyses were conducted in R, using normalized gene expression measures including sex, age-at-death, RNA integrity number, brain tissue source, and flowcell as covariates [16]. Statistical difference was measured using an unpaired Student's t-test.

Single nuclei RNAseq in human brains

Human parietal cortices were processed to isolate nuclei, and the nuclei were then sequenced using the 10X Chromium single cell Reagent Kit v3, with 10,000 cells per sample and 50,000 reads per cell for each of the 74 samples as previously described [17, 18]. The CellRanger (v3.0.2 10Xgenomics) software was used to align the sequences and quantify gene expression. We used the GRCh38 (3.0.0) reference to prepare a pre-mRNA reference. Filtering and QC were done using the Seurat package (3.0.1) on each subject individually. After the Uniform Manifold Approximation and Projection (UMAP) analysis was performed with the top 14 PCs, we then used Seurat *FindNeighbors* and *FindClusters* functions to identify unique cell states or subclusters. Samples included in the subsequent analyses are summarized in Supplemental Table 4.1. To identify associations between cell-type transcriptional state and

disease status or genetic strata (control, sporadic AD (sAD), TREM2), we applied linear regression models to test the cell state compositions of each subject. The proportions were normalized using a cube root transformation and were corrected by sex and age of death. Differentially expressed genes among the individual cell states were identified using a linear mixed model that corrected for sex and subject. To determine if there was unique functionality or potentially altered expression levels associated with disease/genetic carriers in the alternative cell states, we employed linear mixed model that predicted the expression level of each gene, modeled as zero-inflated negative binomial distributions and corrected for sex and age of death. Donors were modeled as random variables as previously described [17]. Data can be publicly accessed at http://ngi.pub/SNARE.

Mouse Models

Animal care and surgical procedures were approved by the Animal Studies Committee of Washington University School of Medicine in accordance with guidelines of the United States National Institutes of Health. APPswe/PS1ΔE9 transgenic mice (APP/PS1; The Jackson Laboratory; 034829) [19] of both sexes were used in this study. APP/PS1 mice were maintained on a C57bl6;C3B6 mixed background.

Pld3-KO mice were generated using CRISPR/Cas9 technology. gRNAs were designed to target an early conserved exon (mPld3.g19; TGCTGTGAGCACCGGCAAGGNGG). Guide activity was assessed in mouse neuroblastoma cells (N2A) using a T7E1 mismatch detection assay as previously described [13]. RNA was injected into the pronuclei of fertilized, viable murine oocytes isolated from a set of C57Bl/6xCBA (hybrid) female mice. Founders were identified using mPLD3 screening primers SM406.Cel.F 5’ CATGGGCACTGTATCCCATCT

3’ and SM406.Cel.R 5’ AGGACACAAAAACGTCACCCT 3’, which generated a parental band (575bp) and fragments (307 and 268bp). Subsequent generations were backcrossed to C57Bl/6;C3B6 (Supplemental Figure 4.2).

APP/PS1 mice were crossed with the *Pld3*-KO mice to generate APP/PS1x*Pld3*$^{+/-}$. APP/PS1x*Pld3*$^{+/-}$ were crossed to obtain APP/PS1x*Pld3*-KO (APP/PS1x*Pld3*$^{-/-}$) mice and APP/PS1x*Pld3*-WT (APP/PS1x*Pld3*$^{+/+}$) littermates. Animals of both sexes were used in the study.

Intracranial AAV-mediated expression of PLD3 and shPLD3

Adeno-associated virus (AAV8) particles were generated that express AAV-CMV-hPLD3-WT-GFP, AAV-CMV-GFP (control), AAV-U6-shPLD3-GFP, and AAV-U6-shScrambled-GFP (control). Viral particles were injected into the hippocampus of APP/PS1 mice of both sexes to produce widespread transduction in hippocampal neurons as previously described [20, 21]. Two uL of AAV particles (1.5 X 10^{12} vg/ml) were stereotaxically injected bilateral hippocampi (2µl over 10 minutes) in 3-month-old APP/PS1 transgenic mice (prior to plaque appearance) [22, 23]. Virus is detectable at least 4-5 months post-injection [21, 24].

In Vivo Microdialysis

Prior to plaque accumulation (5 months of age) and two months post AAV8-injection, hippocampal ISF Aβ levels were quantified using microdialysis in APP/PS1 mice as previously described [25, 26]. The use of a 38-kDa MWCO semi-permeable membrane allows for molecules smaller than this cut-off to diffuse into the probe. The probe was flushed with perfusion buffer at a constant rate (1.0µl/minute) and collected into a refrigerated fraction

collector, and then assayed by sandwich ELISA ($A\beta_{x\text{-}40}$). A mouse monoclonal anti-$A\beta_{40}$ capture antibody (mHJ2) made in-house was used in conjunction with a biotinylated central domain detection antibody (mHJ5.1) and streptavidin-poly-HRP-40 (Fitzgerald Industries, Acton, MA)[27]. During microdialysis, mice were housed in cages that permit free movement and ad-libitum food/water, while ISF Aβ was sampled. Baseline levels of ISF Aβ were sampled every 60 minutes between hours 5-12 (after the microdialysis probe insertion) and averaged to determine the baseline ISF Aβ levels in each mouse. At hour 12, mice were administered the γ-secretase inhibitor Compound E (20mg/kg), intraperitoneally, which enabled us to determine the elimination half-life of ISF Aβ [28]. Aβ half-life was calculated using first-order kinetics. Microdialysis was performed with sham and littermate controls. Statistical difference was measured using an unpaired Student's t-test.

To evaluate the impact of *Pld3* on Aβ kinetics, APP/PS1x*Pld3*-WT and APP/PS1x*Pld3*-KO mice were implanted at one-month post-injection with a microdialysis probe with a 38-kDa MWCO probe, and ISF was collected as described above. After 12 hours, γ-secretase inhibitor LY411575 (3mg/kg in 50:50PBS:PEG400) was administered intraperitoneally to define the elimination half-life of ISF Aβ. Aβ half-life was calculated as described above. Microdialysis was performed with sham and littermate controls. Statistical difference was measured using an unpaired Student's t-test.

Brain Tissue Preparation

APP/PS1x*Pld3*-WT and APP/PS1x*Pld3*-KO mice were anesthetized with sodium pentobarbital and perfused with 0.3% heparin in PBS at nine months of age. Brains were dissected and cut into two hemispheres. The right hemisphere was snap-frozen on dry ice and

stored at 80°C for biochemical analyses. The left hemisphere was fixed in 4% paraformaldehyde for 24 hours, followed by 30% sucrose in PBS at 4°C. Coronal sections (50 µm) were cut on a freezing-sliding microtome. Collected slices were stored in cryoprotectant solution (0.2 M phosphate-buffered saline, 30% sucrose, and 30% ethylene glycol) at -20°C.

Immunohistochemistry

APP/PS1x*Pld3*-WT and APP/PS1x*Pld3*-KO brains were cut into 50µm sections from the rostral anterior commissure to the caudal hippocampus. Brains sections (n=20 mice per group) were incubated in 0.3% H_2O_2 in Tris-buffered saline (TBS) for 10 minutes and blocked in 3% milk in TBS-X for 30 minutes. Tissue was incubated in HJ3.4B antibody (anti-Aβ-1-13; 2.4 µg/ml; a generous gift from the Holtzman lab) overnight [29]. Sections are then incubated in Vectastain ABC elite solution in TBS (1:400) for 1 hour before incubating in 3,3'-Diaminobenzidine (DAB) solution. Sections were then mounted onto slides with Cytoseal (Thermo Scientific 8312-4). A Nanozoomer Digital Scanner (Hamamatsu Photonics) was used to create high-resolution digital images for the HJ3.4-stained brain slices. Total plaque coverage, total plaque count, and average plaque size were analyzed using NIH ImageJ software. Total plaque coverage was expressed as a percentage of the total area for each slice and averaged across the three slices per animal. Plaque count was expressed as the plaque count per nm^2 averaged across the three slices per animal. Plaque size was expressed in μm^2 averaged across all three slices for each mouse. Both the hippocampus and cortex were analyzed separately for each slice. Statistical difference for plaque size, percentage of total area, and plaque count per square millimeter was measured using an unpaired Student's t-test.

X-34 Plaque Staining

To evaluate X-34 positive plaque burden, frozen coronal brain sections (50 µm) were mounted on Superfrost Plus slides, permeabilized with 0.25% Triton X-100 in PBS for 30 minutes and stained with X-34 (0.01mM; Sigma SML1954) dissolved in 40% ethanol in PBS, pH 10 for 20 min. The tissue was then washed with 40% ethanol in PBS and mounted with Fluoromount G mounting medium. Slides were imaged using Cytation7 (BioTek) and quantified using NIH ImageJ software. A Cytation7 cell imaging multi-modal imager was used to create high-resolution images of the X-34 scanned brain sections. Total plaque coverage, total plaque count, and average plaque size were analyzed using NIH ImageJ software. Total plaque coverage was expressed as a percentage of the total area for each section and averaged across three sections per animal. Plaque count was expressed as the plaque count per square millimeter averaged across the three sections per animal. Plaque size was expressed in square microns averaged across all three sections for each mouse. Both the hippocampus and cortex were analyzed separately for each section. Statistical difference for plaque size, percentage of total area, and plaque count per square millimeter was measured using an unpaired Student's t-test.

Immunofluorescence

Coronal brain sections (50µm) were permeabilized in 0.25% Triton X-100 for 30 min at room temperature. Slices were then stained with X-34 (0.001 mM; Sigma SML1954) dissolved in 40% ethanol in PBS for 20 min and blocked in 3% BSA/3% Normal Donkey serum in 0.1% Triton X-100 in PBS. X-34-stained samples were immunostained with antibodies HJ3.4 (2.4ug/mL; α-Aβ1-13) or Iba1 (Abcam ab5076) and CD68 (BioRad MCA1957) at 4°C overnight. Three slices per animal were stained. Secondary antibodies of Alexa Fluor 488-conjugated donkey anti-rat IgG, Alexa Fluor 647-conjugated donkey anti-goat, and Alexa Fluor 647 donkey anti-mouse (Invitrogen). Slides were mounted with Fluoromount G mounting media.

High resolution 40x images were obtained using the Zeiss LSM 880 Confocal microscope with Airyscan. Z-stacks were analyzed using NIH ImageJ software, where max projection images (those with the highest signal intensity) were selected for each fluorescent channel. The Iba1 and CD68 signals were quantified within 15µm of the X-34-positive plaques. Iba1 and CD68 colocalization was also quantified. An outlier analysis was run using the ROUT method with a Q-value of 1%. Three outliers were removed from the APP/PS1x*Pld3*-KO mice in the Iba1 analysis. Statistical difference was measured using an unpaired Student's t-test.

To quantify HJ3.4 and X-34 colocalization, Z-stacks were analyzed using NIH ImageJ software, where max projection images were selected for each fluorescent channel. Plaque composition was quantified by measuring the percentage of HJ3.4 staining within X-34-positive areas. Nonfibrillar plaque area was normalized to the total X-34 area. A ROUT outlier analysis with a Q-value of 1% was run for each of these quantifications. No outliers were removed from the analysis of percent area. Four outliers were excluded in the APP/PS1x*Pld3*-WT mice, and three outliers were excluded in the APP/PS1x*Pld3*-KO mice in the nonfibrillar plaque area analysis. Statistical difference was measured using an unpaired Student's t-test.

4.4 Results

AD risk variant PLD3 p.A442A is sufficient to alter PLD3 splicing and Aβ levels

Three highly conserved, rare variants in *PLD3* increase AD risk: p.M6R, p.V232M, and p.A442A [4]. *PLD3* p.A442A (G>A) was associated with increased AD risk in four independent case-control datasets (p=3.78×10-7; OR=2.12) [4]. *PLD3* p.A442A was predicted to modify a splicing enhancer-binding site, SRSF1, *in silico* [4]. In the brains of *PLD3* p.A442A carriers,

total *PLD3* and exon 11-containing transcript expression were reduced compared to controls [4]. However, these association studies did not allow us to attribute the causality of the risk variant to the phenotype.

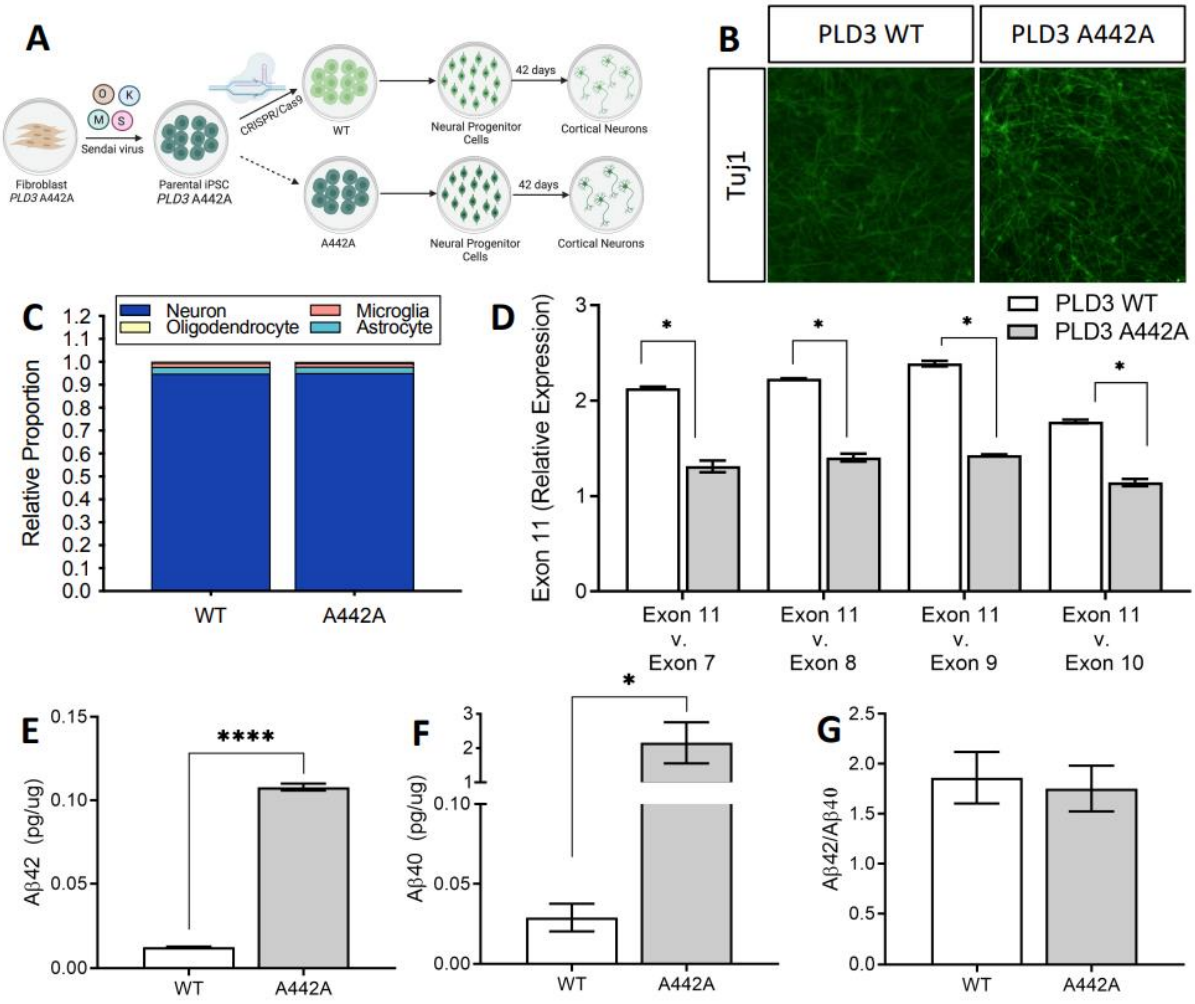


Figure 4.1: iPSC-neurons expressing *PLD3* p.A442A phenocopy splicing defects observed in human brains A. Fibroblasts from a *PLD3* p.A442A variant carrier were reprogrammed into induced pluripotent stem cells (iPSCs). CRISPR-Cas9 technology was used to generate an isogenic control line. IPSCs were then differentiated into cortical neurons (see Methods). Downstream assays were performed after 42 days in culture. B. iPSC-derived neurons stained with Tuj1 illustrate a similar capacity of p.A442A and isogenic controls (*PLD3* WT) to form neurons. C.

Digital deconvolution of iPSC-derived neurons from transcriptomic data illustrates a similar enrichment of neurons in *PLD3* p.A442A and isogenic controls *(PLD3* WT). D. Expression of *PLD3* exon 11 compared to *PLD3* exons 7, 8, 9, and 10. E-G. Sandwich ELISA of media from iPSC-derived neurons (pg/mL) and corrected for total protein measured by BCA (pg/µg). Aβ42 (E), Aβ40 (F), Aβ42/40 (G). Graphs represent mean ± SEM. *<0.05, ****<0.00005. Analyzed by two-tailed Student's *t* test.

Here, we coupled genome-editing with stem cell models to determine whether *PLD3* p.A442A is sufficient to alter *PLD3* splicing and phenocopy AD-related phenotypes. Primary dermal fibroblasts were obtained from a patient carrying a single copy of the *PLD3* p.A442A variant. Fibroblasts were de-differentiated into induced pluripotent stem cells using non-integrating Sendai virus. The resulting iPSC were characterized for pluripotency markers, the presence of the *PLD3* p.A442A variant, and chromosomal integrity (Supplemental Figure 4.1). To determine the causality of *PLD3* p.A442A on AD-related phenotypes, we used CRISPR/Cas9 to correct the A allele to G (wild-type) (Figure 4.1A) [13]. *PLD3* p.A442A and isogenic controls (*PLD3* WT) were then differentiated into cortical neurons using a growth factor-mediated approach as previously described (Figure 4.1A) [13], where they illustrated a similar capacity to form Tuj1-positive neurons (Figure 4.1B). To further verify the similarity between the cells in their capacity to form neurons, we estimated the relative proportion of neurons in the cultures using bulk transcriptomics and deconvolution methods that include all the major brain cell types [15]. We found that differentiated cultures from *PLD3* p.A442A and isogenic controls exhibited a similar enrichment of neurons (~95%; Figure 4.1C). These findings are consistent with a variant that impacts a late-onset disease, where we would not predict a significant developmental defect.

Having demonstrated that *PLD3* p.A442A and isogenic controls share a similar capacity to form neurons, we next asked whether the *PLD3* p.A442A variant was sufficient to alter *PLD3*

splicing in a manner consistent with our prior observations in human brains from *PLD3* p.A442A carriers [4]. RNA isolated from neurons expressing *PLD3* p.A442A and isogenic controls was converted to cDNA, and *PLD3* exons 7, 8, 9, 10, and 11 were amplified and quantified. We found that *PLD3* exons are significantly reduced in the *PLD3* p.A442A neurons, which is restored upon correction of the variant allele to WT (Figure 4.1D). To determine whether *PLD3* p.A442A neurons exhibit changes in Aβ, which would be consistent with a variant that impacts amyloid plaque deposition, we measured extracellular Aβ by sandwich ELISA in the media of *PLD3* p.A442A and isogenic control neurons. After correcting for total protein, we observed a significant increase in Aβ42 and Aβ40 in media from neurons expressing *PLD3* p.A442A (Figure 4.1E and 4.1F) without changing the Aβ42/40 ratio (Figure 4.1G) when compared to isogenic controls. Together, these findings illustrate that in nearly identical, isogenic neurons, the presence of the *PLD3* p.A442A is sufficient to alter *PLD3* transcripts and extracellular Aβ levels.

PLD3 expression is altered in LOAD brains

Having demonstrated that the AD risk variant in *PLD3* (*PLD3* p.A442A) was sufficient to alter *PLD3* transcripts and Aβ levels, we sought to determine whether *PLD3* is altered in LOAD. We examined *PLD3* expression in laser-captured microdissected neurons across multiple brain regions from AD cases and neuropathology-free controls. *PLD3* expression was significantly lower in AD brains compared with control brains in the entorhinal cortex, hippocampus, medial temporal gyrus, and superior frontal gyrus (Figure 4.2), regions that exhibit amyloid and tau pathology. Interestingly, *PLD3* expression was unaltered in the primary visual cortex, which is largely spared of AD pathology (Figure 4.2) [30]. *PLD3* expression was also significantly reduced in an independent cohort of temporal cortices isolated from AD and control

brains (β=-0.36; $p=3.23\times10^{-4}$) [31]. These findings are consistent with prior reports of reduced *PLD3* expression in LOAD brains [4].

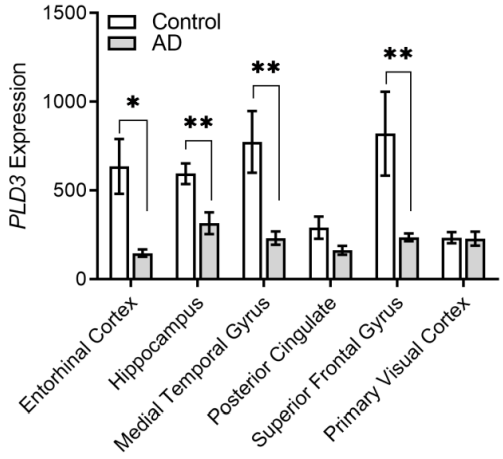


Figure 4.2: *PLD3* expression is significantly reduced in brain regions vulnerable to AD pathology. Laser capture of microdissected neurons from the brains of neuropathology confirmed control and AD brains [32]. Quantification of *PLD3* expression in laser microdissected neurons isolated from AD and control brains (AU). The graph represents mean ± SEM. *p<0.05. Analyzed by two-tailed Student's *t* test.

Pld3 regulates Aβ in APP/PS1 mice

PLD3 expression is reduced in brains from *PLD3* p.A442A carriers and in LOAD brains (Figure 4.2) [4], and overexpression or silencing of PLD3 in mouse neuroblastoma cells leads to inverse changes in Aβ levels [4]. Thus, we sought to determine whether modulating *PLD3* expression is sufficient to alter Aβ *in vivo*. In mice, Aβ is primarily generated in neurons and released into the ISF, where it can be cleared by extracellular proteolysis, transported into CSF or across the blood-brain barrier, or by cellular uptake and degradation. The steady-state level of ISF Aβ, thus, reflects these production and degradation/clearance mechanisms. We hypothesized that reducing endogenous *Pld3* expression, as observed in human AD brains, would elevate ISF

Aβ levels. To address this hypothesis, 3-month-old APP/PS1 mice were injected with AAV8 particles containing shPld3 or shScrambled (control) and evaluated at five months of age by *in vivo* microdialysis (Figure 4.3A). At five months of age, shPld3 was sufficient to significantly reduce endogenous *Pld3* transcript level in the hippocampus compared with scrambled controls by 28% (Figure 4.3B). This modest reduction of *Pld3* did not alter steady-state ISF Aβ levels (Figure 4.3C and 4.3D; p=0.27). Next, to test the impact of *Pld3* silencing on the Aβ elimination rate (half-life), Aβ levels were monitored after treatment with a γ-secretase inhibitor (Figure 4.3C). The secretase inhibitor rapidly blocks Aβ generation within minutes, then ISF is sampled hourly to calculate the rate of elimination of existing Aβ. Silencing of *Pld3* resulted in a 135% increase in Aβ elimination half-life (Figure 4.3C and 4.3E; p=0.0025). Thus, PLD3 is likely involved in Aβ clearance. The striking impact of a modest *Pld3* decrease in Aβ levels in the APP/PS1 mice led us to investigate the impact of a global knockout of *Pld3* on Aβ (Figure 4.3F). Global *Pld3* knockout mice were generated using CRISPR/Cas9. A guideRNA targeting an early, highly conserved exon was validated *in vitro* and injected into murine oocytes (see Methods; Supplemental Figure 4.2). Founders were established and backcrossed to C57Bl/6;C3B6 prior to breeding with APP/PS1 mice (Supplemental Figure 4.3C). Consistent with prior reports, *Pld3* KO mice were viable and did not exhibit gross defects [9, 33]. *Pld3*-deficient APP/PS1 mice exhibited a 35% increase in steady-state ISF Aβ at four months of age (Figure 4.3G-4.3I). In agreement with the AAV-mediated knockdown, *Pld3*-deficient APP/PS1 mice exhibited a 49% increase in Aβ elimination half-life following the administration of a γ-secretase inhibitor (Figure 4.3G and 4.3I). Thus, *Pld3* reduction in the brain is sufficient to reduce the turnover of ISF Aβ.

In vitro overexpression of *PLD3* was sufficient to reduce extracellular Aβ [4]. Thus, we asked whether overexpression of *hPLD3* in APP/PS1 mice could rescue the ISF Aβ phenotype (Figure 4.3A). The hippocampus of APP/PS1 mice was bilaterally injected with AAV8 particles containing hPLD3 or GFP (control) at three months of age, and two months later, ISF Aβ was

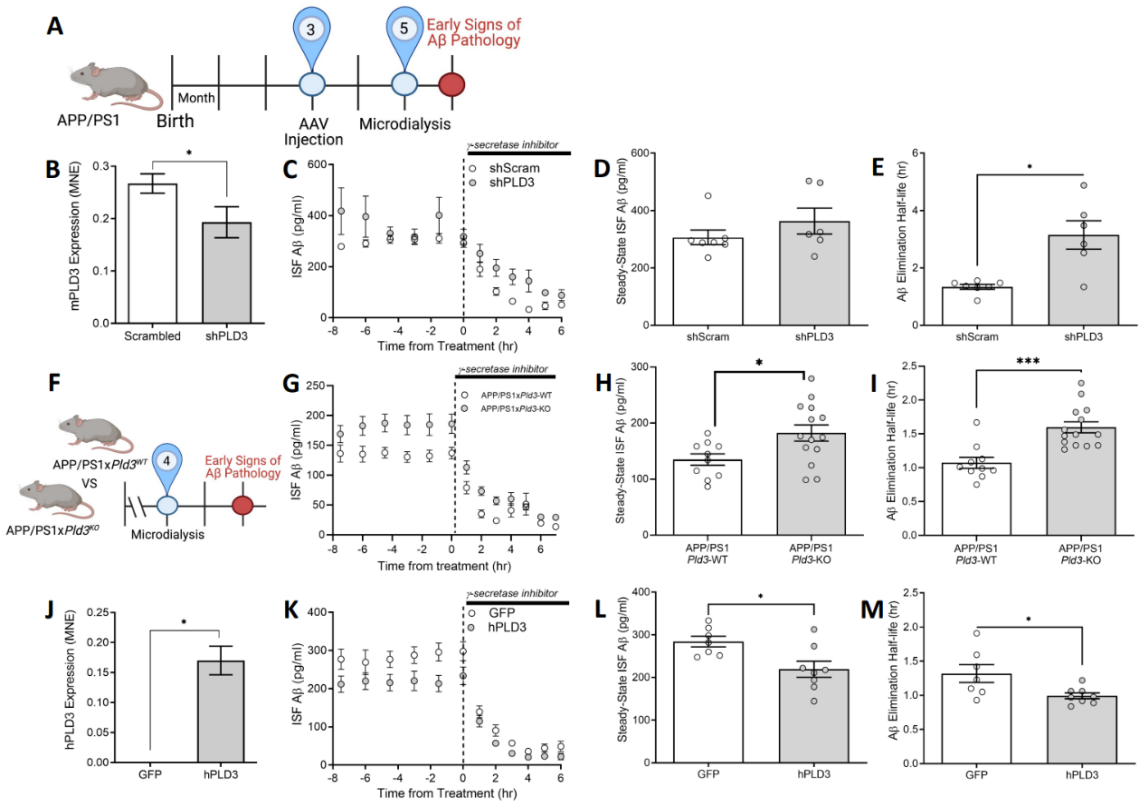


Figure 4.3: Bi-directional expression of *Pld3* alters Aβ turnover *in vivo*. A-E. The impact of *Pld3* silencing on ISF Aβ. A. Diagram of the experimental timeline: APP/PS1 mice were injected with shScramble shPld3 (compared to *shScram* control)-containing AAV8 particles at three months of age and were evaluated by *in vivo* microdialysis at five months of age. *shScramble* (n=7) and *shPld3* (n=6). B. Knockdown of endogenous *Pld3*. C. Aβ levels in ISF sampled over 14 hours in *shScram*, and *shPld3* injected APP/PS1 mice. D. Steady-state levels of ISF Aβ. E. Elimination half-life of ISF Aβ. F-I. The impact of *Pld3* KO on ISF Aβ. F. Diagram outlining the experimental timeline: APP/PS1x*Pld3*-WT and APP/PS1x*Pld3*-KO mice were evaluated by *in vivo* microdialysis at four months of age. APP/PS1x*Pld3*-WT (n=10), APP/PS1x*Pld3*-KO (n=14). G. Aβ levels in ISF sampled over 14 hours in APP/PS1x*Pld3*-WT and APP/PS1x*Pld3*-KO mice. H. Steady-state levels of ISF Aβ. I. Elimination half-life of ISF Aβ. J-M. APP/PS1 mice were injected with hPLD3 (compared to GFP control)-containing AAV8 particles at three months of age and were evaluated by *in vivo* microdialysis at five months of age. GFP (n=7), hPLD3 (n=8). J. Overexpression of *hPLD3*. K. Aβ levels in ISF sampled over 14 hours in *GFP* and *hPLD3* injected APP/PS1 mice. L. Steady-state levels of ISF Aβ. M. Elimination half-life of ISF Aβ. Graphs represent mean ± SEM. *<0.05, ***<0.0005. Analyzed by two-tailed Student's *t* test.

measured by microdialysis (Figure 4.3A). Overexpression of *hPLD3* significantly reduced steady-state levels of ISF Aβ and Aβ elimination half-life by approximately 25% (Figure 4.3J-M). Taken together, our findings illustrate that PLD3 expression regulates Aβ turnover in APP/PS1 mice.

Pld3-deficiency alters plaque composition

Impairment in protein clearance has been implicated in amyloid plaque accumulation and AD pathogenesis [34, 35]. Aβ aggregation in the extracellular space (ISF) into soluble oligomers or insoluble amyloid plaques is a critical driver of AD pathogenesis, and conversion of monomeric Aβ into these aggregates is facilitated at higher concentrations [36]. Thus, we sought to determine whether increased ISF Aβ in four months old APP/PS1x*Pld3*-KO mice could impact amyloid plaque pathology in older animals (Figure 4.4A). To assess plaque pathology, APP/PS1x*Pld3*-KO mice were sacrificed at nine months of age, and brain sections were co-stained with HJ3.4 (total Aβ) and X-34 (β-sheet rich dense cores; Figure 4.4B). Plaque composition was then analyzed as the percent of X-34 stain within HJ3.4-positive plaques (termed: fibrillar plaques) and the extent of HJ3.4-positivity outside X-34 plaques (termed: Non-fibrillar plaque area). In APP/PS1x*Pld3*-KO mice, the percentage of fibrillar plaques was significantly reduced compared with APP/PS1xPld3-WT mice (Figure 4.4C). Conversely, the non-fibrillar plaque area was significantly increased compared with APP/PS1xPld3-WT mice (Figure 4.4D). In complementary analyses, we found that Aβ plaque size was significantly increased in the cortex of APP/PS1x*Pld3*-KO compared with APP/PS1x*Pld3*-WT mice (Supplemental Figure 4.3) without a change in the overall plaque burden as defined by the percentage area of HJ3.4-positive immunostaining (e.g., plaque density). X-34 staining remained

unchanged in the absence of *Pld3* (Supplemental Figure 4.4). Thus, *Pld3* KO impacts plaque composition, shifting the pathology to a less fibrillar structure [37].

Pld3 deficiency impact microglial recruitment to amyloid plaques

Table 4.1: Differential microglia gene expression in APP/PS1x*Pld3*-KO compared with APP/PS1x*Pld3*-WT brains

Gene	Log2FoldChange	p-value
Trem2	0.48	1.07E-03
Tyrobp	0.57	1.06E-03
Ctsd	0.25	4.18E-03
Cst7	0.56	2.91E-02
Cd68	0.35	6.27E-02
Aif1	0.33	1.08E-01
Tmem119	0.04	6.49E-01
P2ry12	0.05	5.99E-01

The absence of *Pld3* in the APP/PS1 mice resulted in more non-fibrillar plaques. This shift in plaque composition is similar with findings from *Trem2*- and *ApoE*-deficient APP/PS1 mice [38-41]. Loss of these AD risk genes also significantly reduced microglial recruitment to the amyloid plaques [38-41]. Thus, we hypothesized that the loss of *Pld3* may alter the microglial response in APP/PS1 mice. To test this hypothesis, fixed brain tissue from the APP/PS1x*Pld3*-KO and APP/PS1x*Pld3*-WT mice were stained for total microglia (Iba1), activated microglia (CD68), and dense core Aβ plaques (X-34) (Figure 4.5A). The amount of activated microglia as a percentage of total microglia was similar between APP/PS1x*Pld3*-KO and APP/PS1x*Pld3*-WT mice (Figure 4.5D). However, APP/PS1x*Pld3*-KO mice exhibited a significant reduction in the recruitment of microglia around the X-34-positive plaques (Figure

4.5B). No significant change was observed in the amount of CD68-positive, activated microglia around the X-34-positive (Figure 4.5C and 4.5D). *Pld3* deficient APP/PS1 mice also exhibited a significant increase in expression of microglia genes associated with neurodegeneration including *Trem2*, *Tyrobp*, *Ctsd*, and *Cst7* (Table 4.1) without a corresponding change in homeostatic microglia genes (Table 4.1). Thus, loss of *Pld3* impacts microglia function in response to amyloid plaques.

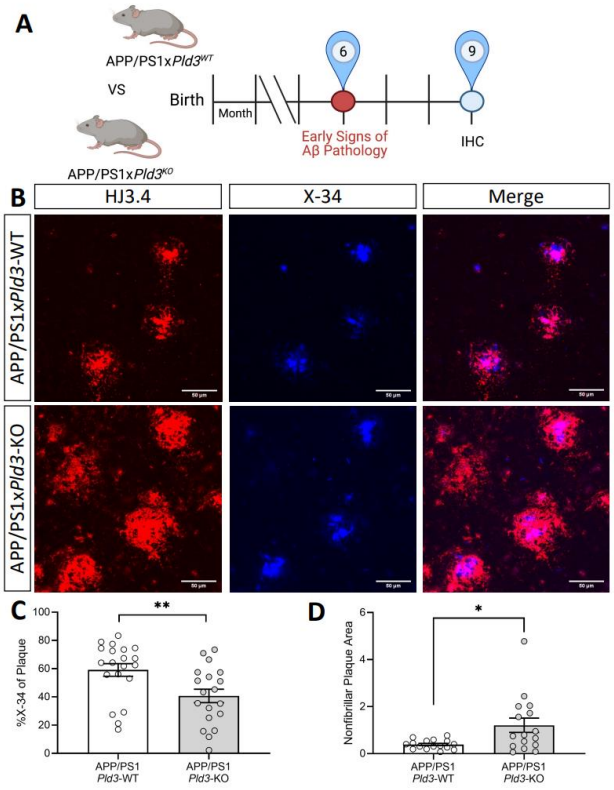


Figure 4.4: Loss of *Pld3* alters plaque composition in APP/PS1 mouse cortex. A. Experimental timeline. APP/PS1x*Pld3*-WT (n=20), APP/PS1x*Pld3*-KO (n=15). B. Representative confocal images of mouse cortex co-stained with HJ3.4 (total Aβ) and X-34 (β-sheet rich dense cores). C-D. Quantification of the plaque composition. C. Percent of X-34 within a HJ3.4-positive area. D. Area HJ3.4 outside of X-34-positive area (nonfibrillar area). The total area of X-34 normalized signal microns. Graphs represent mean ± SEM. **, p=0.0010; ***, p=0.0003. Analyzed by two-tailed Student's *t* test with a ROUT outlier analysis (Q=1%).

A role for PLD3 in microglia

Given the association of *Pld3* loss with altered microglia function in mouse models, we sought to determine whether *PLD3* is altered in microglia in human brains. Nuclei were isolated and sequenced from frozen AD and age-matched control brains (Figure 4.6A)[17, 18]. AD brains were further classified based on the presence of *TREM2* risk variants (named: TREM2). Unsupervised clustering of the brain nuclei revealed 15 cell-type specific clusters that correspond to the major cell-types found in the brain [17]. We isolated microglia from other cells and reexamined the alternative transcriptional states that we further classified into nine subclusters (Figure 4.6B). *PLD3* expression was significantly overexpressed in Mic.1 and reduced Mic.2 microglia subclusters compared to all microglia clusters (Figure 4.6B; p=2.71×10-5 and 2.27×10-6, respectively; Supplemental Table 4.2). In contrast, homeostatic microglia (Mic.0) did not show differential expression of *PLD3* (Figure 4.6B; p=0.52; Supplemental Table 4.2). Microglia in Mic.1 have an expression signature consistent with microglia associated with neurodegeneration (e.g. disease associated or activated response microglia) [33, 42, 43], while Mic.2 clusters are enriched among *TREM2* variant carriers and exhibit upregulated resting state microglia markers with minimal elevation of genes associated with activated microglia [17].

To understand how *PLD3* expression changes in microglia with disease, we examined control, sporadic AD and *TREM2* risk variant carriers. *PLD3* expression was significantly reduced in homeostatic microglia in sporadic AD brains and *TREM2* risk variants compared to controls (Figure 4.6C; p=1.04×10-3 and p=2.46×10-2, respectively; Supplemental Table 4.3). *PLD3* expression was further dysregulated in disease associated Mic.1 cluster in *TREM2* risk variant carriers compared with controls (Figure 4.6D; p=4.13×10-3; Supplemental Table 4.3).

To further clarify the relationship between PLD3 and microglia function, we analyzed *PLD3* expression in single cell RNAseq data obtained from human iPSC expressing inducible CRISPRi machinery that were transduced with 81 sgRNAs and differentiated into iTF-Microglia (Figure 4.6E) [44]. Unsupervised clustering analyses revealed nine distinct microglia subclusters (Figure 4.6E), representing distinct transcriptional states. Among these subclusters, *PLD3* was significantly overexpressed in clusters 1, 2, and 3 and significantly reduced in clusters 4, 5, 7, and 9 (Figure 4.6F and 4.6G; Supplemental Table 4.4). Clusters 1-3 correspond with interferon-induced gene activation states [44], while clusters 4-9 are enriched for genes associated with chemokine/cytokine activation states [44]. Cluster 3, where *PLD3* is significantly elevated, is enriched in *SPP1* expression, a marker of disease associated microglia [44]. Additionally, cluster 7, where *PLD3* is significantly reduced, is enriched in markers of microglia proliferation [44]. Together, these data support a role for PLD3 in microglia activation in health and disease.

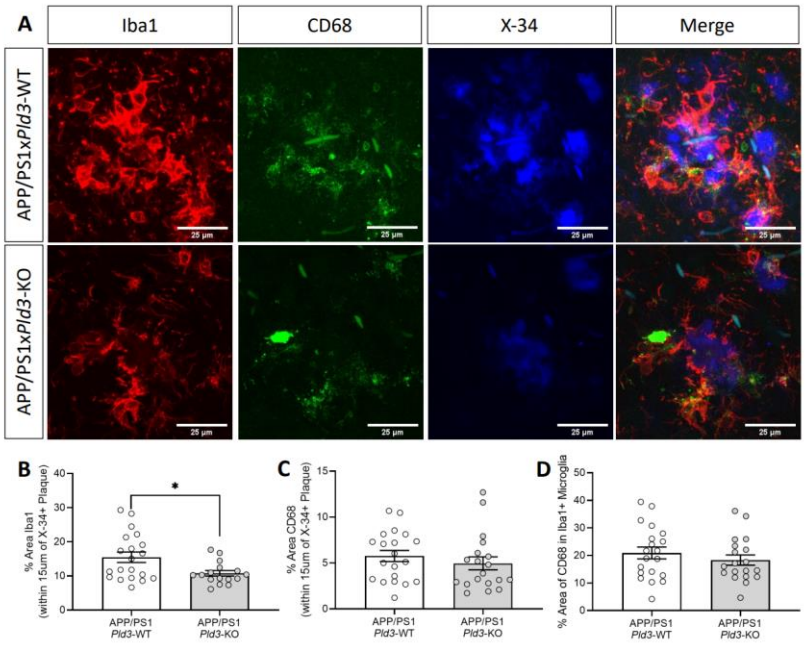


Figure 4.5: Loss of *Pld3* alters the microglial response to Aβ pathology. A. Representative images of APP/PS1x*Pld3*-WT and APP/PS1x*Pld3*-KO mice co-stained with Iba1 (total microglia), CD68 (activated

microglia), and X-34 (β-sheet-rich dense cores). APP/PS1x*Pld3*-WT (n=20), APP/PS1x*Pld3*-KO (n=19). B. Quantification of Iba1 localization within 15 µm of the X-34+ dense core plaques (*, p=0.03). C. Quantification of CD68 localization within 15 µm of the dense plaques. D. Quantification of Iba1 and CD68 colocalization. Graphs represent mean ± SEM. Analyzed by two-tailed Student's *t* test with a ROUT outlier analysis (Q=1%).

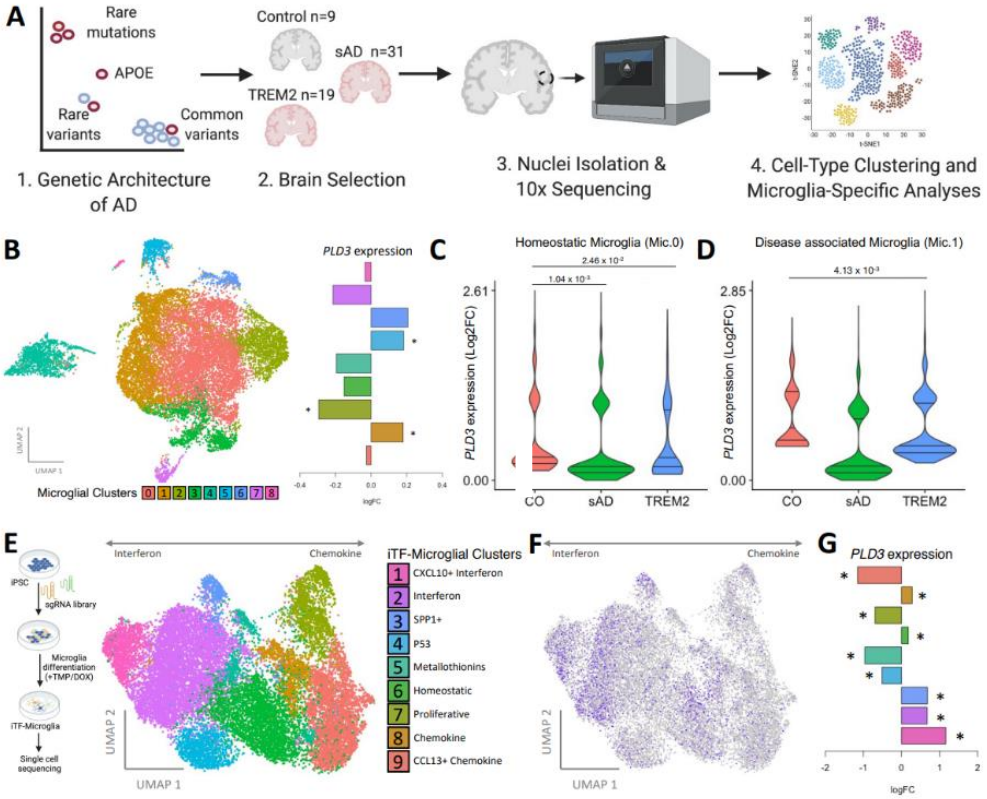


Figure 4.6: *PLD3* is enriched in specific microglia states in human brains. A. Diagram of the study design for human brain sequencing. B. UMAP plot depicting segregation of human brain microglia into nine major subclusters, left. Bar plot of the log2 fold change of *PLD3* by microglia subcluster, right. *, p<0.05. C-D. Violin plot of *PLD3* expression from control (CO), sporadic AD (sAD), and *TREM2* risk variant carriers in homeostatic (Mic.0; C) and disease associated (Mic.1; D). E-G. Single cell RNAseq data obtained iTF-Microglia CROP-seq described previously [44]. E. UMAP plot reveals 9 microglia clusters. F. Diagram of study design for iTF-Microglia, left. UMAP plot of PLD3 expression, right. Cells are colored by the *PLD3* expression levels. G. Bar plot of the log2 fold change of *PLD3* by microglia subcluster. *, p<0.05.

4.5 Discussion

In this study, we sought to understand the contribution of PLD3 to pathways that promote AD pathology. We demonstrate that the AD risk variant, *PLD3* p.A442A, is sufficient to alter *PLD3* splicing and Aβ levels in iPSC-derived neurons in a manner consistent with similar findings in AD brains [4]. Additionally, we describe a role for PLD3 in LOAD, whereby modifying *PLD3* expression in APP/PS1 mice is sufficient to regulate Aβ turnover in the ISF. The observed reduced ISF Aβ turnover, in turn, leads to a change in amyloid plaques in aged animals. We observed that loss of *Pld3* in APP/PS1 mice results in a shift in plaque composition to a more nonfibrillar structure. This altered plaque composition is accompanied by impaired microglial recruitment to the plaques, consistent with prior reports from *Trem2* deficient mice. In human brains, *PLD3* is enriched in disease associated microglia and expression is altered in AD brains. Together, these results suggest that *PLD3* plays cell-autonomous and non-cell autonomous roles in AD pathogenesis.

Deciphering the contribution of risk variants and pathogenic mutations to AD pathogenesis has led to groundbreaking discoveries of Aβ metabolism, synaptic function, and immune function to AD and revealed novel therapeutic targets [45]. Emerging sequencing technologies in increasingly larger cohorts have revealed the contribution of rare variants to AD risk [45, 46]. Nevertheless, resolving the contribution of rare variants to disease can be challenging when relying on association studies and autopsy brain tissue that captures a snapshot of disease.

Here, patient-derived cell culture models represent a tractable, human platform that recapitulates disease-specific phenotypes and when coupled with genome engineering, allows for

the study of genotype x phenotype relationships. This study demonstrates that iPSC-derived neurons are highly informative and recapitulate early pathogenic events in AD.

In this study, we used genome editing technology to molecularly pinpoint the contribution of the A allele to PLD3 and AD-related phenotypes. While we cannot exclude the possibility that genomic factors beyond PLD3 p.A442A contribute to the risk profile in the iPSC donor line used in this study, we can attribute the defect in PLD3 splicing and the increase in Aβ levels to this synonymous variant. The increase in both Aβ42 and Aβ40 is consistent with the effects of other known pathogenic mutations, including APP KM670/671NL [47, 48]. The absence of an effect of *PLD3* p.A442A on the Aβ42/40 ratio suggests that Aβ recycling and trafficking. This is consistent with recently reported functions of PLD3 as a type II membrane protein functioning in endosomes and lysosomes, the primary site of APP cleavage [49, 50]. Together, these human stem cell findings suggest a role for PLD3 p.A442A in altering APP/Aβ recycling and trafficking in a manner that elevates total Aβ levels.

PLD3 p.A442A was predicted to disrupt a splicing enhancer-binding site [4]. We observe defective *PLD3* splicing in iPSC-derived neurons from a *PLD3* p.A442A carrier, which replicates the observations in brains from *PLD3* p.A442A carriers [4]. We go on to demonstrate that correcting the risk allele with CRISPR/Cas9 is sufficient to restore the splicing defect. The functional impact of distinct PLD3 isoforms remains unknown; however, as the functional roles of PLD3 are resolved, this will be an important area to explore.

We show that PLD3 is a major regulator of ISF Aβ turnover *in vivo*. Hippocampal reduction of endogenous *Pld3* in adulthood via AAV8-mediated knockdown or global knockout of *Pld3* in the background of APP/PS1 mice resulted in a strong increase in ISF Aβ half-life,

suggesting that Aβ is turned over more slowly in the absence of *Pld3*. Aβ clearance mechanisms have been proposed to drive LOAD [35]. Following secretion from presynaptic neurons, Aβ is either taken up and degraded in the lysosomes of post-synaptic neurons, taken up and degraded in the lysosomes of glial cells, degraded by extracellular proteases, is transported to CSF, or transcytosed across the blood-brain barrier (BBB). Amyloid accumulation occurs in an Aβ concentration-dependent manner [36]; thus, dysregulation of ISF Aβ clearance drives amyloid accumulation and AD pathogenesis. Neurons from *Pld3* KO mice exhibit lysosomes with increased density and size [33]. PLD3 is enriched in lysosomes surrounding amyloid plaques in human AD brains and mouse models of amyloid accumulation [9]. Thus, *Pld3* may regulate ISF Aβ through lysosome-mediated clearance mechanisms in neurons or other glial cells.

The absence of *Pld3* in APP/PS1 mice led to a shift in the composition of amyloid plaques to being more diffuse and less fibrillar. While amyloid plaques may adopt a series of morphologies and architecture, a major structure is characterized by a dense "fibrillar" core of Aβ surrounded by more diffuse "non-fibrillar" of Aβ deposits [51]. Non-fibrillar Aβ is proposed to contribute to its higher toxicity, possible because either its structure is more toxic or they serve as a reservoir for more diffusible Aβ oligomers [37, 52]. Thus, a PLD3-mediated shift to more non-fibrillar plaques is consistent with more toxic effects given the same amount of overall Aβ deposition. Silencing AD risk genes, including *Trem2* and *ApoE,* result in a similar shift of plaque composition shift in APP/PS1 mice [38, 39, 41]. Thus, modeling the reduction of *PLD3* observed in *PLD3* p.A442A carriers, and LOAD brains in an animal model of amyloid accumulation leads to a phenotype consistent with a gene that exacerbates disease.

In prior studies where gene silencing in amyloid mice led to a change in plaque formation and composition, a role for an altered microglial response to amyloid plaques was implicated

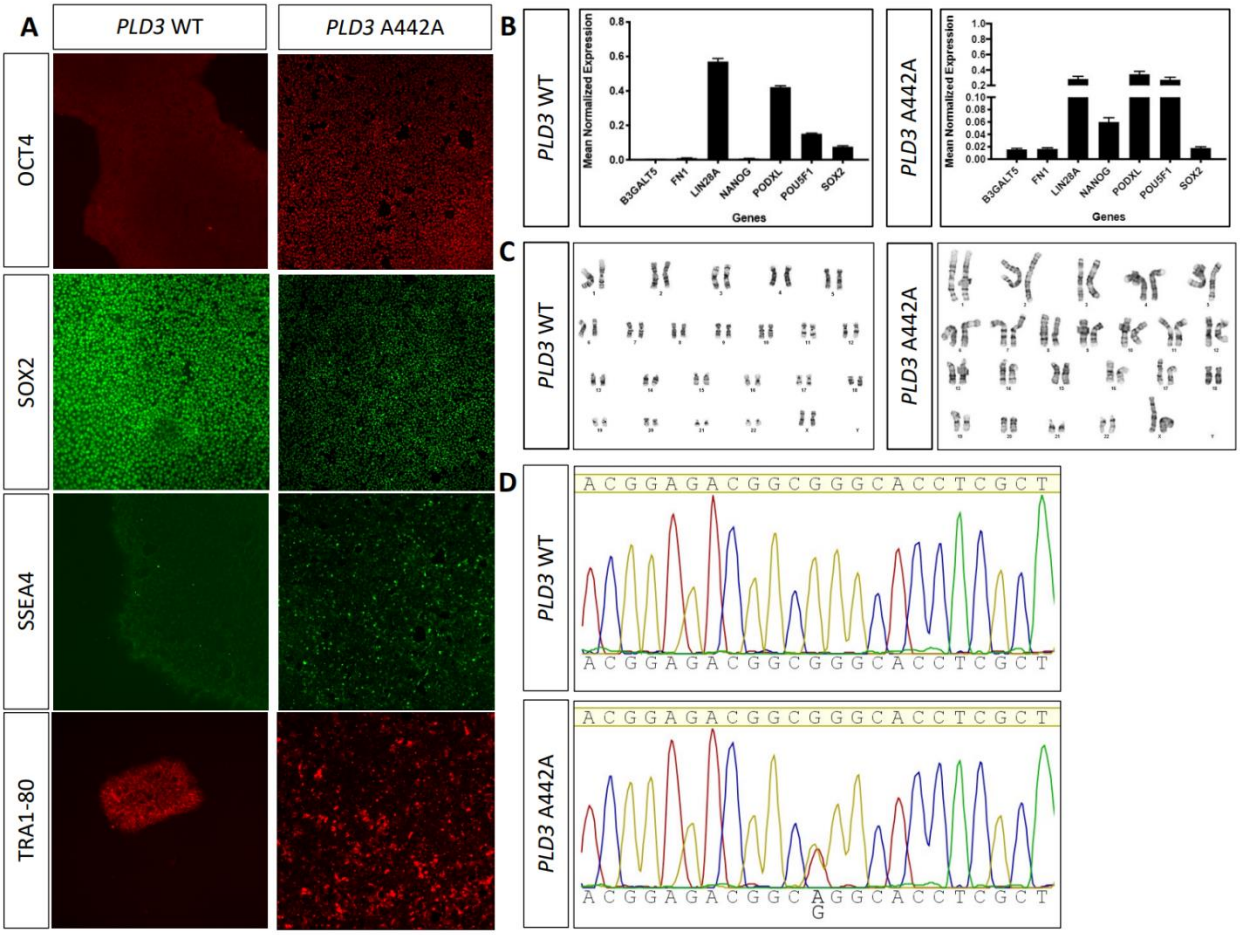
[38, 39, 41]. APP/PS1x*Pld3*-KO and APP/PS1x*Pld3*-WT mice exhibited a similar abundance of Iba1 positive microglia. Yet, recruitment of Iba1-positive microglia to X-34-positive plaques was significantly reduced in APP/PS1x*Pld3*-KO mice compared to APP/PS1x*Pld3*-WT mice. This could suggest a role for PLD3 in recruiting microglia to surround and alter Aβ structure and limit Aβ-induced toxicity similar to mechanisms described for TREM2 [38]. In mice, *Pld3* mRNA is expressed in microglia [53]. Microglia isolated from amyloid mouse models ($APP^{NL\text{-}F\text{-}G}$) reveal an activation state enriched for MHC class II, tissue repair genes, and enrichment of AD risk genes, including *Pld3* [54]. Thus, loss of *Pld3* in the global knockout may impact the molecular identity of microglia, which impairs the recruitment and responsiveness of the glia to plaques.

In human microglia, PLD3 plays a role in microglia that is disrupted in AD. Microglia maintain distinct transcriptional states that likely reflect functional changes due to environmental stimuli [55]. We demonstrate that *PLD3* expression is enriched in disease associated microglia (Brain Mic.1 and iTF-Microglia cluster 3) and depleted in population of microglia that are found in *TREM2* risk variant carriers (Brain Mic.2). Mic.2 reflect a dampened activation state, distinct from homeostatic microglia (Mic.0) with an upregulation of resting state microglia markers (*TMEM119, P2RY13, MED12L*) and modest elevation of activated markers (*ABCA1, C5AR1,* and *CD83*) [17]. This finding along with the observation that *PLD3* expression is reduced in disease associated microglia (Mic.1) in *TREM2* risk variant carriers suggests a potential interaction between these AD risk genes. These results also support the parallels between our mouse model findings and those in *Trem2* deficient mice. In addition to association with disease associated microglia, PLD3 and TREM2 have also been implicated in lysosomal function [9, 33, 40, 49, 50].

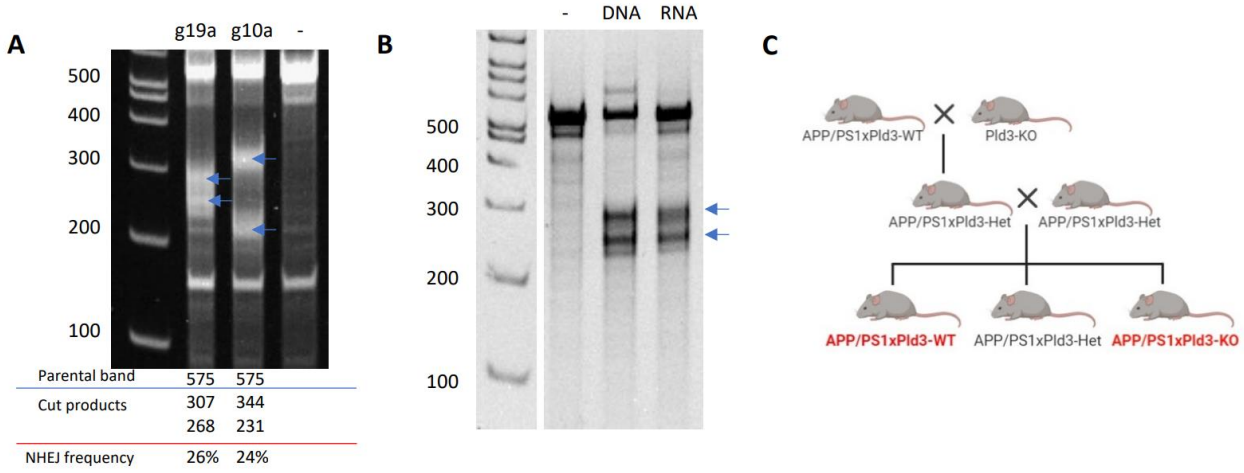
Overall, we observed a modest impact on amyloid plaque pathology in APP/PS1x*Pld3*-KO mice. The modest impact is highly consistent with PLD3 as a disease modifier rather than a fully penetrant, causative mutation. Alternatively, this could reflect redundant mechanisms for mouse Pld3.

Here, we demonstrate a therapeutic potential for PLD3. *hPLD3* overexpression by AAV8 in APP/PS1 mice resulted in a significant decrease in ISF Aβ levels and accelerated Aβ turnover. *PLD3* levels are significantly reduced in AD brains, and *PLD3* expression is positively correlated with cognition in humans and mouse models [9]. Thus, by promoting Aβ turnover and facilitating the microglial response to amyloid plaques, *PLD3* occupies a crucial role in brain health.

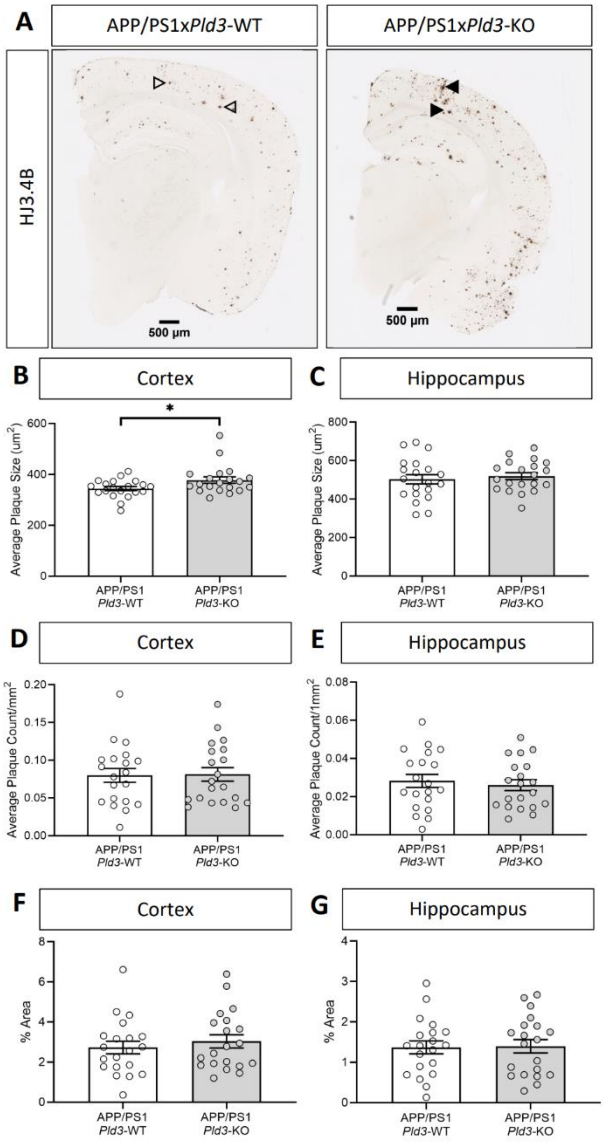
4.6 Supplemental Figures



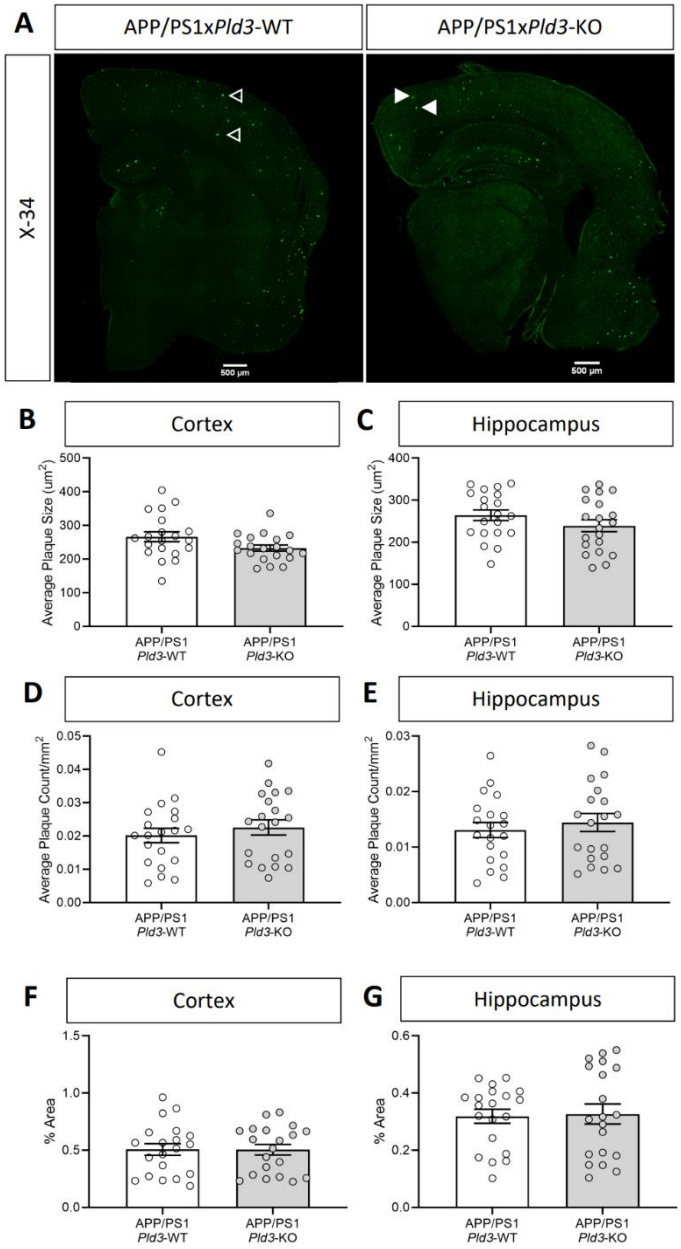
Supplemental Figure 4.1: Characterization of the *PLD3* p.A442A iPSC-derived neurons. A. Representative images of *PLD3* p.A442A and the corrected WT iPSCs stained for NANOG, OCT4, SOX2, SSEA4, and TRA1-80. B. qPCR from known markers of pluripotency. C. Karyotype. D. Sanger sequencing.



Supplemental Figure 4.2: Generation of a *Pld3*-deficient amyloid mouse model. A. Mismatch detection assay. B. RNA activity validation. C. Breeding scheme for the *Pld3*-deficient mouse with APP/PS1 mutant mice to develop a transgenic APP/PS1x*Pld3*-KO mouse line along with APP/PS1x*Pld3*-WT littermate controls.



Supplemental Figure 4.3: Loss of *Pld3* significantly increases plaque size without changing plaque area. A. Representative images of mice brain cross-sections stained for total Aβ (HJ3.4) with arrows specifying plaques (open arrows for WT; closed arrows for KO). APP/PS1x*Pld3*-WT (n=20), APP/PS1x*Pld3*-KO (n=20). B-C. Quantification of average plaque size in the cortex (B) and hippocampus (C). D-E. Quantification of average plaque count per mm^2 in the cortex (D) and the hippocampus (E). F-G. Quantification of the plaque burden by the percentage of the total area for the cortex (F) and the hippocampus (G). Graphs represent mean ± SEM. *, p>0.05.



Supplemental Figure 4.4: Loss of *Pld3* does not change dense core plaques. A. Representative images of mice brain cross sections stained with X-34 with arrows specifying plaques (open arrows for WT; closed arrows for KO). APP/PS1x*Pld3*-WT (n=20), APP/PS1x*Pld3*-KO (n=20). B-C. Quantification of average plaque size in the cortex (B) and hippocampus (C). D-E. Quantification of average plaque count per mm^2 in the cortex (D) and hippocampus (E). F-G. The quantification of the plaque burden by the percentage of the total area for the cortex (F) and hippocampus (G). Graphs represent mean ± SEM.

4.7 Supplemental Tables

Supplemental Table 4.1: Human brain demographics for snRNAseq

	Total Number	Sex (% male)	Mean Age at Death (years)	APOE4	Mean Postmortem Interval (years)
Controls	9	33%	90	11%	10.9
sAD	31	45%	81	54%	11.9

Supplemental Table 4.2: PLD3 expression in human brain microglia

Cluster Name	LogFC	z-score	p-value	BH corrected p-value
Mic.0	-0.0262225	-0.6410652	5.21E-01	7.32E-01
Mic.1	0.1800801	4.19659881	2.71E-05	2.86E-04
Mic.2	-0.2949385	-4.7275062	2.27E-06	1.26E-04
Mic.3	-0.1519921	-1.274392	2.03E-01	5.14E-01
Mic.4	-0.1953743	-1.718988	8.56E-02	2.51E-01
Mic.5	0.1829342	1.98158159	4.75E-02	1.75E-01
Mic.6	0.20610645	1.89898926	5.76E-02	1.96E-01
Mic.7	-0.2146737	-1.3839443	1.66E-01	4.50E-01
Mic.8	-0.0345632	-0.1138777	9.09E-01	9.99E-01

Supplemental Table 4.3: PLD3 expression within microglia subclusters by disease status

Comparison	LogFC	z-score	p-value	BH corrected p-value	Subcluster
sAD vs CO	-0.4017806	-3.2799941	1.04E-03	1.43E-01	Mic.0
TREM2 vs CO	-0.2766865	-2.247029	2.46E-02	3.91E-01	Mic.0
sAD vs CO	-0.3455155	-1.8251283	6.80E-02	1.00E+00	Mic.1
TREM2 vs CO	-0.4217827	-2.8679334	4.13E-03	3.21E-01	Mic.1

Supplemental Table 4.4: PLD3 expression in iTF-Microglia CROP-Seq

Cluster Name	Estimate	Std. Error	z value	Pr(>|z|)
cluster 1	1.163684751	0.079301251	14.67422936	9.43E-49
cluster 2	0.673908846	0.041847298	16.10399883	2.39E-58
cluster 3	0.679645559	0.12978185	5.236830561	1.63E-07
cluster 4	-0.511168775	0.081414971	-6.278559975	3.42E-10
cluster 5	-0.966514606	0.105007855	-9.204212437	3.44E-20
cluster 6	0.178261422	0.050290361	3.544643891	3.93E-04
cluster 7	-0.696815579	0.075041761	-9.285703981	1.61E-20
cluster 8	0.277388403	0.093662032	2.961588568	3.06E-03
cluster 9	-1.155055839	0.051935689	-22.24011787	1.41E-109

4.8 References

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4.8

Chapter 5: Conclusions

5.1 Introduction

Since it was first observed and characterized by Aloysius Alzheimer back in 1908, Alzheimer disease (AD) has remained one of the biggest medical challenges to humanity. However, the lack of effective therapeutics should not be mistaken as a lack of understanding of the disease. Over decades of AD research, significant contributions have been made to the understanding of AD genetics and core disease mechanisms. Through these efforts, the research has been able to shed light on the breadth of genes that affect AD, the cellular pathways involved, and the mechanistic steps that drive disease. In this dissertation, I outlined our work in expanding our knowledge through three genes: *LMNA*, *RAB10*, and *PLD3*.

5.2 Dissertation work furthers research into genetics driving AD pathology

LMNA and the role of nucleoskeletal integrity in AD

When studying a particular disease, much can be gained from looking at similar diseases that share characteristics. A perfect example of this is the nucleoskeletal dysfunction observed in AD that occurs in more well-studied laminopathies. In **Chapter 2**, we demonstrate how mRNA expression from laser-captured microdissected neurons leads to dysregulation in the expression of *LMNA* and *ZMPSTE24*, causing an imbalance of mature lamin A protein in a manner that resembles what is observed in Hutchinson Guilford Progeria Syndrome (HGPS). As a result, the many of the same nucleoskeletal dysfunction observed in HGPS is also observed in AD [1, 2]. This can result in changes in the nucleoskeletal dysfunction, such as the formation of tubular

invaginations in the nuclear membrane [3]. These alterations to the nuclear shape can cause changes to chromatin structure, abnormal gene expression, and increased DNA damage [1, 2, 4]. Furthermore, when HGPS was induced in iPSC-derived neurons through forced progerin expression, many of the genes disrupted by progerin were found to match those disrupted in AD, notably lysosomal signaling. Irregularities in the structure of the nuclear lamina can also be caused by influences outside the nucleus, such as alterations to the cytoskeleton driven by tau accumulation can also alter the nuclear lamina through the linker of nucleoskeleton and cytoskeleton (LINC) complex [3]. Therefore, while nuclear defects are observed in AD, it is yet to be seen whether such changes occur as the result of AD pathology or vice versa.

RAB10 variant rs142787485 may confer resilience to AD through a miRNA-centric pathway

As we learn more about the genetics of AD, we must also dedicate our efforts to identifying variants that protect against AD, for understanding such variants could grant us invaluable insight for the development of therapeutics that emulate the mechanistic elements of these variants. In **Chapter 3**, we discuss an example of such a variant and how it may confer resilience to disease. A SNP in the 3'-UTR of *RAB10*, rs142787485, was identified when studying the genomes of individuals at least 75 years old and cognitively normal despite carrying at least a single copy of *APOE4*, which is associated with at least a 3-4 fold increase in disease risk. In the original study, silencing of *RAB10* resulted in a shift of the ratio of Aβ42/40 in a manner that was less prone to aggregation [5]. In agreement with this, RAB10 protein levels were elevated in AD brains, leading us to hypothesize that overexpression of *RAB10* was conducive to AD development and the rs142787485 SNP acted opposite to this by reducing

expression. However, unexpectedly, the SNP was found to have no effect on mRNA expression of *RAB10* and there was no significant allele specific expression between WT and SNP alleles. This leads us to consider post-transcriptional regulation of *RAB10* expression, such as miRNA. Rs142787485 is predicted to disrupt the binding of six miRNAs. However, further biochemical verification is required to investigate this possibility further.

As a member of the Rab family of GTPases, *RAB10* serves as a key regulator of subcellular vesicle and trafficking pathways, from the regulation of ER dynamics to the regulation of recycling endosome tubulization and endosomal function and recruitment of CNT-1 [6-8]. *RAB10* is also associated with lysosomal secretion during stress [9] and requires phosphorylation at threonine 73 (T73) by leucine rich repeat kinase 2 (*LRRK2*), a known risk gene in Parkinson's disease [10]. This is especially intriguing because APP processing occurs within many of these same compartments [11]. Additional protective factors associated with reduced AD risk are also function proximally to the process of APP metabolism, such as the *APP* A673T mutation [12] or the *APOE* R136S Christchurch mutation [13, 14].

PLD3 alters the microglial response and amyloid pathology as a response

In **Chapter 4**, using both *in vitro* and *in vivo* systems, we investigated the role of *PLD3*, an enzyme with genetic variants that were associated with disease risk. Using iPSC-derived cortical neurons, we show that the silent mutation *PLD3* A442A was sufficient to both alter the splicing of *PLD3* and omit exon 11, in corroboration to what was observed in the brains of carriers [15], and increase overall secreted Aβ levels. Furthermore, when *Pld3* expression was reduced in an amyloid mouse model, the overall turnover of Aβ was significantly inhibited, implying that *Pld3* played an important role in the clearance of Aβ. When *Pld3* was knocked out

in this same mouse model, we also observe a change in the microglial response, demonstrated by a significant decrease in microglial recruitment around amyloid plaques. This altered microglial response leads to a shift in the overall makeup of amyloid plaques, resulting in plaques that are less fibrillary and more diffuse in nature, which have been shown to be more toxic overall. This is found to mirror what is observed in amyloid mouse models deficient for *Trem2* [16], a gene found to play an important role in the activation of disease associated microglia (DAM) [17], and when we ran an RNAseq analysis on our amyloid mice deficient for *Pld3*, we observed a shift in expression of genes associated with the DAM response. Furthermore, when we looked at snRNAseq data from human brains, we find upregulation of *PLD3* in activated microglia, further establishing that *PLD3* plays an important role in the microglial response to disease. Conversely, microglia with mutant *TREM2* expressed reduced microglial levels, also establishing the link we are observing between *PLD3* and *TREM2*. Considering this, it may be possible that therapeutic strategies that have been developed for *TREM2*-mediated processes can be leveraged to target *PLD3* as well.

5.3 Future directions: linking AD genetics, intracellular and extracellular processes, and AD pathology

The genetics of LOAD is incredibly complex. In the scope of the work outlined in this dissertation, we examine seemingly disparate genes and how they ultimately drive AD risk. From looking at the genetics, much can be learned about these disease-relevant pathways and how they relate to each other. For example, while we discuss the roles played by nucleoskeletal integrity (**Chapter 2**) and the endo-lysosomal network (**Chapter 3**), it must also be remembered how these pathways are interconnected. Nutrient sensing between the lysosome and the nucleus

control energy metabolism [18] and TFEB-mediated lysosomal biogenesis requires tightly controlled signaling between both the lysosome and the nucleus [19].

Additionally, we examine the contribution of AD risk genes to processes outside of the neuron, with our findings showing how *PLD3* drives the microglial response to Aβ (**Chapter 4**). This provides compelling support for investigations into the contribution of glia cells to AD pathogenesis. Therapeutic approaches that target nuclear-endo-lysosomal networks and promote glia function build off key genetic findings and hold promise for the future.

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Appendix 1: Genes dysregulated by forced progerin expression in iPSC-derived neurons

Gene	Direction in Progerin Transduction	Progerin v. GFP (82yr iPSC-mDA)		Progerin v. GFP (11yr iPSC-mDA)	
		B	p value	β	p value
LMNA	Upregulated	9.375119138	1.32827E-05	10.0911755	8.48901E-06
NOP10	Upregulated	1.732412984	0.000340553	1.52061923	0.000705462
SNHG15	Upregulated	1.695953272	0.000785928	1.526546192	0.001386872
ENHO	Upregulated	1.662578754	0.000393343	1.407485256	0.000987834
NDUFB6	Upregulated	1.628882059	6.66956E-05	1.223009584	0.000351228
ATP5L	Upregulated	1.592370717	0.000117022	1.006282614	0.001526688
NEDD8	Upregulated	1.58923555	0.000376062	1.005728895	0.004272559
PPIB	Upregulated	1.581496767	0.001149768	1.035550459	0.009467005
TMSB10	Upregulated	1.539837612	0.000215936	1.336688033	0.000481771
PRDX4	Upregulated	1.523527472	0.001043477	1.092313821	0.005709165
FTL	Upregulated	1.493552581	0.000767656	1.062409476	0.004515924
TMSB4X	Upregulated	1.487630688	0.000914481	1.124181183	0.003927462
ATOX1	Upregulated	1.475715084	0.000776274	1.337181808	0.001322595
CCDC126	Upregulated	1.471548609	9.38036E-05	1.524986052	7.6036E-05
PSMB3	Upregulated	1.469479933	0.000363831	1.7662128	0.000126458
LOC100128822	Upregulated	1.440876824	0.003203627	1.288058638	0.00555505
TSNAX	Upregulated	1.432132242	0.000142155	1.811161622	3.55279E-05
TCEAL7	Upregulated	1.431234805	0.00054714	1.454932214	0.000499293
UBC	Upregulated	1.421052124	0.000633532	1.185017044	0.001688352
ZNHIT3	Upregulated	1.413750616	0.001009087	1.016970098	0.005454953
PCNA	Upregulated	1.412258184	0.000977948	1.395867244	0.001041677
LOC401397	Upregulated	1.407637811	0.00054046	1.149132939	0.001624053
C4orf52	Upregulated	1.407547781	0.000745946	1.417019042	0.000718971
NDUFA5	Upregulated	1.40568193	0.001312865	1.372483429	0.001490613
EAPP	Upregulated	1.394670142	8.50607E-05	1.031926692	0.000480897
COX14	Upregulated	1.394087166	0.000609251	1.093212166	0.002241283
UBE2T	Upregulated	1.388059153	0.003153204	1.115053251	0.009018116
SVIP	Upregulated	1.381316067	0.001146964	1.96065781	0.000161219
CD164	Upregulated	1.380010993	0.006825565	1.296015267	0.009121577

RPL12	Upregulated	1.36974694	0.001058001	1.217411003	0.001976442
SCOC	Upregulated	1.366874738	0.001005535	1.494146665	0.000617733
ARL6IP5	Upregulated	1.345878412	0.000755084	1.151784162	0.00174209
UBL5	Upregulated	1.344510357	0.000256643	1.014211479	0.001226031
SEC11C	Upregulated	1.339729314	0.001157796	1.20654946	0.002013272
VPS25	Upregulated	1.33720159	0.002481602	1.060228961	0.007711955
ITM2C	Upregulated	1.335797925	0.00070546	1.100869062	0.00198831
TFAM	Upregulated	1.333673096	0.000317022	1.095345791	0.000946755
PRDX1	Upregulated	1.329438264	0.001626438	1.046293861	0.005442053
ABHD10	Upregulated	1.323920811	0.000421969	1.115009335	0.001086651
BUD31	Upregulated	1.323767091	0.000555846	1.08717058	0.001615903
TCEB2	Upregulated	1.323167527	0.002504316	1.03072709	0.008434898
WRB	Upregulated	1.316572465	8.44045E-05	1.309185664	8.72461E-05
PFN1	Upregulated	1.29309319	0.000276098	1.008897825	0.001095648
TCEAL8	Upregulated	1.290579091	0.004530056	1.238193914	0.005535314
RGS2	Upregulated	1.285635194	0.000622585	1.375285198	0.000427553
C5orf15	Upregulated	1.283325922	0.000411436	1.069294428	0.001123676
ATP6V1G1	Upregulated	1.280549183	9.25203E-05	1.038930694	0.000310087
YPEL5	Upregulated	1.259226231	0.001732238	1.388273829	0.00103031
MT3	Upregulated	1.256254073	0.005099663	1.2850998	0.004567633
UQCR10	Upregulated	1.2543698	0.006234145	1.17398857	0.008487298
TMEM14A	Upregulated	1.25326206	0.000111712	1.225318664	0.000127437
DNAJC8	Upregulated	1.249310085	0.001039804	1.073928287	0.00231018
SUMO2	Upregulated	1.246660271	0.000239595	1.326501812	0.00016757
BEX1	Upregulated	1.246459042	0.000175198	1.054059451	0.000455319
NDUFB11	Upregulated	1.246282072	0.003690317	1.120932613	0.006174686
LAMTOR1	Upregulated	1.24261885	0.000224845	1.154551038	0.00034192
ATP5G3	Upregulated	1.227488948	0.000466262	1.109774694	0.000814496
VBP1	Upregulated	1.225197596	0.000246745	1.1676853	0.000324518
QPCT	Upregulated	1.218729435	0.005333479	1.174432155	0.006363023
ZCCHC10	Upregulated	1.216985968	0.001141391	1.216938558	0.00114163
NDUFB1	Upregulated	1.212647595	0.000123582	1.177928905	0.000146358

MMADHC	Upregulated	1.209472174	0.000213209	1.258632949	0.000169429
HSBP1	Upregulated	1.209050371	0.000408007	1.048451016	0.00089813
CAPZA2	Upregulated	1.204062211	0.000428945	1.192510664	0.000452782
CNO	Upregulated	1.201577919	0.000484943	1.12808019	0.000688341
SELT	Upregulated	1.194192075	0.000280393	1.214488025	0.000254671
CCDC72	Upregulated	1.189499315	0.002739677	1.082352271	0.004388627
ATF4	Upregulated	1.189477222	0.000165305	1.048484664	0.000340589
GABARAPL2	Upregulated	1.164210414	0.001013557	1.084828859	0.001479084
AASDHPPT	Upregulated	1.16059799	0.000603085	1.189145455	0.00052693
BANF1	Upregulated	1.157267236	0.005998755	1.135876447	0.006552495
SUB1	Upregulated	1.153842938	0.00037788	1.276906092	0.000212118
EID1	Upregulated	1.148286664	0.000232526	1.229711983	0.000156625
SLIRP	Upregulated	1.13062867	0.011809836	1.309167838	0.00603561
PFDN2	Upregulated	1.123582749	0.000624993	1.002655021	0.001162718
EIF3M	Upregulated	1.119433556	0.013692631	1.187841738	0.01055505
CYB5A	Upregulated	1.108970483	0.006173215	1.30981704	0.002722356
FDFT1	Upregulated	1.106928803	0.000715114	1.197020725	0.000463215
CDC42	Upregulated	1.106027634	0.000264574	1.030596382	0.000394985
DYNLT3	Upregulated	1.103555116	0.000981515	1.364816583	0.000301278
C12orf29	Upregulated	1.100854237	0.007379645	1.042798325	0.009462164
RG9MTD1	Upregulated	1.097127636	0.00469358	1.234738755	0.002603568
FOS	Upregulated	1.096376775	0.005246573	1.019374129	0.007406276
CCT3	Upregulated	1.09583174	0.000291884	1.037716754	0.000397397
ZCRB1	Upregulated	1.093920722	0.000689234	1.022551006	0.000996213
TMBIM6	Upregulated	1.090975514	0.004624553	1.035425691	0.005947867
GTF2B	Upregulated	1.090514909	0.006157066	1.186724489	0.004091316
ILF2	Upregulated	1.087075934	0.000461588	1.008799048	0.000698997
POMP	Upregulated	1.080594528	0.00271545	1.015387046	0.00371312
ZBTB6	Upregulated	1.070254806	0.001627732	1.165439369	0.001033216
IDI1	Upregulated	1.068224421	0.000342885	1.238444019	0.000146769
ISCA1	Upregulated	1.066384941	0.00116214	1.139730622	0.000810485
PRDX6	Upregulated	1.065824536	0.004671756	1.013303186	0.005958031

TTC33	Upregulated	1.065522372	0.000798038	1.016663557	0.001030033
ANAPC13	Upregulated	1.063288186	0.003362158	1.134089648	0.00242506
DDX24	Upregulated	1.063240738	0.000632372	1.047341234	0.000687196
CCNG1	Upregulated	1.061535446	0.000447783	1.034146364	0.000518246
TIMM17B	Upregulated	1.048926853	0.006406986	1.069214238	0.005850419
MRPS35	Upregulated	1.04670965	0.002659618	1.093203808	0.002127518
PGRMC1	Upregulated	1.046018795	0.002961709	1.101093416	0.002279303
CHMP1B	Upregulated	1.045660536	0.002075504	1.320630421	0.000591945
RPS19BP1	Upregulated	1.043381039	0.003391494	1.259895772	0.001277592
SRP9	Upregulated	1.039507762	0.000754306	1.283344584	0.000230944
CCDC90B	Upregulated	1.039162909	0.001232157	1.064962543	0.001080123
MORF4L1	Upregulated	1.03172995	0.000402781	1.088873945	0.000296865
EEF1E1	Upregulated	1.028896714	0.005683054	1.010328598	0.006197528
PPP2R1A	Upregulated	1.018359924	0.00640431	1.037001665	0.005876339
PSMA7	Upregulated	1.014828284	0.001396944	1.398309312	0.000236669
PDRG1	Upregulated	1.010457811	0.000413788	1.048670218	0.000335564
PKIB	Upregulated	1.007233859	0.001785411	1.172290071	0.000791822
JKAMP	Upregulated	1.002594302	0.007475103	1.050402029	0.006005318
DPM1	Upregulated	1.002553264	0.000777388	1.024962041	0.000688507
TAF7	Upregulated	1.000735631	0.000354799	1.031068229	0.000299523
RMRP	Downregulated	-8.851971839	4.30933E-07	-5.281991101	1.03775E-05
RPPH1	Downregulated	-8.619304961	1.595E-05	-5.496631131	0.000228353
MIR3648	Downregulated	-6.585701345	0.000131097	-5.064513293	0.000585255
MIR3687	Downregulated	-6.374819645	7.622E-06	-4.526781303	5.99655E-05
C3orf72	Downregulated	-6.044405494	0.000114288	-4.008067503	0.001156125
TNIP3	Downregulated	-5.827706142	0.000263675	-4.651290485	0.000927715
NOSTRIN	Downregulated	-5.651875552	1.20323E-05	-4.75135728	3.42856E-05
MIR663A	Downregulated	-5.641911575	0.000120688	-3.905852314	0.000963661
GVINP1	Downregulated	-5.615661316	9.87421E-05	-4.935292069	0.000209159
PRDM1	Downregulated	-5.59753266	3.53303E-07	-4.221939062	2.02903E-06
C1orf129	Downregulated	-5.596359896	2.76693E-05	-4.161838477	0.000159349
MARCO	Downregulated	-5.540452894	1.30404E-05	-3.983836365	9.375E-05

TG	Downregulated	-5.514495944	0.000149728	-3.450092491	0.002008437
PEAR1	Downregulated	-5.506832379	0.000225218	-2.957864199	0.006104584
LAMC3	Downregulated	-5.488530257	0.000215513	-3.232439026	0.00376113
BCAS1	Downregulated	-5.456480576	3.55782E-05	-4.201447975	0.000166081
LOC285084	Downregulated	-5.455054283	0.000248615	-4.902979756	0.000455009
CDHR4	Downregulated	-5.419948845	0.000142573	-2.87908578	0.004397591
FLI1	Downregulated	-5.377504396	0.000112121	-3.959509903	0.000641868
SLC14A2	Downregulated	-5.370557061	6.0004E-05	-4.869525804	0.000106867
BHMT2	Downregulated	-5.356535859	5.024E-05	-4.63939721	0.000117279
SH3TC2	Downregulated	-5.295859945	9.78101E-05	-4.139587761	0.00040382
OLAH	Downregulated	-5.259765054	1.60909E-05	-4.155763936	6.59873E-05
STAB2	Downregulated	-5.247178519	0.000108691	-3.757445641	0.000726726
SLC5A1	Downregulated	-5.174231377	0.000877214	-4.349661726	0.002205082
SLFN11	Downregulated	-5.174231377	0.001120685	-4.986952075	0.001364999
VIT	Downregulated	-5.169295031	0.002282804	-4.690799402	0.003731485
KIAA1755	Downregulated	-5.122768245	0.000913254	-3.646520793	0.005251622
SEC14L4	Downregulated	-5.122768245	0.001902222	-3.839248466	0.007887924
LEP	Downregulated	-5.106981704	0.000137876	-5.338755574	0.000106403
SHE	Downregulated	-5.089692078	4.48004E-05	-3.234547268	0.000613887
DISC1	Downregulated	-5.061800716	1.81558E-06	-3.113790338	3.50604E-05
GJA5	Downregulated	-5.047290363	0.001477877	-3.528807428	0.008704362
SNORA53	Downregulated	-5.036319087	3.43144E-06	-2.924236729	9.11993E-05
LOC284801	Downregulated	-5.009382814	0.000139815	-5.08491218	0.000128146
APCDD1L	Downregulated	-4.990037674	0.000324201	-3.089211664	0.004184548
LOC100507156	Downregulated	-4.957243503	0.000215936	-2.479235105	0.008233865
TBXA2R	Downregulated	-4.946797913	2.22189E-05	-3.895023617	9.22825E-05
FOXD2	Downregulated	-4.942787632	0.00360873	-4.113055228	0.008684239
EMR2	Downregulated	-4.912064424	0.000528967	-3.260856587	0.004553361
LOC727710	Downregulated	-4.910864391	4.77869E-05	-4.422427659	8.88356E-05
HOXC8	Downregulated	-4.904399799	0.000299955	-6.120135167	8.31279E-05
TGM5	Downregulated	-4.896462513	0.001352492	-3.623359788	0.006183233
MYH1	Downregulated	-4.874602959	1.67283E-05	-4.550104817	2.53487E-05

LOC283547	Downregulated	-4.830613323	1.73666E-05	-3.99525033	5.42247E-05
SGOL1	Downregulated	-4.815713822	0.000239673	-3.980121234	0.000699696
LOC100216001	Downregulated	-4.802092212	0.000559973	-4.985952113	0.000454053
CMKLR1	Downregulated	-4.773736794	0.003509115	-4.707822221	0.003760406
PDGFRA	Downregulated	-4.743552014	0.000255728	-3.704450935	0.001014026
HMCN1	Downregulated	-4.738559356	2.18124E-05	-3.993285146	6.06965E-05
COL6A6	Downregulated	-4.735745122	0.000113455	-3.284205669	0.000901358
LIPJ	Downregulated	-4.731292346	0.000801441	-3.807004102	0.002535992
MFAP5	Downregulated	-4.731014155	0.000126788	-4.072261461	0.000300831
WWTR1-AS1	Downregulated	-4.730859559	9.82736E-07	-3.905540716	3.20936E-06
LOC100292680	Downregulated	-4.730693033	1.96816E-05	-3.609039764	9.8721E-05
GLI1	Downregulated	-4.725427699	0.000993369	-4.496259914	0.001297593
GPRC5A	Downregulated	-4.725427699	6.72416E-06	-2.759348559	0.000167387
FLT1	Downregulated	-4.718989748	0.000318855	-4.73257643	0.000313693
RIPK3	Downregulated	-4.705527195	0.000252245	-3.312751922	0.001739502
MYOCD	Downregulated	-4.696124722	0.000989698	-3.847626894	0.002817986
MEFV	Downregulated	-4.695765738	0.002679106	-4.334415638	0.004002985
DNM3OS	Downregulated	-4.677473854	0.00013033	-4.115252049	0.00027282
MYH11	Downregulated	-4.658134679	0.000795723	-3.906173956	0.002036115
ATP6V0A4	Downregulated	-4.651540862	0.000175181	-5.006876613	0.000114176
MIR143HG	Downregulated	-4.64688724	0.001262363	-5.427659804	0.000540778
FXYD5	Downregulated	-4.637884346	0.00046176	-3.331405094	0.002722541
PIK3R5	Downregulated	-4.637884346	0.003309274	-3.645159826	0.01039356
KCNA7	Downregulated	-4.600747965	0.00015605	-3.815201322	0.000454257
LOC642236	Downregulated	-4.600747965	2.92499E-05	-2.005986095	0.003101875
ZNF662	Downregulated	-4.594136944	9.32318E-06	-3.399601004	5.71249E-05
C7orf58	Downregulated	-4.593970581	0.000167656	-3.29732144	0.001076115
TRPA1	Downregulated	-4.591804371	0.000131366	-3.343782406	0.000791899
LOC100505702	Downregulated	-4.569260426	0.009482777	-4.762735765	0.007845048
TMEM154	Downregulated	-4.565689391	0.00045769	-3.257870139	0.002793336
IL1R1	Downregulated	-4.565112832	0.000103928	-3.534527394	0.000451527
GLP2R	Downregulated	-4.560773887	0.000179127	-3.272918351	0.001145539

COL17A1	Downregulated	-4.534698246	0.000441313	-2.658793492	0.00705955
SNX29P2	Downregulated	-4.520940316	0.001240574	-4.012114344	0.002321891
MSR1	Downregulated	-4.518789179	0.003898878	-4.004352628	0.006977497
GSDMC	Downregulated	-4.511572035	0.001411976	-4.599485353	0.001274069
APOL1	Downregulated	-4.498741019	9.67896E-05	-3.490753906	0.000416658
TMC1	Downregulated	-4.487868516	0.001529984	-4.646255737	0.001272484
CYP19A1	Downregulated	-4.476801568	0.002331215	-3.701758081	0.005980655
CCBE1	Downregulated	-4.471079396	5.13161E-06	-3.166138375	4.14868E-05
ALPK2	Downregulated	-4.470487764	0.000677571	-3.671353091	0.00194922
LOC100507462	Downregulated	-4.455994656	0.000124029	-4.727935784	8.76569E-05
CCDC36	Downregulated	-4.452095471	8.59507E-05	-3.910229541	0.000183211
PSG5	Downregulated	-4.446717679	0.004244973	-4.040233764	0.006728839
MLLT10P1	Downregulated	-4.440269837	0.00060114	-3.293767997	0.002940342
P2RX7	Downregulated	-4.435319191	5.94255E-06	-4.699760004	4.16732E-06
DNAJC22	Downregulated	-4.42719863	7.21429E-06	-3.825988027	1.75169E-05
LOC100506874	Downregulated	-4.422567169	0.000213712	-2.568614327	0.004000479
MYPN	Downregulated	-4.4193013	0.004847127	-5.216230418	0.00210866
CASP10	Downregulated	-4.405385734	0.000155777	-3.808941257	0.000358516
EXO1	Downregulated	-4.401401233	3.34051E-06	-4.424514117	3.23466E-06
CSNK1A1P1	Downregulated	-4.393019795	1.09649E-05	-3.271924845	6.43783E-05
ADAMTS4	Downregulated	-4.391428201	0.000166285	-3.564638767	0.000544119
SKA1	Downregulated	-4.391067985	9.04748E-06	-4.64027912	6.45956E-06
DAND5	Downregulated	-4.380405426	0.000533962	-5.059650687	0.000236381
C4orf19	Downregulated	-4.364047458	1.69401E-05	-3.45750523	6.82754E-05
S1PR5	Downregulated	-4.361772112	5.11215E-06	-4.081483928	7.67348E-06
FLJ43879	Downregulated	-4.347063275	0.001425124	-3.075951226	0.007982489
ROS1	Downregulated	-4.337960977	0.000773681	-4.540567108	0.000601641
IGSF10	Downregulated	-4.331325403	0.001607813	-3.188072187	0.007390983
TPRG1	Downregulated	-4.331314922	0.000149212	-4.371800556	0.000141359
SLC2A5	Downregulated	-4.330286995	0.000296255	-2.686125229	0.003831602
LOC399715	Downregulated	-4.327710751	0.000167938	-4.093185334	0.000231518
GIPC3	Downregulated	-4.315590103	2.18883E-05	-3.264895868	0.000114952

E2F2	Downregulated	-4.311148213	0.000653798	-4.815479137	0.000352248
KCNQ1OT1	Downregulated	-4.303848674	0.000333334	-2.412001004	0.006909367
RAD51B	Downregulated	-4.301268119	0.000103392	-4.508278575	7.84284E-05
KDR	Downregulated	-4.300641577	0.000999952	-3.7310997	0.002122245
CPM	Downregulated	-4.294258181	0.000158518	-3.831385962	0.000305174
MRVI1	Downregulated	-4.292735426	3.63684E-05	-1.63487644	0.00714073
SOAT2	Downregulated	-4.292596089	0.000312149	-3.46106525	0.001030856
NFATC2	Downregulated	-4.291340844	4.20632E-06	-2.673538694	7.32109E-05
TNFRSF11A	Downregulated	-4.288870473	0.001122579	-3.565571946	0.002945963
ITGBL1	Downregulated	-4.278885301	0.000777973	-4.27108773	0.000785782
MKRN9P	Downregulated	-4.27510631	2.23941E-05	-3.211081293	0.000122569
LOC338817	Downregulated	-4.267898741	1.27868E-05	-3.095236909	8.74628E-05
AGTR1	Downregulated	-4.258984797	0.000162658	-3.309942386	0.000677912
ERG	Downregulated	-4.254542567	0.001013562	-4.173836218	0.001123825
MAP1LC3C	Downregulated	-4.240000872	0.000102664	-3.068510229	0.000649777
SP7	Downregulated	-4.240000872	0.000111635	-2.036514598	0.005841285
NOX5	Downregulated	-4.224258389	0.00123988	-3.535564831	0.003126723
EGFLAM	Downregulated	-4.212443197	0.003607475	-3.405727134	0.00989329
RIBC2	Downregulated	-4.21166636	3.99656E-05	-3.479605576	0.00012348
C3	Downregulated	-4.206622969	0.001469331	-2.923830794	0.008896198
SEC1	Downregulated	-4.20586341	0.000318916	-3.908874059	0.000481798
PAPPA2	Downregulated	-4.198061333	6.36008E-06	-4.01688942	8.32637E-06
ABCA4	Downregulated	-4.188156294	0.000674813	-2.474403976	0.009680024
DNAH11	Downregulated	-4.185287661	9.89679E-05	-3.740667719	0.000190252
ACTL8	Downregulated	-4.179853755	0.000386664	-3.293767997	0.00142723
FLT3LG	Downregulated	-4.179853755	3.09525E-06	-1.960621207	0.000284815
PKP1	Downregulated	-4.179853755	0.00087947	-2.911116204	0.005640592
LOC100130581	Downregulated	-4.160636394	2.30054E-05	-2.026898451	0.001420572
LINC00311	Downregulated	-4.159581997	0.000228549	-4.234049435	0.000206394
ATAD3C	Downregulated	-4.155759359	0.001678249	-3.779690224	0.002740935
ITK	Downregulated	-4.145778327	0.000124011	-2.603595606	0.001662553
C1QTNF2	Downregulated	-4.145261973	0.000523339	-4.105233172	0.000552382

PAPL	Downregulated	-4.141690938	1.47193E-05	-2.034843844	0.000912503
KCNE3	Downregulated	-4.138042623	2.62697E-05	-3.371370759	8.89181E-05
ADCY10	Downregulated	-4.130651903	2.72227E-05	-3.182692121	0.000127642
ELTD1	Downregulated	-4.130217684	7.20976E-05	-3.044189414	0.000419949
RAET1E	Downregulated	-4.122809242	0.000224934	-5.749169854	3.18389E-05
NOX4	Downregulated	-4.114231489	2.8081E-05	-2.411972607	0.000622857
FKBP1AP1	Downregulated	-4.105285689	0.00010563	-3.527758958	0.000254151
TMEM106A	Downregulated	-4.099934422	2.86529E-05	-1.630232754	0.004811439
STX11	Downregulated	-4.090440212	1.16625E-05	-2.492369776	0.000220534
ADAMTSL3	Downregulated	-4.088466338	0.001019031	-4.398703247	0.00068362
EEF1DP3	Downregulated	-4.087573581	0.000786773	-3.054441197	0.003621566
EMCN	Downregulated	-4.084024108	0.000333534	-4.054937229	0.000347313
MR1	Downregulated	-4.080576521	0.001387986	-2.998180947	0.006543738
HOXD-AS1	Downregulated	-4.076628317	0.000408768	-2.790793364	0.003111211
FER1L5	Downregulated	-4.072457593	5.33586E-05	-2.61943503	0.000675567
ADAM20	Downregulated	-4.061110101	0.000479115	-2.641408594	0.004613778
GPR183	Downregulated	-4.058715833	0.001437749	-3.033506777	0.006228518
PYY	Downregulated	-4.052090321	1.67958E-05	-2.399766622	0.000365351
C10orf54	Downregulated	-4.047080943	0.001054401	-3.251323548	0.003301067
MIRLET7BHG	Downregulated	-4.046196566	8.86969E-06	-3.119978689	4.25868E-05
AURKB	Downregulated	-4.042036534	0.001796073	-2.873322987	0.009550648
GSDMA	Downregulated	-4.042036534	0.003593069	-4.251613887	0.002786504
SCIN	Downregulated	-4.031236369	0.000128283	-3.853186111	0.000166786
IQGAP3	Downregulated	-4.023688904	1.53504E-05	-3.026382299	8.42844E-05
C9orf84	Downregulated	-4.015316905	0.00015398	-2.273571902	0.003423851
NEIL3	Downregulated	-4.010562451	3.25902E-05	-3.564290689	6.58057E-05
MME	Downregulated	-4.008599952	0.00071106	-4.024551678	0.00069569
OPN1SW	Downregulated	-3.992022125	0.000108479	-3.352726	0.000297244
C6orf99	Downregulated	-3.986520878	0.000473357	-3.066655864	0.00195749
LCP1	Downregulated	-3.98374802	3.57847E-05	-3.211276471	0.000127977
NCKAP1L	Downregulated	-3.980596422	0.000133772	-3.034569047	0.000626122
ABRA	Downregulated	-3.978580478	0.001131135	-3.010070075	0.004735541

CHI3L2	Downregulated	-3.968561601	0.000348714	-2.794530924	0.002335203
LILRA6	Downregulated	-3.966564377	8.44984E-05	-3.121585255	0.00033771
CIITA	Downregulated	-3.954432699	0.002345285	-3.064820782	0.008141584
TIE1	Downregulated	-3.946206887	0.007777177	-3.736023027	0.009982032
UNQ6975	Downregulated	-3.945383783	0.000207857	-4.926572171	5.66856E-05
USH2A	Downregulated	-3.942181884	0.000111488	-3.660993126	0.000171484
TAF4B	Downregulated	-3.935084568	0.000716727	-3.437887432	0.00148618
POLQ	Downregulated	-3.933969819	0.000856415	-4.041631953	0.000738807
LSP1	Downregulated	-3.92872803	0.004104615	-4.16385201	0.003072465
ZYG11A	Downregulated	-3.927212415	0.000205843	-4.556672305	8.662E-05
CD14	Downregulated	-3.919227858	0.00020558	-3.546588021	0.000363492
GDNF	Downregulated	-3.919110837	3.81238E-05	-2.08106252	0.001405487
BDKRB1	Downregulated	-3.9174062	1.37704E-05	-2.947372306	7.56939E-05
ALOX5AP	Downregulated	-3.913962524	0.000503585	-4.127777117	0.000373602
GPR156	Downregulated	-3.913962524	0.00078807	-2.895067273	0.003815144
ZP1	Downregulated	-3.913045945	0.000208855	-1.901317961	0.009149138
SYCP3	Downregulated	-3.911603249	0.000143698	-2.415987538	0.002069657
TMEM217	Downregulated	-3.908999104	0.000154767	-4.03812822	0.000128111
UHRF1	Downregulated	-3.905579436	0.008024174	-3.990896711	0.007259346
GABRR2	Downregulated	-3.900375824	0.000788041	-2.656806636	0.005697554
FGF18	Downregulated	-3.896426608	0.00074502	-3.879896485	0.000762597
ADAMTS14	Downregulated	-3.89406202	0.010020515	-4.116843635	0.007775584
SLC15A3	Downregulated	-3.89406202	5.515E-06	-2.50655208	7.83711E-05
CAV1	Downregulated	-3.883233954	0.000190395	-2.844614721	0.001085521
COL11A1	Downregulated	-3.871385401	0.000761796	-2.344446889	0.009565199
COL13A1	Downregulated	-3.867324182	0.000206723	-4.029120019	0.000163157
PTPRC	Downregulated	-3.866644087	0.000918988	-3.461816085	0.001660307
LRRC19	Downregulated	-3.85770094	0.00042905	-3.981874688	0.000358908
ACSM5	Downregulated	-3.847370297	0.000196227	-3.717309612	0.000239105
LOC648987	Downregulated	-3.841300148	2.43116E-05	-2.344461778	0.000435461
C8orf46	Downregulated	-3.839971236	0.000417002	-3.828864791	0.000423846
ANKRD26P1	Downregulated	-3.838723904	0.005101438	-4.033038217	0.004008726

GTF2IRD2P1	Downregulated	-3.838723904	0.000101064	-4.121219367	6.65168E-05
SLC2A4	Downregulated	-3.838723904	0.000893345	-4.280400107	0.000489926
TXNRD3NB	Downregulated	-3.833914903	0.001050272	-2.888753469	0.004517581
LOC100506810	Downregulated	-3.825702837	0.001015569	-3.520999957	0.001582127
HGF	Downregulated	-3.816636292	0.000108121	-2.21541609	0.002217432
HNRNPA3P1	Downregulated	-3.816002419	4.9053E-06	-2.282822592	0.000107713
SKA3	Downregulated	-3.81259983	1.0196E-05	-3.609039764	1.42289E-05
BRIP1	Downregulated	-3.809879614	4.33079E-06	-3.882507996	3.85683E-06
SVEP1	Downregulated	-3.798299751	0.00094057	-4.036343367	0.000674493
CCDC168	Downregulated	-3.789824227	0.000214392	-2.534184979	0.001962956
GIPC2	Downregulated	-3.786239125	4.92916E-05	-3.25457981	0.000120314
TNS4	Downregulated	-3.776779176	0.000212636	-2.524980642	0.00195033
PTPRB	Downregulated	-3.772580004	6.96344E-05	-3.229890339	0.000172764
CD40	Downregulated	-3.765604685	0.000919608	-3.326790565	0.001781545
LOC100134368	Downregulated	-3.761535233	0.000195931	-3.016624631	0.000680884
EN1	Downregulated	-3.758688008	0.000426048	-3.516580906	0.000617593
LOC148696	Downregulated	-3.758065766	4.51579E-05	-3.153363443	0.00012711
FERMT1	Downregulated	-3.751516357	9.10089E-05	-3.470946877	0.000143366
ITGB2	Downregulated	-3.745748692	0.005274124	-3.442074749	0.007859499
COL6A3	Downregulated	-3.742227769	0.000129561	-3.263704367	0.000285139
ATP8B5P	Downregulated	-3.73607176	0.000690127	-2.696681723	0.003820806
OTOA	Downregulated	-3.732677484	0.000250757	-3.551351373	0.000332976
PCDHGA12	Downregulated	-3.73031821	4.86539E-05	-1.885482046	0.002253847
TBX15	Downregulated	-3.726764767	4.14051E-05	-4.98415324	7.14298E-06
PTPN22	Downregulated	-3.725848188	2.67095E-06	-2.336626357	4.54129E-05
INHBA	Downregulated	-3.725100483	0.001898244	-3.421311964	0.002938811
BIRC3	Downregulated	-3.721084835	0.00014277	-3.083625208	0.000418443
BCL11B	Downregulated	-3.717187617	0.000443633	-4.357626363	0.000179358
CASC5	Downregulated	-3.711779767	0.000148254	-4.085702409	8.4567E-05
AXDND1	Downregulated	-3.700199999	0.000701419	-4.345548484	0.000284898
CYP27B1	Downregulated	-3.692371155	0.000373353	-2.50484019	0.003003584
LOC440028	Downregulated	-3.692371155	0.00047646	-3.915873262	0.000342274

PIP5K1P1	Downregulated	-3.690233035	0.000591633	-3.825988027	0.000483843
CYP11A1	Downregulated	-3.683090922	0.000401265	-2.673510519	0.002269884
ANKRD20A9P	Downregulated	-3.680136929	7.67137E-05	-3.711348624	7.29834E-05
BCL11A	Downregulated	-3.670413511	0.000391188	-2.487392506	0.003147727
DQX1	Downregulated	-3.665516356	0.000652924	-2.672949566	0.003454241
DPT	Downregulated	-3.665067198	0.000817952	-2.320001707	0.008294662
ROR1	Downregulated	-3.651319323	0.001974871	-4.379750475	0.000746214
SH2D4A	Downregulated	-3.65066535	0.000884634	-3.830139679	0.000680142
MOCOS	Downregulated	-3.647788587	0.000204242	-3.780523736	0.000166158
PLIN1	Downregulated	-3.637628594	0.002027299	-2.900864519	0.006247356
TPTE2	Downregulated	-3.637450627	0.000242331	-3.883509912	0.00016622
SLC38A4	Downregulated	-3.630085919	0.000133684	-2.747092759	0.000651673
COL24A1	Downregulated	-3.62876615	0.000179596	-4.266244571	6.97077E-05
TRIM29	Downregulated	-3.618038081	1.57174E-05	-2.525536005	0.000133516
CD101	Downregulated	-3.615127016	0.000191535	-4.241286707	7.53823E-05
HYMAI	Downregulated	-3.61373826	0.002076738	-3.104070646	0.004468371
SP110	Downregulated	-3.608939819	0.00014956	-4.148655587	6.60464E-05
CAGE1	Downregulated	-3.602689682	4.53045E-05	-2.377211662	0.000503399
HHIP	Downregulated	-3.593321401	0.000672223	-3.350977952	0.000984536
CYP2B7P1	Downregulated	-3.587007597	0.000297741	-3.500484803	0.000342001
CLCF1	Downregulated	-3.584053961	0.000823537	-3.526510141	0.000899494
ODF3L2	Downregulated	-3.580347175	9.08217E-05	-3.467839899	0.000109526
TMC2	Downregulated	-3.577292332	0.001088945	-2.830233758	0.003671241
MKX	Downregulated	-3.57375052	0.000134126	-4.095254563	6.02271E-05
LOC153684	Downregulated	-3.568657545	0.000150123	-1.853558805	0.005121426
BIRC5	Downregulated	-3.566491334	0.00010816	-4.18130425	4.2231E-05
FHAD1	Downregulated	-3.561226001	5.73493E-06	-2.115461156	0.000130275
PSTPIP1	Downregulated	-3.558550934	0.004025646	-3.059271927	0.008275623
EGF	Downregulated	-3.558240793	0.000269931	-4.019602448	0.000133617
C20orf152	Downregulated	-3.555346974	8.2465E-05	-2.10042387	0.001590031
LOC100133985	Downregulated	-3.553918411	8.33703E-05	-2.44221107	0.000711021
KLHL10	Downregulated	-3.553049687	0.003423626	-3.099129044	0.006647607

FAM129C	Downregulated	-3.551793531	4.06801E-05	-2.286574219	0.000522265
FMO4	Downregulated	-3.548874002	0.000452314	-2.966813069	0.001208479
EVC2	Downregulated	-3.543246019	0.000143195	-2.41867504	0.001217684
LYG2	Downregulated	-3.537805745	0.000145377	-3.278337515	0.000225724
COL5A3	Downregulated	-3.533415758	0.000374853	-2.754360805	0.001468187
SP100	Downregulated	-3.526028381	0.003374814	-3.673274941	0.002745519
C4orf22	Downregulated	-3.525579223	0.002260737	-3.606867029	0.002009169
CDC25C	Downregulated	-3.525579223	0.001172542	-3.169692912	0.002056209
IL15	Downregulated	-3.525579223	8.54526E-05	-3.874297123	4.88925E-05
LOC100288637	Downregulated	-3.521339108	0.0001678	-3.229333512	0.000275971
FLJ42289	Downregulated	-3.521126446	0.003045333	-3.625719063	0.002625113
ITGB4	Downregulated	-3.516923892	0.000838192	-3.195779224	0.001403903
LOC100130872	Downregulated	-3.514670168	7.4607E-05	-2.073040673	0.00146599
PLCG2	Downregulated	-3.512137576	0.001836355	-2.736326178	0.006375594
VEPH1	Downregulated	-3.511232497	6.37338E-05	-2.927656106	0.000184624
LILRB3	Downregulated	-3.506082157	0.003061886	-2.979197022	0.006771123
ANO3	Downregulated	-3.503035278	0.001304303	-3.487637224	0.001335293
FLJ14107	Downregulated	-3.503035278	0.002547597	-3.054947005	0.005034303
STAB1	Downregulated	-3.49726262	0.000672353	-2.559921762	0.003480767
ADH6	Downregulated	-3.495278778	8.6128E-06	-2.384522679	8.55281E-05
FBXW10	Downregulated	-3.485417946	0.000403732	-3.180459493	0.000672478
FLJ38109	Downregulated	-3.480480318	0.00120462	-2.687480191	0.004539785
NLRP14	Downregulated	-3.477658628	2.15634E-05	-2.134498248	0.000377163
PCDHGA9	Downregulated	-3.474560566	3.24998E-05	-1.97991982	0.000832392
ABCG2	Downregulated	-3.470241107	0.005840803	-3.832769253	0.003598698
LRRK1	Downregulated	-3.465060851	0.000587845	-3.116887818	0.001049465
SOX7	Downregulated	-3.465060851	0.000279407	-2.92560653	0.000721166
KIF6	Downregulated	-3.460816727	2.6222E-05	-2.712349053	0.000111435
LOC149773	Downregulated	-3.460590829	0.003504598	-3.767780859	0.0022767
FAM176A	Downregulated	-3.457936374	0.000115681	-2.616923422	0.000567957
KIAA1875	Downregulated	-3.452920542	0.000557649	-2.635634037	0.00237215
SLC26A8	Downregulated	-3.450550498	0.000494184	-1.988235968	0.00840271

CDK15	Downregulated	-3.447519622	0.003430193	-4.188558107	0.001251447
TM4SF18	Downregulated	-3.440145392	0.004008354	-3.468553354	0.003848707
KIF4B	Downregulated	-3.435884732	6.00109E-05	-2.239954086	0.00069952
ASB2	Downregulated	-3.434580306	6.21863E-06	-1.727789421	0.000365122
KCNJ14	Downregulated	-3.430957344	0.000113105	-3.256705986	0.000153237
LRRIQ4	Downregulated	-3.430840323	4.54148E-05	-3.067118069	8.81893E-05
LOC152742	Downregulated	-3.427718447	0.004771611	-3.806510705	0.002834987
PAQR5	Downregulated	-3.424706216	2.42139E-05	-2.73166102	9.30117E-05
LOC100506655	Downregulated	-3.414141718	0.001738783	-2.72936499	0.005365908
SND1-IT1	Downregulated	-3.411431711	0.000147331	-4.043696844	5.42313E-05
NLRC5	Downregulated	-3.409728663	0.000343233	-2.178801841	0.003761134
GLI2	Downregulated	-3.408555262	0.00037544	-3.562466031	0.000292291
DYSF	Downregulated	-3.406981949	0.005333165	-3.404037479	0.005355379
EPSTI1	Downregulated	-3.405722557	0.002423162	-3.925148878	0.001149435
BARD1	Downregulated	-3.398506886	8.20691E-05	-3.837927381	3.98882E-05
DENND2D	Downregulated	-3.396605879	0.001761216	-3.241887867	0.002244276
CDC45	Downregulated	-3.392865897	0.00105015	-3.778224863	0.00058277
FUT2	Downregulated	-3.390860969	1.77319E-05	-2.771013029	5.94308E-05
OSCAR	Downregulated	-3.387372505	0.000265639	-2.869769543	0.000674099
TINAGL1	Downregulated	-3.38700125	0.000649953	-3.063035079	0.001124346
INMT	Downregulated	-3.379954984	0.004419813	-3.100057982	0.006691437
HNMT	Downregulated	-3.375484505	0.002227964	-5.832786829	0.000106794
C19orf35	Downregulated	-3.371203694	9.09787E-06	-2.301921707	8.97028E-05
DTL	Downregulated	-3.371203694	1.55384E-05	-3.065481243	2.75724E-05
LOC100129931	Downregulated	-3.368591712	0.001463421	-2.892807132	0.0032133
SATB2	Downregulated	-3.367015668	0.000224433	-3.596749142	0.000153326
PRAM1	Downregulated	-3.362741628	7.62635E-05	-2.704509032	0.000270353
SLC12A1	Downregulated	-3.361607355	0.000764028	-3.630777621	0.000498892
ALPK1	Downregulated	-3.359441144	0.000194908	-3.358288969	0.000195294
EMX2OS	Downregulated	-3.355694637	3.35116E-05	-2.472672668	0.0002021
PRRG4	Downregulated	-3.35548455	0.007491296	-4.416977949	0.00192637
SPDYE5	Downregulated	-3.354078913	4.7816E-05	-1.764161086	0.001805282

S1PR1	Downregulated	-3.349790866	0.001414524	-3.713660291	0.000811411
SP140L	Downregulated	-3.347515389	0.0011055	-2.999174453	0.001977798
TDRD9	Downregulated	-3.346456335	0.000348868	-2.085485512	0.004316304
ZMYND15	Downregulated	-3.340734163	0.001176193	-2.39652897	0.006328979
C14orf182	Downregulated	-3.339841406	0.000189899	-3.265433485	0.000216205
MIP	Downregulated	-3.339784866	0.000666584	-4.399062484	0.000139509
DLGAP5	Downregulated	-3.331769115	0.00106028	-3.96948518	0.000403505
APOBEC3D	Downregulated	-3.329623141	0.002808266	-3.65985537	0.001723492
PSMB9	Downregulated	-3.328945784	0.000211359	-4.355060049	4.37124E-05
LOC440600	Downregulated	-3.327614885	0.000107142	-2.673787611	0.000377362
CDRT1	Downregulated	-3.321750238	0.003184612	-2.975299609	0.005471727
LOC400891	Downregulated	-3.316908962	1.36584E-05	-3.273870313	1.47838E-05
MEI1	Downregulated	-3.314774324	0.000293265	-2.113035784	0.003315281
GPR39	Downregulated	-3.314076256	4.80792E-05	-2.034843844	0.000792022
IGSF6	Downregulated	-3.310336274	0.000311096	-2.351032191	0.002013474
HOGA1	Downregulated	-3.303681729	0.000242964	-4.391229447	4.5955E-05
LOC285540	Downregulated	-3.303400186	0.000310112	-3.914066505	0.000116607
ZBTB20	Downregulated	-3.296194048	3.20287E-06	-2.723278192	1.03022E-05
ZNF850	Downregulated	-3.29339613	0.000231227	-2.7484298	0.000640816
CCDC158	Downregulated	-3.291689742	0.000138857	-2.492686376	0.000673045
ERAP2	Downregulated	-3.291689742	1.57589E-06	-1.773387192	6.73558E-05
KCTD19	Downregulated	-3.288995678	0.000411095	-1.835557272	0.008368353
ITGA11	Downregulated	-3.285753632	0.008720193	-3.785708164	0.004462094
TMPRSS5	Downregulated	-3.285753632	0.000148067	-2.044725472	0.00204455
ARHGAP6	Downregulated	-3.284502001	7.10397E-06	-1.081479374	0.003926396
NKX3-1	Downregulated	-3.277261312	0.001134212	-3.735361164	0.000554484
GREM1	Downregulated	-3.275816441	0.001380847	-3.60328945	0.000826196
DIAPH3	Downregulated	-3.273441143	0.000311749	-3.717241217	0.000150159
FRRS1	Downregulated	-3.272548386	0.001138047	-3.015827278	0.001755916
TLR5	Downregulated	-3.272548386	0.000453857	-2.127302702	0.004413161
LRTM1	Downregulated	-3.27154929	0.001280742	-3.236242315	0.001357007
ALS2CR11	Downregulated	-3.270157388	2.98397E-05	-2.926848084	5.7846E-05

KIF20A	Downregulated	-3.262831993	0.000773248	-3.66651283	0.000404466
BTBD18	Downregulated	-3.261380918	0.001997147	-2.848606307	0.003966807
PRR5L	Downregulated	-3.256874691	0.000262574	-2.689377261	0.000767486
RPGRIP1	Downregulated	-3.256127972	0.000313249	-2.739329294	0.000821124
MALAT1	Downregulated	-3.25075196	2.11811E-06	-2.19163182	2.34951E-05
GOLGA6L10	Downregulated	-3.249555284	0.000103345	-2.477826223	0.00048918
RERGL	Downregulated	-3.249555284	0.000444848	-3.807004102	0.000180526
GALM	Downregulated	-3.247909873	0.002803194	-3.500478623	0.001906753
PPP1R36	Downregulated	-3.247250657	0.001982056	-2.917611217	0.003421981
COLEC11	Downregulated	-3.242619196	2.33497E-05	-1.133956899	0.007533315
COX7A1	Downregulated	-3.242619196	2.14104E-05	-1.600738781	0.001242303
RAD21-AS1	Downregulated	-3.23777792	0.001065064	-2.360518793	0.00536623
PRR11	Downregulated	-3.235418555	0.000197028	-3.031334042	0.000286207
VDR	Downregulated	-3.23504493	0.00017895	-2.82257937	0.000389901
SPTBN5	Downregulated	-3.231878207	0.002485376	-2.632041362	0.006816044
HAS2	Downregulated	-3.231464116	9.53576E-05	-3.027594059	0.000139566
NCAPH	Downregulated	-3.219526715	0.000612625	-2.694798308	0.001603534
LOC158376	Downregulated	-3.2185248	0.00032828	-2.868852964	0.000625309
SERPINE3	Downregulated	-3.2185248	5.01324E-05	-2.422310566	0.000263585
CPS1	Downregulated	-3.216421324	0.002397256	-4.034995627	0.000716776
CAPN12	Downregulated	-3.216115717	0.002228145	-2.62349611	0.006118223
ACTR3C	Downregulated	-3.216033634	6.43579E-06	-1.677775012	0.000306721
NCF2	Downregulated	-3.212401269	0.00111925	-3.072409414	0.001420142
CX3CR1	Downregulated	-3.209559751	0.000276281	-4.081085394	6.83318E-05
ENDOU	Downregulated	-3.207110835	0.000137013	-2.338338248	0.000818255
IGFN1	Downregulated	-3.206120177	0.001802973	-2.85981937	0.003240227
ADAMTS9-AS2	Downregulated	-3.206087465	0.000363915	-2.288784683	0.002262264
HJURP	Downregulated	-3.201873447	0.000786744	-4.183292773	0.000174199
SGCG	Downregulated	-3.194699598	0.000249665	-3.248219304	0.000226992
LOC646626	Downregulated	-3.193171319	0.004672503	-2.878593476	0.007649415
C6orf97	Downregulated	-3.182449907	0.000385818	-2.649102058	0.001062233
TAT	Downregulated	-3.182262263	0.001105984	-3.092582453	0.00128911

WNK4	Downregulated	-3.176903455	0.001003701	-2.269519876	0.005612193
GLIS1	Downregulated	-3.171328781	0.000549473	-3.233964973	0.000492724
LOC100505826	Downregulated	-3.169322948	0.000106943	-1.629829316	0.004048295
RGS20	Downregulated	-3.169322948	3.06917E-05	-2.360882193	0.000174404
TMEM204	Downregulated	-3.169322948	0.000664591	-2.084045696	0.005814409
CPNE6	Downregulated	-3.167369399	0.000219247	-1.8863869	0.003611053
FGF7	Downregulated	-3.161905427	0.00069888	-2.245131686	0.004189871
POTEKP	Downregulated	-3.153974549	0.002767163	-2.760864174	0.005346331
RUNX2	Downregulated	-3.153974549	4.42794E-05	-3.781335933	1.48743E-05
NAT1	Downregulated	-3.145073689	0.004279936	-3.197089149	0.003947904
CFB	Downregulated	-3.142726478	0.000484302	-1.824552901	0.007982852
ROCK1P1	Downregulated	-3.142252912	0.000192191	-2.927364012	0.00028845
LOC100507178	Downregulated	-3.137556535	0.000687777	-2.424479627	0.002704436
RSPO1	Downregulated	-3.134552481	0.000313137	-1.991765522	0.003568523
TROAP	Downregulated	-3.127795078	0.008283443	-3.932619582	0.002728972
MCTP2	Downregulated	-3.127144482	5.5261E-05	-2.902171185	8.59254E-05
KIF14	Downregulated	-3.124135729	0.000208337	-2.706187172	0.00047086
TWIST1	Downregulated	-3.123500551	0.001247642	-4.280451598	0.000216195
CRISPLD2	Downregulated	-3.122409574	0.000620705	-2.381928537	0.002626755
MYLK2	Downregulated	-3.120976364	0.002157694	-3.044661858	0.002451003
PXDNL	Downregulated	-3.118078685	0.000146551	-2.63687026	0.000382852
C21orf7	Downregulated	-3.107099262	0.000899383	-2.684942692	0.001957465
LOC100499405	Downregulated	-3.106851259	0.000128939	-3.09056187	0.00013295
ACRV1	Downregulated	-3.104801975	0.000571542	-1.806765601	0.00904957
E2F8	Downregulated	-3.104801975	0.01052354	-3.63103377	0.005080176
NUF2	Downregulated	-3.104801975	0.002281929	-5.25024666	0.000124521
CD163	Downregulated	-3.104080519	0.001097137	-2.673787611	0.002406004
FGF5	Downregulated	-3.103913342	0.00334149	-3.793983688	0.001178038
DNAH5	Downregulated	-3.103224212	0.00057709	-2.117914267	0.004293053
ANKRD31	Downregulated	-3.102872061	5.81392E-06	-1.949321074	9.51262E-05
CC2D2B	Downregulated	-3.09802075	0.001513489	-3.891838352	0.000435646
MFSD7	Downregulated	-3.09802075	4.11983E-05	-2.976831946	5.22538E-05

PTGS1	Downregulated	-3.097127993	0.002406217	-2.713054885	0.004667031
RAD54L	Downregulated	-3.096158328	4.53691E-05	-2.655633039	0.000112326
NDE1	Downregulated	-3.096060565	0.000472025	-3.90734648	0.000124627
ADAM32	Downregulated	-3.094504908	0.000302679	-2.949221916	0.000397349
C8orf31	Downregulated	-3.092892665	4.65871E-05	-1.472420463	0.002948375
ANP32A-IT1	Downregulated	-3.091474159	0.000207032	-2.125791375	0.001642848
ATP10A	Downregulated	-3.090718821	0.012051267	-3.804817252	0.00459535
HKDC1	Downregulated	-3.087523364	0.004622864	-2.597932397	0.010366816
MST1P2	Downregulated	-3.083915964	0.000548795	-1.75656866	0.009647152
IMPG1	Downregulated	-3.083496484	0.000326487	-2.844958813	0.000513524
PLAC8	Downregulated	-3.079036825	0.005897336	-3.783543579	0.002114651
LINC00315	Downregulated	-3.07546579	0.005062936	-2.736326178	0.008767955
TBX3	Downregulated	-3.072100737	4.31785E-05	-3.609039764	1.63987E-05
COL11A2	Downregulated	-3.070285182	0.000464225	-2.376659169	0.001860607
CDCP1	Downregulated	-3.063354739	2.81736E-05	-2.545141948	8.48616E-05
CCNB2	Downregulated	-3.060644532	0.004251252	-3.357156555	0.002676819
EDNRA	Downregulated	-3.060644532	0.002410206	-2.646040055	0.004982696
LOC100132215	Downregulated	-3.057935576	0.000213496	-2.569963668	0.000570657
DIO2	Downregulated	-3.057203707	2.48931E-05	-3.713966004	7.65015E-06
MPL	Downregulated	-3.05649288	7.40504E-06	-2.044725472	8.29617E-05
FBXO43	Downregulated	-3.052921845	9.616E-05	-1.460277244	0.005274364
ASPM	Downregulated	-3.052492791	0.000382936	-3.677110311	0.000131592
CAPN14	Downregulated	-3.048662035	9.76445E-05	-3.302690514	6.09016E-05
EYS	Downregulated	-3.044999998	0.000725617	-2.392070015	0.002612992
CCDC38	Downregulated	-3.043553564	2.8071E-05	-2.204261009	0.000188312
CDCA2	Downregulated	-3.036592376	0.005498407	-3.550520054	0.002532346
TLR1	Downregulated	-3.036592376	0.01113836	-3.312751922	0.007502737
MST1R	Downregulated	-3.030398742	0.003626366	-2.94641854	0.004167182
TNFSF13B	Downregulated	-3.027258729	0.000628395	-2.663581285	0.001260635
HLA-F-AS1	Downregulated	-3.026742374	0.003803728	-4.166661546	0.000711258
GSG2	Downregulated	-3.018889708	0.002955819	-3.117748291	0.002508963
HOXC4	Downregulated	-3.018889708	0.008332246	-3.014522852	0.008387774

CCDC147	Downregulated	-3.016723497	0.001415431	-2.66502398	0.002697543
PLAUR	Downregulated	-3.016659309	0.001370459	-2.387644556	0.004527347
C9orf47	Downregulated	-3.015665803	0.00257079	-3.83837198	0.000713455
APOBEC3F	Downregulated	-3.013218476	0.000638826	-3.227900486	0.000435409
CLDN11	Downregulated	-3.012343117	0.000338497	-2.427700717	0.001116135
LOC401074	Downregulated	-3.007045002	0.001377614	-2.481386242	0.003704719
SSPO	Downregulated	-3.006675881	0.001448975	-2.949156121	0.001604737
TBX1	Downregulated	-3.006640433	3.66805E-05	-2.869769543	4.84372E-05
CCDC150	Downregulated	-3.001724928	4.0027E-05	-1.893290065	0.000576492
SLC11A1	Downregulated	-3.000977224	0.000313369	-2.495104834	0.000875948
IL21R	Downregulated	-2.997426995	0.000641456	-3.425595791	0.000303369
PODN	Downregulated	-2.993352616	0.006853476	-3.209526483	0.004914922
PRG4	Downregulated	-2.991622376	0.008531613	-2.90418395	0.009762109
FLJ12825	Downregulated	-2.989900653	0.007975465	-3.227229151	0.005569116
MEIS1	Downregulated	-2.9873642	0.002358927	-2.501146488	0.005697918
LOC100134713	Downregulated	-2.981480158	0.001022689	-2.563555852	0.00227106
XRCC2	Downregulated	-2.981267464	0.000162155	-1.854323754	0.00222292
ENAM	Downregulated	-2.980620387	0.000160385	-2.582356491	0.000364606
ABCA6	Downregulated	-2.980150332	0.000487841	-3.33084309	0.000260102
ITGA1	Downregulated	-2.977417951	0.009671836	-3.540957674	0.004272148
BRCA2	Downregulated	-2.967813688	3.71477E-05	-1.504687191	0.0017534
TRPV4	Downregulated	-2.965651394	0.00066351	-2.01579097	0.00495184
TLCD2	Downregulated	-2.958673891	9.94549E-05	-2.608939488	0.000206619
KIF2C	Downregulated	-2.958324789	3.18354E-05	-2.336018539	0.000128797
ANKRD1	Downregulated	-2.957239083	0.010058085	-3.254095766	0.006474663
PRH2	Downregulated	-2.953844519	1.43876E-05	-1.803989878	0.000265332
BHMT	Downregulated	-2.953267441	0.000519179	-1.695451583	0.008897603
NOTUM	Downregulated	-2.953267441	0.004503562	-3.564882321	0.001734024
C6orf132	Downregulated	-2.951450444	4.45699E-05	-2.86745753	5.29268E-05
PKD1L1	Downregulated	-2.949984386	0.000222405	-1.738792473	0.003849092
BDKRB2	Downregulated	-2.943385814	0.000283226	-2.778332484	0.000392796
CEP55	Downregulated	-2.943385814	0.009580689	-3.41782549	0.004752029

C2orf65	Downregulated	-2.937836959	0.010597936	-3.57800928	0.004201275
CCDC144A	Downregulated	-2.937836959	0.002295126	-2.764073734	0.003130677
MOV10L1	Downregulated	-2.937018077	0.001299919	-2.36337605	0.003975849
PIWIL2	Downregulated	-2.936418951	0.000362828	-1.732576223	0.005814697
LOC100505806	Downregulated	-2.934283516	0.000499365	-2.527051897	0.00113287
TGFBI	Downregulated	-2.929718667	0.007773758	-3.107757121	0.005893164
MCM10	Downregulated	-2.92964041	1.22285E-05	-1.689218949	0.000316032
LOC100132774	Downregulated	-2.925871205	1.74352E-05	-2.147582312	0.000110063
PTPN14	Downregulated	-2.918966697	0.000242371	-3.390602246	0.000101707
CAV2	Downregulated	-2.917147379	0.001510719	-3.002887962	0.001295231
LOC388692	Downregulated	-2.913733572	0.000170369	-3.190670165	0.000100377
FLJ35024	Downregulated	-2.911362519	0.000276567	-4.010288738	4.25266E-05
FLJ12334	Downregulated	-2.908746424	0.00029672	-2.821602923	0.000352607
PLIN4	Downregulated	-2.908687247	0.000204412	-2.171086487	0.001048475
CTSW	Downregulated	-2.903616431	0.001440808	-2.495785499	0.003151681
ABCA17P	Downregulated	-2.901489345	2.45841E-05	-2.018097146	0.000209343
KIAA0101	Downregulated	-2.891839067	1.88566E-05	-2.244763087	8.552E-05
LDHAL6A	Downregulated	-2.888101507	0.000249409	-2.304621535	0.000880885
FKBP9L	Downregulated	-2.885247073	0.001487659	-2.256633384	0.005170041
HTR4	Downregulated	-2.881588841	0.000689192	-3.714062815	0.000163898
LINC00482	Downregulated	-2.881072487	0.000418317	-1.751883818	0.005681335
ANKFN1	Downregulated	-2.879501449	5.91608E-05	-3.849448551	1.03217E-05
MYH15	Downregulated	-2.87876786	9.55487E-05	-2.82680874	0.000106319
TOB2P1	Downregulated	-2.87520784	2.1895E-05	-2.816558514	2.47887E-05
EXPH5	Downregulated	-2.871412684	0.000791657	-2.76939245	0.000964072
AGAP11	Downregulated	-2.865278605	0.000248026	-1.86446786	0.002575175
ESPL1	Downregulated	-2.865050547	0.011865114	-3.560730669	0.004311107
METTL7A	Downregulated	-2.862298039	0.000346969	-4.503805265	2.4334E-05
IFI44L	Downregulated	-2.862203166	0.006764214	-4.316882266	0.000828843
NFIB	Downregulated	-2.861227047	0.001860233	-4.49279483	0.000152393
COL8A1	Downregulated	-2.855307336	0.001207296	-2.770805126	0.001417072
PI16	Downregulated	-2.853099691	0.000242199	-2.236645146	0.000943444

NR5A2	Downregulated	-2.848847718	0.013832095	-3.171192596	0.008592467
KIF23	Downregulated	-2.848371249	0.002239119	-3.595100248	0.000644278
MYO15A	Downregulated	-2.843027433	7.51719E-05	-1.577495128	0.002033492
RFX8	Downregulated	-2.840160375	0.000905629	-2.537313369	0.001655659
BLM	Downregulated	-2.837955988	0.000133976	-1.486863181	0.00446509
ABI3BP	Downregulated	-2.83775629	0.000222918	-2.751944596	0.000265772
RAC2	Downregulated	-2.836323411	0.001714351	-2.372296157	0.004251921
LOC729020	Downregulated	-2.835233762	0.000777313	-2.282760869	0.00245674
FLJ41484	Downregulated	-2.834611521	0.002064878	-2.765673175	0.002344837
COLEC10	Downregulated	-2.831058077	0.000152199	-2.132803949	0.000755267
ANGPT1	Downregulated	-2.826019421	0.010781747	-4.249986481	0.001456952
PRDM6	Downregulated	-2.82555683	0.00034422	-3.251323548	0.000153915
PRELID2	Downregulated	-2.820975013	0.001380379	-1.874828098	0.010327228
ACSL5	Downregulated	-2.820623693	0.001136108	-2.596598546	0.001762772
FRK	Downregulated	-2.817882414	0.00348485	-2.671805205	0.004532206
HCG25	Downregulated	-2.813779466	0.000432072	-3.350977952	0.000159319
LRRC2	Downregulated	-2.813052118	0.004202099	-4.338064958	0.000423258
PARPBP	Downregulated	-2.807597554	0.001842092	-2.234089439	0.005783858
ACY1	Downregulated	-2.803012886	0.001455227	-2.269883276	0.004278058
GRB7	Downregulated	-2.801953832	0.000115496	-3.087679327	6.5233E-05
AOX1	Downregulated	-2.801477947	0.002242242	-2.904739663	0.001858209
FANCD2	Downregulated	-2.801209793	2.64587E-05	-2.971135554	1.85528E-05
COL12A1	Downregulated	-2.795186317	0.00306215	-3.404482577	0.001093745
MGC23270	Downregulated	-2.789631688	0.000146273	-2.821831703	0.000136829
CHEK2	Downregulated	-2.784754047	0.000323357	-2.338826464	0.000854403
BMPER	Downregulated	-2.780746033	2.68655E-05	-3.17957454	1.19506E-05
ACRC	Downregulated	-2.776950671	7.57084E-06	-2.290732921	2.43265E-05
PKN3	Downregulated	-2.774120521	0.003286592	-2.336116579	0.007541532
CLEC14A	Downregulated	-2.771982402	0.000100455	-3.059271927	5.61341E-05
LOC100128788	Downregulated	-2.767515071	0.00486067	-4.030733591	0.000686775
JPH2	Downregulated	-2.766069684	0.001571911	-2.231923229	0.004675559
IGF1	Downregulated	-2.765780558	0.000850963	-4.019501909	0.000101876

IGFBP3	Downregulated	-2.765655624	0.004589322	-3.146209949	0.00240662
MBOAT1	Downregulated	-2.765021213	0.00177945	-3.644702988	0.000395161
EFCAB5	Downregulated	-2.763700548	0.000252651	-1.553362534	0.005409728
FAM160A1	Downregulated	-2.76352075	0.001591099	-3.071463569	0.000903432
KLHL30	Downregulated	-2.757950219	0.010020099	-3.541746744	0.003031391
ARHGAP9	Downregulated	-2.752998476	0.006104807	-3.584878797	0.001622578
ANPEP	Downregulated	-2.748716845	0.000680244	-2.648787177	0.000833453
DENND2C	Downregulated	-2.745486123	0.000190076	-2.915722872	0.000134115
TRPC4	Downregulated	-2.740143935	0.000364713	-2.555204125	0.000539694
FLJ31813	Downregulated	-2.733097972	0.000116882	-1.617602794	0.002148434
LOC100129845	Downregulated	-2.733097972	0.000376199	-1.855552856	0.003012011
LINC00312	Downregulated	-2.726236113	0.000283946	-3.364199265	8.38895E-05
RAD51	Downregulated	-2.725933105	0.000271343	-2.688222102	0.000293765
PABPC4L	Downregulated	-2.72278055	0.003477784	-2.448075717	0.005844479
CNTD2	Downregulated	-2.710554028	6.54316E-05	-1.452650435	0.002155581
MARK2P9	Downregulated	-2.710554028	0.001557587	-2.334767213	0.003357673
HERC2P3	Downregulated	-2.710554028	0.000334902	-3.628461832	6.15779E-05
CYP2A6	Downregulated	-2.707811258	0.000504805	-1.923990073	0.003118345
STARD13	Downregulated	-2.705604797	0.001613182	-1.859671956	0.010135023
GHRLOS	Downregulated	-2.702141716	0.000732878	-2.217021641	0.002109347
GSG1	Downregulated	-2.697614712	0.000712945	-1.878724642	0.004688373
SLC26A4	Downregulated	-2.697164362	0.003586767	-3.054608026	0.001901382
SHCBP1	Downregulated	-2.688848128	0.000740687	-1.984275844	0.003648556
CXorf69	Downregulated	-2.688097817	0.000242594	-1.799091619	0.002184721
COL7A1	Downregulated	-2.683612826	0.000459828	-1.578223695	0.007203059
MYLK3	Downregulated	-2.68008293	0.001112055	-2.942960971	0.000667866
LOC731275	Downregulated	-2.67944146	0.002434202	-3.002059541	0.001343306
C19orf40	Downregulated	-2.675944003	0.001121432	-3.199811218	0.000419129
ALS2CL	Downregulated	-2.675649871	0.00018272	-1.633447148	0.002719008
ENTPD3-AS1	Downregulated	-2.67342144	0.002132228	-3.187695767	0.000835912
CLCNKB	Downregulated	-2.667475706	0.000785598	-2.720486254	0.000705177
FAM53A	Downregulated	-2.667475706	0.002423307	-2.041805032	0.008874545

LOC100133315	Downregulated	-2.665455123	1.32422E-06	-1.059545217	0.00033371
SLC35F2	Downregulated	-2.661732783	0.003264144	-3.01287217	0.001727626
CLDN2	Downregulated	-2.658424986	0.000377779	-1.391869445	0.010440452
TNFAIP8	Downregulated	-2.657781141	0.001594359	-2.119476133	0.005015062
FLJ32224	Downregulated	-2.655038371	0.000500002	-1.540886001	0.008208651
VTCN1	Downregulated	-2.649125654	0.000121987	-2.798467346	8.84608E-05
LYN	Downregulated	-2.64841286	0.010881955	-3.513370716	0.002823832
TSHZ2	Downregulated	-2.648358019	0.00020315	-3.310652468	5.49988E-05
TM6SF2	Downregulated	-2.644931761	3.21156E-05	-1.530174912	0.000757907
ETS1	Downregulated	-2.638529494	0.003036625	-3.364298668	0.000845629
LOC100101266	Downregulated	-2.638359073	0.000281976	-1.607285371	0.004013864
ZNF90	Downregulated	-2.637257779	0.002037371	-1.946765367	0.008982591
NME9	Downregulated	-2.636713663	8.6211E-05	-3.001762364	3.99579E-05
UNC13D	Downregulated	-2.636698286	0.00013664	-1.152049586	0.010609524
ANKRD18B	Downregulated	-2.630615571	0.001452388	-3.64485004	0.000239097
EBLN2	Downregulated	-2.630321692	0.000180978	-2.308413893	0.000381431
TP53TG5	Downregulated	-2.629872534	0.000982659	-1.811114356	0.006556084
DAPK2	Downregulated	-2.629353927	0.000446129	-2.195497568	0.001200293
HELB	Downregulated	-2.622244201	0.001651994	-2.495254584	0.002140389
ORC1	Downregulated	-2.619555111	0.00299072	-2.092718775	0.008816738
SEPT7L	Downregulated	-2.619555111	0.008925368	-3.914066505	0.001205888
DLEU2	Downregulated	-2.617347466	0.000233516	-1.307246531	0.008818116
PPP1R13L	Downregulated	-2.612230523	0.002497108	-2.19117032	0.005954099
NUDT13	Downregulated	-2.610546093	0.000195994	-1.565151379	0.003168299
MMP12	Downregulated	-2.607328589	0.003289814	-2.151787874	0.00828563
NOS3	Downregulated	-2.601779734	0.000806943	-1.887070924	0.004293309
CEP128	Downregulated	-2.600571186	8.93221E-06	-2.25166675	2.13955E-05
BCL2L15	Downregulated	-2.600384646	0.000518231	-3.124505694	0.000182639
RPS10P7	Downregulated	-2.597828416	0.001183461	-1.893392375	0.005902175
LOC100506068	Downregulated	-2.587745351	0.001274456	-2.849921571	0.000755805
GYPC	Downregulated	-2.587473734	0.002210519	-3.448171583	0.000469717
AGMAT	Downregulated	-2.586270454	0.00209684	-2.593837028	0.002065326

CCRL1	Downregulated	-2.586064622	0.005096097	-2.464755015	0.006410461
TDRD6	Downregulated	-2.580260485	0.00017202	-1.812724614	0.001236464
SLC19A3	Downregulated	-2.579419401	0.000479675	-2.190752234	0.001174432
WDR65	Downregulated	-2.575694668	5.01481E-05	-2.628494577	4.44397E-05
MYOM3	Downregulated	-2.569354162	0.012914417	-3.420401734	0.003376321
SLC17A9	Downregulated	-2.568589213	0.001075929	-2.891496238	0.000562611
DHRS3	Downregulated	-2.566890368	0.001815535	-2.961356223	0.000845465
MATN1	Downregulated	-2.562696475	0.000131069	-1.421929942	0.003298942
BTN3A2	Downregulated	-2.561654795	0.004507258	-2.602774143	0.004168912
TBX2	Downregulated	-2.560299472	0.001981405	-3.538175709	0.000339917
CD37	Downregulated	-2.558126737	0.000312073	-1.909074461	0.001557822
PCDHGB3	Downregulated	-2.558126737	0.000271215	-2.316877482	0.000474735
MKI67	Downregulated	-2.557741762	0.013518822	-3.997760459	0.001560858
FAIM3	Downregulated	-2.556990533	0.000194114	-2.31548524	0.000342224
LOC100128881	Downregulated	-2.553975085	0.001083596	-1.631674196	0.010064675
DNAH12	Downregulated	-2.543042151	0.000290258	-2.297233445	0.000514793
SYPL2	Downregulated	-2.542286814	0.000443523	-2.260445173	0.000849772
HLA-DPA1	Downregulated	-2.538704669	0.001058876	-2.635273474	0.000864834
ABCA10	Downregulated	-2.537688149	9.28893E-05	-2.501974645	0.000100947
MSH5-SAPCD1	Downregulated	-2.529268988	0.000594547	-1.853558805	0.003094925
PCOLCE2	Downregulated	-2.529268988	3.37766E-05	-1.555639876	0.000566294
SNORA48	Downregulated	-2.529268988	0.002373172	-2.542814616	0.002308876
EFCAB6	Downregulated	-2.527698901	0.000274368	-1.925220749	0.001239519
SYNPO2	Downregulated	-2.527308803	1.51754E-05	-2.493691327	1.6457E-05
PRO0611	Downregulated	-2.527096253	0.000119542	-2.174331819	0.000284711
MPP4	Downregulated	-2.524224579	3.44011E-05	-3.163013721	8.79688E-06
MELK	Downregulated	-2.521957971	0.002038089	-1.999803079	0.006447945
CASS4	Downregulated	-2.520252027	0.013098464	-2.937265696	0.006547429
C3orf35	Downregulated	-2.519387361	6.59061E-05	-1.950470439	0.000291825
ITIH2	Downregulated	-2.519090296	0.001121198	-2.391824273	0.001478598
SLC2A9	Downregulated	-2.517855023	0.006924178	-2.791841834	0.004217327
LOC641298	Downregulated	-2.517042466	0.002954428	-2.008728865	0.008761651

KCNAB3	Downregulated	-2.516093325	0.001785853	-2.319124155	0.002720275
INPP4B	Downregulated	-2.515596952	0.002550965	-2.630312246	0.002027329
SYT15	Downregulated	-2.514092814	0.000111876	-1.562480582	0.001600832
ITGB3	Downregulated	-2.512682623	0.002306365	-1.92070935	0.008545728
CCDC33	Downregulated	-2.510319514	0.000161819	-1.629829316	0.001775254
ENPP3	Downregulated	-2.507327201	0.009327541	-3.450298669	0.001960766
PVRL4	Downregulated	-2.505997695	0.000227307	-3.060704861	7.08686E-05
NOXRED1	Downregulated	-2.503915507	0.000133459	-1.271365396	0.005182303
SIX1	Downregulated	-2.503329969	0.004211264	-3.916355409	0.000391331
LOC100268168	Downregulated	-2.501521432	0.000256221	-2.560345658	0.000224276
LOC389641	Downregulated	-2.496843416	0.009282462	-2.706863779	0.006386819
COL4A3	Downregulated	-2.494612442	0.000601885	-3.004322766	0.000210492
SLC7A5P2	Downregulated	-2.494188738	0.000835563	-1.788860776	0.004678704
SHOX2	Downregulated	-2.491688985	0.000282276	-2.321436511	0.00042136
MSLN	Downregulated	-2.488356877	0.011664386	-2.926263166	0.005530951
FOXH1	Downregulated	-2.486824539	0.009205932	-2.911297413	0.004374623
C1orf38	Downregulated	-2.4839041	0.004090359	-2.465778385	0.00424036
ADAP2	Downregulated	-2.483699142	0.000246031	-2.504099928	0.000234767
EMP2	Downregulated	-2.479221577	0.000292727	-3.011041994	9.50681E-05
BMP3	Downregulated	-2.477722241	0.004389342	-3.674121606	0.000553735
DUOX1	Downregulated	-2.474984556	0.000151196	-1.595561181	0.00173267
MYBL2	Downregulated	-2.471394057	0.002429249	-3.602103677	0.000314336
FERMT3	Downregulated	-2.469402818	1.39989E-05	-1.572697647	0.000203296
RANBP3L	Downregulated	-2.467840614	0.000478703	-2.911931286	0.000186835
USP18	Downregulated	-2.466202428	0.001808297	-3.546131688	0.000245391
LRRC8E	Downregulated	-2.464269579	0.000924365	-3.445337705	0.000139576
FOXM1	Downregulated	-2.454901298	0.000553432	-2.250289256	0.000893297
KANK4	Downregulated	-2.454491101	0.001587504	-3.735996228	0.000153207
ZNF587B	Downregulated	-2.454381179	0.000129167	-1.13813843	0.007748159
RGPD3	Downregulated	-2.453765094	0.000142083	-2.384241967	0.000167868
PTH1R	Downregulated	-2.451957091	0.002091864	-2.156813945	0.00400343
SLC28A3	Downregulated	-2.451702995	0.002274326	-2.611518	0.00163682

MTMR11	Downregulated	-2.451320483	5.3829E-05	-1.723282096	0.000415202
ANKRD19P	Downregulated	-2.451183537	0.000139521	-1.492051219	0.002174075
WFIKKN1	Downregulated	-2.451064334	0.000489231	-1.660697838	0.003844684
LOC729799	Downregulated	-2.450137946	4.9276E-05	-1.981269415	0.000171561
CDH15	Downregulated	-2.445799	0.000545505	-2.798467346	0.000255081
ADAM12	Downregulated	-2.443160796	0.000701827	-2.845574704	0.000298851
CCDC88B	Downregulated	-2.43991944	7.03766E-05	-1.125454922	0.004865781
HR	Downregulated	-2.43795231	0.008718709	-3.134559481	0.002577938
FAM194A	Downregulated	-2.436988814	1.0475E-05	-1.698786619	9.10172E-05
NPEPL1	Downregulated	-2.436062426	0.006438797	-2.216776268	0.009945456
ATP8B4	Downregulated	-2.433586225	0.000194561	-1.506904605	0.002673589
RNF125	Downregulated	-2.432923765	0.002536784	-2.787872924	0.001243718
CASQ1	Downregulated	-2.430237442	0.000827479	-2.24079274	0.001282713
FAM65C	Downregulated	-2.424458599	0.011477455	-2.515226263	0.009741673
CLSPN	Downregulated	-2.421590773	0.000165571	-2.278459154	0.000235208
DMC1	Downregulated	-2.419383127	3.51347E-05	-3.268391346	5.67821E-06
POLN	Downregulated	-2.417597425	0.000384985	-3.468898321	4.72021E-05
C8orf73	Downregulated	-2.416328284	4.68663E-06	-2.467785892	4.11836E-06
IL17RA	Downregulated	-2.412995896	0.000601549	-3.404018833	8.37495E-05
NEB	Downregulated	-2.412363834	0.000182418	-2.830264666	7.17035E-05
CASP8	Downregulated	-2.41092561	0.000367145	-2.882745657	0.000131572
C2	Downregulated	-2.406870393	0.002355583	-2.210619939	0.003622228
SOX6	Downregulated	-2.405837778	0.000168374	-3.338730124	2.4237E-05
RBL1	Downregulated	-2.403672922	1.77975E-05	-1.651880957	0.000164709
SECTM1	Downregulated	-2.402606848	0.002802747	-3.729543814	0.000257552
RRN3P2	Downregulated	-2.399864078	0.002563126	-2.329104004	0.00298409
FOXP3	Downregulated	-2.396899632	0.003603757	-2.096272218	0.006889449
GINS4	Downregulated	-2.395645659	0.000189238	-2.440463023	0.000170018
CNTD1	Downregulated	-2.389781013	0.008514794	-2.300101203	0.010126616
LINC00471	Downregulated	-2.388497952	0.001892946	-1.872825875	0.006358176
ZNF69	Downregulated	-2.385679143	7.63852E-05	-1.444315967	0.001303555
C22orf43	Downregulated	-2.384515679	0.000278722	-1.921535341	0.000928306

CD4	Downregulated	-2.384515679	0.000796966	-2.017141176	0.00194854
LOC100287036	Downregulated	-2.384515679	0.000383418	-1.459310857	0.005113771
IFI16	Downregulated	-2.381294474	0.005619635	-3.643631547	0.00061763
ARHGAP10	Downregulated	-2.373439108	0.001386702	-3.315855103	0.000216879
TBC1D3P1-DHX40P1	Downregulated	-2.366474319	0.000802938	-2.506616268	0.000584858
MYBPHL	Downregulated	-2.364615175	0.000730106	-3.117890765	0.00015264
ECT2L	Downregulated	-2.363963819	0.000335633	-1.624946889	0.00255275
FGF1	Downregulated	-2.36341443	0.000261572	-1.644814315	0.001909889
3-Mar	Downregulated	-2.360648761	0.002181278	-2.468210579	0.001729634
PPARG	Downregulated	-2.359066321	0.00291402	-2.791841834	0.001210879
NLRP1	Downregulated	-2.354870993	0.009777808	-2.396380007	0.00903428
LOC284454	Downregulated	-2.353156313	0.004802309	-2.954897718	0.001509725
ALDH3B1	Downregulated	-2.352764083	0.001675801	-2.484510466	0.001255407
KL	Downregulated	-2.347983948	0.012733977	-3.631194212	0.001534822
SUSD2	Downregulated	-2.347983948	0.003434392	-2.113813448	0.005739445
IRF7	Downregulated	-2.345671008	0.000158982	-1.5310739	0.001698893
MXRA5	Downregulated	-2.336113136	0.002527565	-2.601954792	0.001441417
KCNJ2	Downregulated	-2.335608948	0.000240058	-3.112816677	4.46631E-05
LOC100130093	Downregulated	-2.33399374	0.001720054	-2.167774069	0.002522451
PGM5P2	Downregulated	-2.33263555	0.000831508	-1.789396756	0.003341573
TMOD4	Downregulated	-2.331654479	0.000123927	-2.113974886	0.000218611
PKDREJ	Downregulated	-2.326871774	0.000247017	-1.208541425	0.007706642
DKFZP564C196	Downregulated	-2.324081334	0.000302191	-1.602411383	0.002285651
HLA-DMA	Downregulated	-2.319256812	1.41184E-05	-1.291564446	0.000439596
LRRC70	Downregulated	-2.315874168	0.000876147	-1.698786619	0.004373617
TMPRSS9	Downregulated	-2.313465085	0.000535848	-2.79879296	0.000181772
MICALCL	Downregulated	-2.313213482	0.003610098	-1.967693298	0.007852486
DEPDC1	Downregulated	-2.313068429	0.004195298	-2.47935856	0.002967932
COL15A1	Downregulated	-2.309910959	0.000305018	-2.044970145	0.000604449
MUC5B	Downregulated	-2.309379773	0.000538997	-2.646040055	0.000249965
FAM18B2	Downregulated	-2.307677619	0.000476086	-1.68370092	0.002585183
WDR76	Downregulated	-2.298954732	0.000197424	-2.219696707	0.000241513

ITGA5	Downregulated	-2.297721216	0.008138896	-3.291025869	0.001357238
IRF1	Downregulated	-2.297489056	0.000316532	-2.256704494	0.000350352
DGKH	Downregulated	-2.292232153	0.000397039	-2.305281458	0.000384538
NUDT4	Downregulated	-2.289864514	0.002724164	-2.816195115	0.000915949
GBP1	Downregulated	-2.286555574	0.008508701	-2.53644506	0.005225683
SLC28A2	Downregulated	-2.286555574	0.00100152	-4.226053325	2.92129E-05
TNFRSF10A	Downregulated	-2.286555574	0.004901057	-4.418949376	0.000139306
BMP6	Downregulated	-2.285023237	0.002141806	-2.876526947	0.000623314
HLA-L	Downregulated	-2.284274347	0.00029011	-1.376349322	0.00434225
CSGALNACT1	Downregulated	-2.280690928	0.002402011	-2.722689052	0.000941792
ESCO2	Downregulated	-2.277187293	0.000138276	-2.053827769	0.000250901
HEATR4	Downregulated	-2.273489819	0.003272366	-2.036573594	0.005612794
LOC729177	Downregulated	-2.271245352	0.000367459	-1.854446491	0.001125069
KIF15	Downregulated	-2.268938243	0.003014619	-2.183225568	0.00365616
DNAH17	Downregulated	-2.267642364	0.000547362	-1.993291584	0.001108832
APOL6	Downregulated	-2.265396293	0.000125896	-2.51875478	6.75322E-05
LOC387723	Downregulated	-2.265047968	0.002884111	-3.076384013	0.000564641
FAM54A	Downregulated	-2.263562472	0.002789335	-2.979752385	0.000647317
LOC100129858	Downregulated	-2.26317427	0.000600726	-1.381850569	0.007562193
CHRNA10	Downregulated	-2.261178924	0.00036505	-1.287111669	0.006925406
EMX2	Downregulated	-2.261134866	0.001006927	-1.601399355	0.005865428
LRRK2	Downregulated	-2.256767002	0.000872264	-3.171091212	0.000127393
PCDHB19P	Downregulated	-2.255231331	0.001179169	-2.471068819	0.000717735
LINC00173	Downregulated	-2.252252776	0.002110968	-1.749052612	0.007340058
RELL1	Downregulated	-2.250102419	0.000114729	-2.277873694	0.000106783
ASB3	Downregulated	-2.246686603	7.80534E-05	-1.457491712	0.000916386
GALNTL2	Downregulated	-2.243138238	0.002572384	-2.382030703	0.001886341
AGPAT9	Downregulated	-2.240611555	0.000173285	-2.275560341	0.000158429
WDR62	Downregulated	-2.240340597	0.001701837	-2.306016472	0.001461241
GRAMD2	Downregulated	-2.234494487	0.000691305	-2.748828925	0.000215187
OTOGL	Downregulated	-2.233662039	0.006817504	-3.470260982	0.000711039
ANGPTL4	Downregulated	-2.233344545	0.001407599	-1.617806579	0.007081736

LCNL1	Downregulated	-2.232088389	0.002767566	-3.396076857	0.000284702
SNORD116-20	Downregulated	-2.231039918	0.000171461	-1.303790968	0.003207683
BUB1	Downregulated	-2.230273595	4.09944E-05	-3.306955607	3.758E-06
DKK1	Downregulated	-2.229729114	0.00236449	-1.95248447	0.004598675
DPF3	Downregulated	-2.225127201	0.004818421	-1.918442742	0.009655051
RGS5	Downregulated	-2.224165773	0.001007922	-2.281756491	0.000877356
EBF2	Downregulated	-2.220676949	0.000630471	-2.476459629	0.000342493
CENPF	Downregulated	-2.219861867	0.003906229	-3.001961874	0.000807658
PHACTR3	Downregulated	-2.218165007	0.000450415	-1.688182832	0.001976165
ITIH4	Downregulated	-2.21622949	2.64334E-05	-1.896180855	6.70306E-05
RHBDL2	Downregulated	-2.21436062	0.000975569	-2.33504921	0.000730334
HSF4	Downregulated	-2.211987508	0.001050578	-1.945899318	0.002070612
C21orf49	Downregulated	-2.211316955	0.000565336	-2.343547324	0.00040859
GTSE1	Downregulated	-2.210958031	0.000832143	-3.306521434	8.40516E-05
KIAA1656	Downregulated	-2.20994575	0.001014211	-1.675035214	0.004251583
PRIMA1	Downregulated	-2.204254009	0.001013416	-2.567980454	0.000436615
SLC25A34	Downregulated	-2.201230027	0.000135309	-1.379689897	0.001816811
COL4A4	Downregulated	-2.200029929	0.001456355	-3.195862367	0.000182689
C6orf163	Downregulated	-2.199012221	0.00047565	-1.527598668	0.003310843
MCM9	Downregulated	-2.194164094	0.00038812	-1.955027593	0.000737736
TOMM20L	Downregulated	-2.194096716	1.45193E-05	-1.683040346	7.10963E-05
ZNF490	Downregulated	-2.190725927	0.001402808	-1.51561053	0.008732
CACNA2D3	Downregulated	-2.184010436	0.000123918	-1.467937824	0.001158183
IMPA2	Downregulated	-2.183980731	0.002949115	-2.253485034	0.002514671
RPL19P12	Downregulated	-2.181221239	0.000722377	-2.262465755	0.000590321
LMOD1	Downregulated	-2.179891047	0.001995797	-1.712820428	0.006605121
CCDC163P	Downregulated	-2.178488859	0.002629969	-3.506463019	0.000194679
PHEX	Downregulated	-2.171552772	0.003051031	-2.919605269	0.000635319
KLRG1	Downregulated	-2.168627002	1.51012E-05	-1.759170812	5.30427E-05
KIAA1462	Downregulated	-2.167216398	0.000340039	-2.602961733	0.000118433
ERBB3	Downregulated	-2.16530382	0.000207902	-2.558145382	7.86766E-05
NFATC1	Downregulated	-2.164980084	0.004898281	-3.66627671	0.00029776

MLN	Downregulated	-2.160786191	0.000729171	-2.118816163	0.000811911
OXT	Downregulated	-2.160786191	0.002595545	-1.909074461	0.004811026
TAGAP	Downregulated	-2.160557916	8.13802E-05	-1.77485051	0.00025509
LY6G5C	Downregulated	-2.157011964	8.98648E-05	-1.294818136	0.001578689
GP1BA	Downregulated	-2.153050487	7.2795E-05	-1.043679872	0.003924126
SYCP2	Downregulated	-2.152763708	0.001039067	-2.850779042	0.00021647
C15orf42	Downregulated	-2.151962258	0.000214657	-2.239965941	0.000170352
ZNF469	Downregulated	-2.149664442	0.00069007	-2.884584822	0.000129866
C3orf49	Downregulated	-2.148738353	0.004772039	-1.96228549	0.007349654
CCDC7	Downregulated	-2.148539488	5.24294E-05	-1.465653939	0.000479449
KCNK6	Downregulated	-2.141802266	0.003806917	-2.325409515	0.002515669
PKD1L3	Downregulated	-2.140223824	0.001707014	-2.301477529	0.001160697
CEP152	Downregulated	-2.137894222	7.1686E-06	-1.396303973	9.25943E-05
KRT15	Downregulated	-2.135021041	0.005741993	-2.994534614	0.00101907
PLCB3	Downregulated	-2.134867597	0.001262781	-1.68126425	0.004304165
TAS2R20	Downregulated	-2.134225265	0.005195091	-2.782157241	0.00134933
KIAA1614	Downregulated	-2.133389954	6.19383E-05	-1.182215477	0.001725629
MYO15B	Downregulated	-2.129462868	0.004569936	-1.943352624	0.007073685
ARHGAP31	Downregulated	-2.125791651	0.010340162	-2.93539181	0.002168759
IZUMO4	Downregulated	-2.12364981	2.53527E-05	-1.661236221	0.000109035
LOC221442	Downregulated	-2.120701017	0.00798816	-2.274981014	0.005745008
USP43	Downregulated	-2.120584633	0.000347466	-2.017031187	0.000460609
PDE1A	Downregulated	-2.11444932	0.000162766	-1.684858151	0.000590827
ATP8B3	Downregulated	-2.112678533	0.000128766	-1.060920978	0.005306365
BAIAP2L2	Downregulated	-2.112541079	0.00050688	-1.699155218	0.001652884
ABCC3	Downregulated	-2.112060737	0.000570998	-2.236060596	0.000415123
SPATA5	Downregulated	-2.110078387	9.8166E-05	-1.363386267	0.001155929
AGBL2	Downregulated	-2.104166818	0.001300068	-3.061321212	0.000160029
FAM71F2	Downregulated	-2.103653163	2.63787E-05	-2.533099351	8.56246E-06
CAPN3	Downregulated	-2.101867946	0.000521502	-1.925596291	0.000845411
RARB	Downregulated	-2.100703615	5.1529E-05	-1.381727114	0.00057794
PDGFRB	Downregulated	-2.09654005	0.011044172	-2.838061797	0.002591288

C10orf140	Downregulated	-2.089240813	0.001325781	-2.092694676	0.001314159
GPR126	Downregulated	-2.083741747	0.003155488	-4.137795994	7.04344E-05
KRTAP5-7	Downregulated	-2.08272659	0.001632957	-2.403326641	0.0007561
RHOJ	Downregulated	-2.077497128	0.003102802	-2.978716617	0.000452444
HERC2P7	Downregulated	-2.076153902	0.000399447	-2.377862257	0.000184194
SNX22	Downregulated	-2.075341345	0.003055648	-2.182187813	0.002366471
RBMS3	Downregulated	-2.072380996	0.002271681	-2.883234447	0.000379916
NLRC3	Downregulated	-2.071090803	0.001395801	-1.704397464	0.003801358
GRIN2C	Downregulated	-2.067810978	0.000996847	-1.740173374	0.002475135
FAM129A	Downregulated	-2.065775973	0.00022114	-4.027426732	4.08514E-06
SH3D21	Downregulated	-2.064147437	7.70932E-05	-1.004960907	0.004029259
TPTE2P1	Downregulated	-2.063109607	0.000489356	-1.304891606	0.005379575
NMI	Downregulated	-2.062826086	0.004581705	-2.223090072	0.00316263
UCP3	Downregulated	-2.06123829	0.000265106	-1.806240368	0.0005581
ADAMTS6	Downregulated	-2.053609302	0.004724055	-2.342271636	0.002448217
CFD	Downregulated	-2.051875067	0.000874704	-2.314899663	0.000449017
ARAP3	Downregulated	-2.050976217	0.002271809	-2.263693095	0.001354637
LOC439949	Downregulated	-2.049095059	0.00195113	-1.846879613	0.003318008
CLMP	Downregulated	-2.042887682	0.003282942	-2.469921358	0.00122571
AFAP1L1	Downregulated	-2.041153071	0.013089521	-2.84630902	0.002713551
ABCA9	Downregulated	-2.0392107	0.000333413	-1.9899999	0.000382792
LOC100506746	Downregulated	-2.038605495	0.000936647	-1.831704485	0.001659697
THSD4	Downregulated	-2.038113362	0.006404268	-3.173714297	0.000652564
RAB41	Downregulated	-2.037773229	0.000220411	-1.562113824	0.000974395
DUSP19	Downregulated	-2.036003145	0.001509586	-2.332787119	0.000724462
DLC1	Downregulated	-2.034696586	0.000243419	-1.959482018	0.000301793
LDB3	Downregulated	-2.033627597	0.000743543	-2.815144453	0.000117225
LOC648809	Downregulated	-2.033507492	4.25879E-05	-1.163762835	0.001039379
GSTM2P1	Downregulated	-2.030902845	0.000290465	-2.945963424	3.28634E-05
PCDHB11	Downregulated	-2.028356467	0.00033551	-1.391376539	0.002579005
LOC728377	Downregulated	-2.02513518	0.005059728	-3.27978021	0.000398154
RASA4	Downregulated	-2.021001944	0.001640511	-1.753190251	0.00340429

NPHP3	Downregulated	-2.019875829	0.000370796	-2.208157186	0.000223205
LOC388849	Downregulated	-2.018817606	0.000495036	-1.117095192	0.010111295
E2F7	Downregulated	-2.017902777	0.006314088	-2.097605578	0.005248273
LOC619207	Downregulated	-2.017280661	4.42128E-05	-1.325123242	0.000504526
EHBP1L1	Downregulated	-2.016359686	0.000115804	-2.302959443	5.28969E-05
ABCA1	Downregulated	-2.012862014	0.006803257	-2.73175307	0.001472326
MUC1	Downregulated	-2.012646268	0.005894447	-2.194242114	0.003874833
PHACTR2	Downregulated	-2.009318884	0.00055384	-2.169396914	0.000360363
FMN1	Downregulated	-2.007627708	0.001217556	-2.450245262	0.000407234
CARNS1	Downregulated	-2.00596745	0.002823254	-1.931618406	0.003414789
ATP2C2	Downregulated	-2.001250056	0.000897979	-1.522107963	0.003741345
STL	Downregulated	-2.000763839	0.001722883	-1.592725819	0.00543004
COL16A1	Downregulated	-2.000132467	0.001263919	-2.656447642	0.000262327
LAMA4	Downregulated	-1.999437527	0.000355517	-1.527359894	0.001555073
MND1	Downregulated	-1.996132378	0.002751842	-2.571817418	0.000718107
GLI3	Downregulated	-1.993743694	0.001821066	-2.522065069	0.000510206
NFKBIZ	Downregulated	-1.992894	0.00074577	-2.826487266	0.000102037
LOC100505894	Downregulated	-1.990784087	0.003791143	-2.468726657	0.001248968
LMOD3	Downregulated	-1.988936832	0.000206538	-2.984691118	1.87223E-05
CATSPER3	Downregulated	-1.985365797	0.000725603	-2.479235105	0.000207668
LINC00174	Downregulated	-1.982206493	0.000603573	-1.342109205	0.004643398
DOCK5	Downregulated	-1.980968997	0.004656934	-1.921340796	0.00539873
NRXN3	Downregulated	-1.980730732	0.006676796	-2.24764344	0.003620299
ITGA10	Downregulated	-1.979723403	0.000677049	-1.590291829	0.002184391
TTN	Downregulated	-1.979547878	1.7516E-05	-1.684778169	4.61191E-05
MYOZ3	Downregulated	-1.976897373	0.001125209	-2.39495762	0.000390828
TAS2R31	Downregulated	-1.976499498	0.000225993	-1.003867599	0.007954072
IL27RA	Downregulated	-1.973945792	0.001295365	-1.469512914	0.005782104
SCARNA12	Downregulated	-1.973588434	0.002943965	-1.888150587	0.003675355
PDE6C	Downregulated	-1.973357084	0.009813025	-2.790188713	0.001804696
OPLAH	Downregulated	-1.972463306	0.000340812	-3.13726734	2.23752E-05
NPR3	Downregulated	-1.971975144	0.001843602	-2.180352491	0.00108166

PRSS36	Downregulated	-1.965914451	0.005180865	-2.449608054	0.001708004
DPH3P1	Downregulated	-1.96457744	0.001575278	-1.402029438	0.008373708
TAF1L	Downregulated	-1.964564067	0.000266827	-1.688757336	0.000624764
KIAA1530	Downregulated	-1.963694939	7.18782E-05	-1.158352321	0.001416991
DOK3	Downregulated	-1.960826729	0.000177314	-1.48005952	0.000863232
LOC387646	Downregulated	-1.960748576	0.000209945	-2.191850297	0.00010997
MIR940	Downregulated	-1.960517226	0.000228258	-1.261346519	0.002533973
HSPB6	Downregulated	-1.957984634	0.003355253	-2.655690333	0.000671865
P2RX5-TAX1BP3	Downregulated	-1.956520464	0.000453187	-2.307614558	0.000177003
CENPN	Downregulated	-1.954902035	3.96595E-05	-1.997927112	3.48183E-05
FBXO32	Downregulated	-1.953750742	0.002698832	-3.32889482	0.000144206
LOC285593	Downregulated	-1.949103261	0.000627748	-1.454321189	0.002969806
APOLD1	Downregulated	-1.94655072	0.000734016	-1.738118936	0.001354471
LRGUK	Downregulated	-1.945469014	0.007059271	-1.929105343	0.007342979
CDCA7	Downregulated	-1.943837928	0.00018138	-1.799091619	0.000282779
IL1RAP	Downregulated	-1.936914364	0.00323878	-1.742251438	0.00544889
NID1	Downregulated	-1.933124453	0.007342904	-2.607559064	0.001657468
ATP2A1	Downregulated	-1.932818015	0.000180115	-1.200533629	0.002457888
PCDH12	Downregulated	-1.932676322	0.000817825	-1.993321722	0.000690323
EFNA4	Downregulated	-1.928126564	0.001602852	-1.459310857	0.006468451
SAMD9	Downregulated	-1.928126564	0.010108858	-2.316676045	0.004263349
ASF1B	Downregulated	-1.927954405	0.010973064	-2.414043579	0.003808435
ULK4	Downregulated	-1.927260848	1.54605E-05	-1.813482628	2.23299E-05
CDC6	Downregulated	-1.921065925	0.00596738	-2.200339791	0.003067692
HSF2BP	Downregulated	-1.920815547	0.001218168	-1.461615484	0.004924512
RFTN2	Downregulated	-1.92010046	0.000582345	-2.431736456	0.000152068
MCC	Downregulated	-1.919346834	0.006673272	-2.608104043	0.001431084
C3orf32	Downregulated	-1.918072777	0.006265542	-1.969610078	0.005522232
HAR1A	Downregulated	-1.918072777	0.000603643	-1.703125565	0.001154666
TNFRSF25	Downregulated	-1.916660908	0.000660286	-1.298441354	0.005010949
LOC100506649	Downregulated	-1.91507963	0.001948827	-1.870743857	0.002200494
FLJ39653	Downregulated	-1.911749749	0.000427143	-1.585725202	0.001193231

ADM2	Downregulated	-1.909007249	0.013390455	-2.992928049	0.001518027
KLHL34	Downregulated	-1.908549899	0.006736247	-1.98974494	0.005527897
MGC16275	Downregulated	-1.907516284	0.004225123	-2.271352782	0.001739619
LTBR	Downregulated	-1.904500457	0.005712943	-1.943844927	0.00517893
LAMA3	Downregulated	-1.904298467	0.006537129	-1.839250095	0.007689725
CORO6	Downregulated	-1.903690766	9.57613E-05	-1.059255897	0.002477807
LOC100288846	Downregulated	-1.901393479	0.001389639	-2.25985459	0.000542653
C9orf100	Downregulated	-1.896151691	6.39173E-05	-1.821085625	8.11419E-05
JAK3	Downregulated	-1.895940147	0.00147303	-1.402430948	0.006683276
ANGPTL6	Downregulated	-1.895528833	0.000112558	-1.381850569	0.00068066
HSD17B11	Downregulated	-1.894381837	0.004901334	-2.607753627	0.000943686
C16orf74	Downregulated	-1.893534781	0.000271429	-1.708805496	0.000484751
CHDH	Downregulated	-1.892676182	0.006572372	-3.638000185	0.000205072
ZHX2	Downregulated	-1.891486999	0.000584634	-2.022784478	0.000401778
ENPEP	Downregulated	-1.888961007	0.000532949	-2.199497657	0.000225279
LOC100507501	Downregulated	-1.884207389	0.003819014	-3.239212119	0.000204265
MAK	Downregulated	-1.882574962	0.003356107	-2.20821034	0.001474286
SLC39A11	Downregulated	-1.881267472	0.001209331	-2.142092424	0.000595813
LOC100506451	Downregulated	-1.87809271	0.00136153	-1.650640785	0.002667898
ATG9B	Downregulated	-1.876909881	0.000106954	-1.423369719	0.00052109
UCKL1-AS1	Downregulated	-1.876729623	0.011843518	-1.985656569	0.009204645
MMS22L	Downregulated	-1.872820061	0.001843808	-1.496399076	0.005676234
TMC3	Downregulated	-1.872074885	0.001891331	-1.533260818	0.00516
GPR179	Downregulated	-1.86956055	0.009755922	-1.956243097	0.007933942
CCNE1	Downregulated	-1.86903616	0.004984652	-1.907229581	0.004517847
SARDH	Downregulated	-1.868405765	0.000187621	-1.329112146	0.001253369
ATHL1	Downregulated	-1.864826964	0.007709493	-2.460123555	0.001966981
PLEKHG4B	Downregulated	-1.86090644	0.000193736	-1.947168805	0.000149049
ARHGEF26	Downregulated	-1.856743377	0.000861909	-3.504959057	2.17834E-05
ALDH8A1	Downregulated	-1.852390113	0.002783974	-1.548861052	0.006686054
AMH	Downregulated	-1.847299933	0.000946631	-1.179834953	0.009002134
MIR137HG	Downregulated	-1.844962407	5.5646E-05	-1.172308403	0.000751058

PIWIL4	Downregulated	-1.843135053	0.000892885	-2.431092536	0.000188522
C5	Downregulated	-1.842860352	0.002649129	-1.846007156	0.002626183
CATSPER2	Downregulated	-1.841445488	0.000888466	-1.613150018	0.001801482
RNF144B	Downregulated	-1.839657466	0.003967366	-2.450689298	0.000891822
AIFM3	Downregulated	-1.837840441	0.011120415	-1.978262026	0.007969984
FAM186B	Downregulated	-1.837840441	0.003892876	-1.488458652	0.010515593
RAPGEF3	Downregulated	-1.836736373	0.000950947	-1.166460648	0.009272018
TUBD1	Downregulated	-1.832806076	0.001194041	-2.739297747	0.000124741
GALNT6	Downregulated	-1.832273349	0.012615001	-1.952766916	0.009507181
LOC389791	Downregulated	-1.82707386	0.003825409	-1.54504444	0.008512913
ERBB4	Downregulated	-1.826808732	0.000185018	-2.374703752	3.95609E-05
LRP5L	Downregulated	-1.826690456	0.000126971	-1.121699456	0.001910073
C7orf10	Downregulated	-1.826482228	0.008860231	-2.285869471	0.003009889
TPX2	Downregulated	-1.824866215	0.000609161	-2.142677123	0.000246526
C8orf51	Downregulated	-1.82325965	0.000709603	-2.700895741	7.48994E-05
PFN1P2	Downregulated	-1.821161143	0.001757753	-2.168856669	0.000686654
CCDC102B	Downregulated	-1.821006546	0.001071126	-1.485370555	0.003103361
PLB1	Downregulated	-1.817861241	0.004237246	-1.8599014	0.003785248
SNORD22	Downregulated	-1.814847339	0.003692297	-1.528154329	0.008401986
SPHK1	Downregulated	-1.814847339	0.005208807	-2.972078403	0.000386869
LGALS3	Downregulated	-1.814704864	0.000132965	-2.258060192	3.6549E-05
CYP20A1	Downregulated	-1.814171336	0.000128334	-1.484016076	0.00040606
FBXO36	Downregulated	-1.810607415	0.002400759	-1.679388296	0.003513402
ANO9	Downregulated	-1.804687346	0.004428344	-2.677407933	0.000557814
GNN	Downregulated	-1.804687346	0.01166132	-2.448075717	0.00272975
AIM1	Downregulated	-1.803147578	0.000234233	-2.105830428	9.51496E-05
CD27	Downregulated	-1.802410004	0.002124547	-1.620727018	0.003643613
RPL23AP64	Downregulated	-1.793649192	0.000241461	-1.676800993	0.000354307
PNPLA7	Downregulated	-1.79305736	0.000757967	-2.278809163	0.00019646
SERPINF2	Downregulated	-1.788667867	1.65497E-05	-1.017807115	0.000451237
ZNF563	Downregulated	-1.787247937	0.000945378	-1.516991472	0.002252486
MDM4	Downregulated	-1.781225596	0.000617734	-1.225283996	0.004386618

CDH23	Downregulated	-1.778424835	0.001497628	-2.351643891	0.000322546
TAF8	Downregulated	-1.777541517	0.000578287	-2.260082891	0.000147543
DCHS2	Downregulated	-1.776912739	0.000997389	-2.240398813	0.00027452
LOC100132247	Downregulated	-1.771042127	0.000107571	-1.361995714	0.000484617
LOC646214	Downregulated	-1.766155003	0.003077601	-1.583491613	0.005271332
HAPLN3	Downregulated	-1.765645487	0.00222738	-1.605077726	0.003611852
ISPD	Downregulated	-1.761592962	7.1038E-05	-1.226579405	0.000569074
FBLN2	Downregulated	-1.760935516	0.002081579	-2.020121955	0.00100545
DHRS4L1	Downregulated	-1.756412112	0.000243642	-1.789391112	0.000218985
P2RX5	Downregulated	-1.753418965	0.000493536	-1.229423278	0.003266566
ATG16L2	Downregulated	-1.752990269	5.95091E-05	-1.208290873	0.000509724
SH2D3A	Downregulated	-1.752452955	0.000199745	-1.718965488	0.000223186
ARRDC2	Downregulated	-1.750863258	0.00034868	-1.550698274	0.000686959
GHR	Downregulated	-1.748988409	0.002086171	-2.433015298	0.000346363
BRCA1	Downregulated	-1.743962338	0.003635913	-2.485137955	0.000558818
NRG4	Downregulated	-1.743434757	0.000419572	-1.330588153	0.001823394
LPIN3	Downregulated	-1.742976085	0.000447443	-1.785543746	0.000390689
LOC645166	Downregulated	-1.73951993	8.4608E-05	-1.468118519	0.000226932
B3GNT7	Downregulated	-1.737675316	0.002080879	-1.889866176	0.001338425
SLCO2A1	Downregulated	-1.736787738	0.001221684	-2.09447782	0.000437113
MYLK4	Downregulated	-1.736140354	0.002743116	-2.190013905	0.00080368
LOC400680	Downregulated	-1.735684021	0.000321448	-2.239331228	7.33832E-05
MYLK	Downregulated	-1.734371868	0.010869404	-2.378269288	0.002381506
SCNN1D	Downregulated	-1.73304078	0.003386554	-1.42356136	0.008692898
CA13	Downregulated	-1.732707819	0.001262421	-1.322808039	0.005006044
CENPL	Downregulated	-1.727247471	0.002978693	-2.131506561	0.000989346
FST	Downregulated	-1.716381912	0.01025163	-3.720407228	0.000179139
PCSK5	Downregulated	-1.707166702	0.00026894	-2.524925354	2.6971E-05
VWCE	Downregulated	-1.706855544	0.000530595	-1.194989936	0.003511865
NR6A1	Downregulated	-1.703634913	0.00137353	-1.485076007	0.002805003
FHOD1	Downregulated	-1.697207319	0.001648674	-2.271692612	0.000333816
XPNPEP3	Downregulated	-1.695935656	0.002497076	-1.726810743	0.002276101

MAP7D3	Downregulated	-1.693312277	0.002574326	-1.82870907	0.001728546
TMOD1	Downregulated	-1.690789846	0.010838185	-2.475617053	0.001688285
NEK8	Downregulated	-1.683421244	2.70749E-05	-1.687453658	2.66883E-05
ESR2	Downregulated	-1.683200175	0.001351677	-1.294307215	0.005143361
DMKN	Downregulated	-1.680112907	0.000302685	-1.921139932	0.000139955
PLCE1	Downregulated	-1.67861847	0.000121426	-1.161251196	0.000972952
C18orf56	Downregulated	-1.675359364	0.001817989	-1.387115903	0.004719531
SLC25A35	Downregulated	-1.675359364	0.0046294	-2.017141176	0.001810266
FANCI	Downregulated	-1.6671913	0.000336367	-2.2518789	5.86565E-05
CCDC154	Downregulated	-1.662828732	0.00455202	-1.401360997	0.010148865
LOC100506023	Downregulated	-1.661601613	0.00015643	-1.518585545	0.000262643
PTGIS	Downregulated	-1.657680523	0.001044099	-1.178906538	0.005937134
PRRX1	Downregulated	-1.651510993	0.013293921	-2.56271512	0.001588719
C9orf3	Downregulated	-1.651147982	0.001687334	-1.660431252	0.001638314
DNAH7	Downregulated	-1.645168621	7.54247E-05	-1.201746367	0.000460973
FBXO17	Downregulated	-1.643834828	0.000706322	-1.234971373	0.003195528
MIR149	Downregulated	-1.642796542	0.003491517	-1.331722329	0.009490661
CD44	Downregulated	-1.641947425	0.01253907	-3.577822978	0.000225931
FGFR4	Downregulated	-1.639876103	0.002467514	-1.291564446	0.007912809
TEP1	Downregulated	-1.630367957	0.000166232	-1.1893417	0.000977963
GNL3L	Downregulated	-1.630072583	0.001277995	-1.169065268	0.006816668
TRIM38	Downregulated	-1.629736513	0.005366689	-2.840444373	0.000281512
CLMN	Downregulated	-1.629221573	0.000285159	-1.761858998	0.000181995
CHST5	Downregulated	-1.623680671	0.003541103	-1.724836101	0.002610583
LTB4R	Downregulated	-1.620976006	0.001434162	-1.264878245	0.005056625
HMBOX1	Downregulated	-1.616230947	0.000363284	-1.236896591	0.001571486
ZNF573	Downregulated	-1.616095169	0.005060477	-1.622295592	0.00496762
PLEKHG6	Downregulated	-1.614781506	0.009987802	-1.833141946	0.00554154
MACROD2	Downregulated	-1.613432533	0.000664126	-1.44486795	0.001210231
LOC344967	Downregulated	-1.611903307	0.002409617	-1.208361597	0.009705619
GMEB1	Downregulated	-1.607857058	0.00048519	-1.298792511	0.001550566
GATSL2	Downregulated	-1.605973945	0.002915939	-1.359306624	0.00659028

ZNF221	Downregulated	-1.605646246	0.002898116	-1.341782699	0.006957878
C10orf103	Downregulated	-1.603098156	0.004465291	-1.399327052	0.008501899
SGK494	Downregulated	-1.600797648	0.001112854	-1.326730301	0.00296791
HYAL1	Downregulated	-1.600751726	0.007133338	-2.828014719	0.000366516
LOC100507053	Downregulated	-1.594638575	0.000186984	-1.607940986	0.000178224
LOC283440	Downregulated	-1.592034429	0.006655742	-3.001583536	0.000232693
ITGB1BP2	Downregulated	-1.59111785	0.001881841	-1.467373339	0.00285418
LOC100131067	Downregulated	-1.589947834	0.002171875	-1.242891693	0.007302612
DNAH1	Downregulated	-1.589362768	0.001658446	-1.467420604	0.002509631
C20orf132	Downregulated	-1.589105467	0.000465711	-2.159032072	7.97268E-05
MMP25	Downregulated	-1.588679855	0.000723143	-1.088749304	0.005132657
CDCA8	Downregulated	-1.588242843	0.000179764	-1.556544712	0.000201933
EDARADD	Downregulated	-1.587853912	0.003110587	-1.90785707	0.001196483
EFNA5	Downregulated	-1.576622344	0.000737799	-1.861127624	0.000291574
BNC2	Downregulated	-1.573215576	0.000311215	-2.695037215	1.29638E-05
NEK2	Downregulated	-1.572133925	0.009269537	-2.288230905	0.001449728
PDE11A	Downregulated	-1.567645524	0.007855016	-1.593275522	0.007285649
RYR3	Downregulated	-1.567400468	0.001150473	-1.329579641	0.00272217
DDR2	Downregulated	-1.563013016	0.004953302	-1.780657166	0.002588896
JMJD7	Downregulated	-1.559783104	0.0006184	-1.299732043	0.001656504
ZAK	Downregulated	-1.559280087	0.006607657	-2.760363623	0.000330339
CCDC18	Downregulated	-1.557763977	0.000860255	-1.147317702	0.004217568
COL9A2	Downregulated	-1.55707087	0.014365544	-1.868103842	0.006317439
MYL3	Downregulated	-1.554855314	0.009906519	-2.129582744	0.002153145
LOC100131655	Downregulated	-1.551557181	0.010545513	-2.223859407	0.001827931
SRCRB4D	Downregulated	-1.54958998	0.000479399	-1.183743756	0.002053822
DDX60L	Downregulated	-1.549037964	0.008005927	-3.694743494	7.45377E-05
MTL5	Downregulated	-1.548904736	0.011034527	-1.582569937	0.010024516
MOB3B	Downregulated	-1.547577486	0.000300997	-1.179002698	0.00135011
C4orf47	Downregulated	-1.54742377	0.006964957	-1.902071032	0.002531112
DSCR6	Downregulated	-1.547419937	0.011616283	-1.874946833	0.004766507
YJEFN3	Downregulated	-1.546884485	0.000359007	-1.153201876	0.001783841

KIFC1	Downregulated	-1.542628792	0.012559979	-2.114220912	0.00282351
PILRB	Downregulated	-1.538056661	0.000608912	-1.214001479	0.002165938
LOC100288198	Downregulated	-1.537456339	0.009216601	-1.57536213	0.008246497
PROC	Downregulated	-1.536650664	0.00834871	-2.422310566	0.000834087
ACACB	Downregulated	-1.533551275	0.005282365	-2.247350685	0.000729823
SSPN	Downregulated	-1.533173632	0.013136722	-2.423181496	0.001420832
SLC26A1	Downregulated	-1.532930233	0.0023279	-1.176576702	0.008457021
IBA57	Downregulated	-1.530418922	0.001520766	-1.354061639	0.002867403
C17orf53	Downregulated	-1.527784365	0.002935046	-1.625568853	0.002136676
LOC728989	Downregulated	-1.525741609	0.006304651	-1.482333238	0.007219988
GRHL1	Downregulated	-1.521297095	0.00088719	-1.304404506	0.002011929
CYP2D6	Downregulated	-1.519706773	0.012840334	-1.634457063	0.009292826
TTLL3	Downregulated	-1.515557843	0.001084542	-1.094440611	0.005708276
FAM46C	Downregulated	-1.51552862	0.004035056	-2.402299995	0.000345984
CPT1A	Downregulated	-1.515427028	0.005363216	-2.618870018	0.000295243
ZSCAN22	Downregulated	-1.515378709	0.000212928	-1.218106539	0.000727877
PIEZO1	Downregulated	-1.51306633	0.002172659	-1.808316597	0.000841924
AKR7A3	Downregulated	-1.511986808	0.012411964	-1.613150018	0.009303225
C1orf101	Downregulated	-1.5108823	0.000912252	-1.746779923	0.00040872
TONSL	Downregulated	-1.510807387	0.002320495	-1.606660323	0.001685194
LOC285456	Downregulated	-1.509504806	0.002327379	-1.338025412	0.00426779
CILP2	Downregulated	-1.508223937	0.001009028	-1.006973333	0.007752018
ASB14	Downregulated	-1.505282787	0.008134398	-1.42276268	0.010504044
RTDR1	Downregulated	-1.50403523	0.005657251	-1.507318425	0.005598548
TIAM2	Downregulated	-1.502389418	0.000408852	-1.269020501	0.001037735
POLR2J3	Downregulated	-1.49939304	8.35383E-05	-1.355980733	0.0001504
CCDC77	Downregulated	-1.497063641	0.002753672	-1.570760217	0.002152269
LOC728758	Downregulated	-1.495870118	0.001066512	-2.273747315	9.99499E-05
ARHGEF1	Downregulated	-1.495740254	0.005365563	-1.359599647	0.008400372
PRR16	Downregulated	-1.494074324	0.001421486	-1.63093061	0.000887345
TEN1-CDK3	Downregulated	-1.494074324	0.003436927	-1.610845391	0.002346766
LOC100131208	Downregulated	-1.488161606	0.002720513	-1.334642768	0.004678457

FAM13A-AS1	Downregulated	-1.488119365	0.000723156	-1.142358361	0.002928839
NPAS2	Downregulated	-1.485567907	0.00044263	-1.206023117	0.001384393
PION	Downregulated	-1.477335539	0.004753826	-2.000622632	0.000996675
FMNL3	Downregulated	-1.476549914	0.000669719	-1.071519405	0.003620809
NOXO1	Downregulated	-1.473867562	0.00373057	-1.282447768	0.007288898
ASPRV1	Downregulated	-1.473578936	0.002027505	-1.109589781	0.008167028
SIRT4	Downregulated	-1.466721378	0.00223401	-1.724568216	0.000947452
DCDC2B	Downregulated	-1.466675356	0.005710333	-1.367739424	0.007927433
MYO7A	Downregulated	-1.462644436	0.000388225	-1.644515618	0.000199026
C10orf68	Downregulated	-1.46171294	0.004126802	-1.485076007	0.003816007
RRM2	Downregulated	-1.460821409	0.004946018	-4.138726352	1.445E-05
OBSCN	Downregulated	-1.451649981	0.001267415	-1.148041655	0.004230253
RGS11	Downregulated	-1.450494108	0.003527396	-1.475123941	0.003242413
LOC440300	Downregulated	-1.447401566	0.001312443	-1.2856998	0.002439382
FAM70B	Downregulated	-1.446364541	0.001049994	-1.827793654	0.000286074
ATAD5	Downregulated	-1.445167641	0.000399486	-1.597149099	0.00022623
LENG8	Downregulated	-1.445142124	0.002462303	-1.084989473	0.009824629
NBEAL2	Downregulated	-1.442992663	0.001274611	-1.233499151	0.002884942
C8orf77	Downregulated	-1.441662912	0.000901569	1.037121052	0.004933435
POLE	Downregulated	-1.435910321	0.000157449	-1.207141205	0.000424338
LINC00085	Downregulated	-1.435120997	0.001159483	-1.563271735	0.00072858
C15orf52	Downregulated	-1.434342491	0.008598688	-2.618277561	0.000382827
LOC401010	Downregulated	-1.433927207	0.001150912	-1.154196383	0.003546523
LOC642846	Downregulated	-1.433750172	0.006480451	-1.821469038	0.001972477
CYP27C1	Downregulated	-1.430494813	0.009025259	-1.720685408	0.003745971
ANKRD36	Downregulated	-1.42597882	0.000338743	-1.071453865	0.001621881
TMC7	Downregulated	-1.425459949	0.001704097	-1.115881758	0.005825045
PDZD2	Downregulated	-1.42461756	0.000223889	-1.262895112	0.000443728
GAL3ST4	Downregulated	-1.423030512	0.000544028	-1.309428138	0.000860301
HYDIN	Downregulated	-1.419188716	0.005647135	-1.402849005	0.005967781
CSMD2	Downregulated	-1.417412789	0.00013386	-1.322413204	0.000200068
RNF112	Downregulated	-1.412344785	0.001209238	-1.006933791	0.00667664

LAMP3	Downregulated	-1.407625165	0.007987927	-1.839052241	0.002152498
LOC100130987	Downregulated	-1.406530971	0.000674828	-1.352266266	0.000837383
LOC100289019	Downregulated	-1.406146657	0.000573184	-1.052980438	0.002683071
OAF	Downregulated	-1.403788201	0.008569316	-2.582583999	0.000364782
LEPREL1	Downregulated	-1.400704501	0.012196641	-1.923079291	0.002704579
AGER	Downregulated	-1.394172763	0.001435433	-1.58075294	0.000728318
ROBO3	Downregulated	-1.392078281	0.007196106	-1.398070607	0.007053192
FDXACB1	Downregulated	-1.39188591	0.003384708	-1.142554398	0.008715491
CDKN3	Downregulated	-1.390848885	0.003824573	-1.579814907	0.002002803
LOC100132832	Downregulated	-1.388060392	0.010323819	-1.411601075	0.009572055
RREB1	Downregulated	-1.38761776	0.009985799	-2.183751072	0.001042532
LOC100507577	Downregulated	-1.384681297	0.000442455	-1.119268835	0.001416042
EML3	Downregulated	-1.383580839	0.00088801	-1.654378471	0.000328611
TRPC3	Downregulated	-1.37993983	0.001645318	-3.548682831	6.93453E-06
LOC646851	Downregulated	-1.376074405	0.000242137	-1.277585095	0.000369411
FZD4	Downregulated	-1.374515318	0.002399072	-1.856551072	0.00047618
NPIPL3	Downregulated	-1.373617072	0.010533832	-1.391869445	0.009928934
TMEM30B	Downregulated	-1.373169386	0.004687014	-2.613477234	0.000144336
MEGF6	Downregulated	-1.372998212	0.00305903	-1.352304211	0.003301755
HIF3A	Downregulated	-1.37200445	0.000832503	-1.579611716	0.000380672
PCSK4	Downregulated	-1.371412956	0.000801335	-1.131151677	0.002232973
CENPE	Downregulated	-1.370817661	0.0016526	-1.894781487	0.000278765
SSC5D	Downregulated	-1.370126526	0.006582025	-1.322126871	0.007774137
DEPDC4	Downregulated	-1.368304941	0.011538644	-2.008152306	0.001795934
FRMPD4	Downregulated	-1.367972981	0.00013853	-1.461315112	9.41779E-05
B3GALT5	Downregulated	-1.366914265	0.003830165	-1.860562234	0.000762641
TMEM51	Downregulated	-1.361625749	0.001998671	-1.330942801	0.002248984
SLC12A8	Downregulated	-1.361476807	0.001455694	-2.01611488	0.00016339
ETV6	Downregulated	-1.36052377	0.002502138	-1.604620455	0.001049969
LOC283922	Downregulated	-1.36034168	0.001208406	-1.042700467	0.004718868
NTN3	Downregulated	-1.359117584	0.0018236	-1.304509352	0.002256322
ARID3A	Downregulated	-1.354833911	0.002199531	-1.488895086	0.001340709

FES	Downregulated	-1.351397584	0.011158441	-2.720728867	0.000305095
LRRC16A	Downregulated	-1.349495769	0.008033814	-1.61342541	0.003401908
CLCNKA	Downregulated	-1.347716832	0.00369419	-1.271479227	0.004916013
UTRN	Downregulated	-1.347249664	0.008680455	-1.404508055	0.007162414
MACC1	Downregulated	-1.345860123	0.003385858	-1.455262972	0.002276631
ARHGAP25	Downregulated	-1.341791693	0.00766137	-2.218639013	0.000578711
NRIP2	Downregulated	-1.341486181	0.000123945	-1.414038476	9.10455E-05
GPLD1	Downregulated	-1.340046657	6.43572E-05	-1.112547232	0.000191052
BMP8A	Downregulated	-1.33908156	0.006828625	-1.827008387	0.001437495
MAF	Downregulated	-1.337056798	0.005616027	-3.122523288	5.40239E-05
TTF2	Downregulated	-1.335243374	0.002504373	-1.144006599	0.005395105
SGK1	Downregulated	-1.333950181	0.002660772	-1.027178521	0.009385083
TRMT2B	Downregulated	-1.333334821	0.00226813	-1.74151895	0.000540272
MCM8	Downregulated	-1.332309758	0.000360613	-1.575725164	0.000137649
ZNF276	Downregulated	-1.330350052	0.000748425	-1.068784596	0.002397885
PDE7B	Downregulated	-1.330101646	0.004143833	-2.048808348	0.00041927
MAP3K5	Downregulated	-1.325349984	0.000386641	-1.236623929	0.00056978
LIPT1	Downregulated	-1.319411508	0.004225862	-1.863809031	0.000693954
TENC1	Downregulated	-1.316465701	0.001060351	-1.080202164	0.002983653
BCO2	Downregulated	-1.316112404	0.002410948	-1.22608471	0.003451671
KCNMB3	Downregulated	-1.314774611	0.004862645	-1.485076007	0.002652457
CNIH3	Downregulated	-1.312896245	0.010395176	-1.863544223	0.001891298
RTKN2	Downregulated	-1.310846914	0.001104009	-1.413213012	0.000733475
KNTC1	Downregulated	-1.309368235	0.000622698	-1.059475957	0.001944542
HRC	Downregulated	-1.306876567	0.009843336	-1.476936598	0.005575133
SLC16A4	Downregulated	-1.305272383	0.00093818	-2.058192685	7.00396E-05
SYTL2	Downregulated	-1.299133987	0.002146022	-1.165774188	0.003716873
CCDC84	Downregulated	-1.299097063	0.005973494	-1.301620513	0.005918595
PLAGL1	Downregulated	-1.295001764	0.005866236	-2.065510568	0.000515516
PPFIBP2	Downregulated	-1.294439232	0.000474569	-1.335641864	0.00039803
NFIA	Downregulated	-1.291371385	0.011671483	-3.183359238	0.000100411
HSPG2	Downregulated	-1.287869472	0.005207575	-2.087129425	0.000410229

SERINC4	Downregulated	-1.284636731	0.00448385	-1.235804844	0.005409767
ADAMTS16	Downregulated	-1.283093381	0.013689583	-2.013403616	0.001552355
VAMP8	Downregulated	-1.283028196	0.001260859	-1.734984967	0.000236038
MGC27345	Downregulated	-1.281731427	0.000510767	-1.283585009	0.000506666
PPIEL	Downregulated	-1.277294422	0.00214123	-1.339253159	0.001672516
CNKSR1	Downregulated	-1.277281243	0.003729803	-1.115173235	0.007173027
OIP5	Downregulated	-1.276845179	0.008593129	-1.681359617	0.002243713
CROCC	Downregulated	-1.275416205	0.002050681	-1.038804568	0.005710006
MYOM1	Downregulated	-1.274879757	0.012508185	-1.624516721	0.004045582
LOC146880	Downregulated	-1.274838827	0.000316009	-1.349150686	0.000228691
BDNF-AS1	Downregulated	-1.274366972	0.008818646	-1.88069573	0.001270389
BUB1B	Downregulated	-1.270713434	0.00426056	-1.974279626	0.00041233
LOC441454	Downregulated	-1.269273395	0.002066687	-2.320001707	7.04555E-05
ZNF530	Downregulated	-1.267736448	0.00268143	-1.468499381	0.00124401
RCN3	Downregulated	-1.26321572	0.00573058	-1.189494372	0.007605327
CCDC142	Downregulated	-1.259698849	0.001153147	-1.342415735	0.000817034
DDX58	Downregulated	-1.258695854	0.005264548	-1.803022147	0.000823636
LOC286437	Downregulated	-1.255098471	0.012814022	-1.763754172	0.002544418
AP1G2	Downregulated	-1.253725604	0.00056346	-1.118353075	0.001053632
IKBKB	Downregulated	-1.252379946	0.000556155	-1.701985799	9.59885E-05
CTAGE1	Downregulated	-1.249016016	0.003975471	-2.954375735	3.27612E-05
HSPBAP1	Downregulated	-1.244200357	0.005293637	-1.102560656	0.009312854
KCND1	Downregulated	-1.243003215	0.000765396	-1.125828046	0.001307574
PPARGC1B	Downregulated	-1.240881881	0.006353234	-1.57419844	0.001944213
NEXN	Downregulated	-1.240839703	0.006469575	-2.629408828	0.000114208
MSS51	Downregulated	-1.2406426	0.003532573	-1.374325266	0.002099403
RTTN	Downregulated	-1.239377135	0.000243729	-1.258873986	0.000222863
GSDMB	Downregulated	-1.235521214	0.000159581	-1.450527722	6.22911E-05
FBLN1	Downregulated	-1.233790305	0.0019805	-1.947846543	0.000158353
FBXL13	Downregulated	-1.229448988	0.001094139	-1.199416829	0.001249411
CCDC69	Downregulated	-1.228816966	0.012644359	-1.764669653	0.002240842
FAM72B	Downregulated	-1.228816966	0.005669645	-1.485076007	0.00220826

SLC25A45	Downregulated	-1.227408083	0.005878212	-1.788796309	0.000850005
FRZB	Downregulated	-1.222875025	0.012367215	-2.193584939	0.000664051
POLE2	Downregulated	-1.221382244	0.010883807	-1.254589116	0.009651691
LOC100131691	Downregulated	-1.220844181	0.002060876	-1.313539056	0.001403401
PLK4	Downregulated	-1.208460129	0.000368368	-1.634670593	6.39564E-05
LOC401321	Downregulated	-1.201066725	0.001372403	-1.495419144	0.000412936
RAD9A	Downregulated	-1.1990649	0.001173688	-1.452438754	0.000408809
CASP6	Downregulated	-1.193732346	0.000724322	-1.983655752	3.86978E-05
TPK1	Downregulated	-1.19251822	0.012617438	-1.501079254	0.004338753
LRRC37A4	Downregulated	-1.191228054	0.001406082	-1.338243261	0.000749965
GLDC	Downregulated	-1.187524656	0.00027414	-1.801480189	2.36266E-05
MTBP	Downregulated	-1.187019901	0.012305729	-1.464247203	0.004657069
CHRD	Downregulated	-1.181606171	0.001803957	-1.538692456	0.000429418
C9orf169	Downregulated	-1.181107183	0.003273586	-1.25338712	0.002421814
B3GNTL1	Downregulated	-1.176379602	0.004479793	-1.000770953	0.009585927
TOM1L1	Downregulated	-1.171940872	0.002854469	-1.147776675	0.003171105
SLC26A5	Downregulated	-1.17120465	0.008191245	-1.738556002	0.001129441
IFIT3	Downregulated	-1.168787294	0.006751449	-1.731780289	0.000911043
DNAH10	Downregulated	-1.151048674	0.004393442	-1.177299972	0.00393223
SCUBE3	Downregulated	-1.15015705	0.00026009	-1.458528922	6.52198E-05
PROM2	Downregulated	-1.149855503	0.0015539	-1.3486536	0.000656379
ERN1	Downregulated	-1.148180582	0.000960329	-1.548579347	0.0001791
MIR210HG	Downregulated	-1.146239735	0.002790574	-1.925753759	0.000162551
HEATR7A	Downregulated	-1.145710824	0.004774034	-1.137265639	0.004948457
BAHCC1	Downregulated	-1.138789019	0.001323982	-1.035261813	0.002183672
H1FX-AS1	Downregulated	-1.13696826	0.005928383	-1.719396336	0.000700975
CLEC16A	Downregulated	-1.135300929	0.000937095	-1.234690729	0.000591273
ATP8B1	Downregulated	-1.131208277	0.013033617	-1.775547168	0.001459813
SNTB2	Downregulated	-1.129168421	0.00770111	-1.624337826	0.00124411
FAM26F	Downregulated	-1.125591527	0.006991752	-1.5580912	0.001367347
EDA	Downregulated	-1.120211448	0.001993804	-1.098998496	0.002201415
TRPS1	Downregulated	-1.109773772	0.012692042	-2.026400763	0.000622034

STC2	Downregulated	-1.109318164	0.00816491	-1.321825595	0.003520739
C19orf57	Downregulated	-1.10850964	0.000448154	-1.530365865	6.96622E-05
FUT4	Downregulated	-1.098173594	0.009586556	-1.470001934	0.002334066
SLC13A3	Downregulated	-1.096363732	0.00768214	-1.567135697	0.001283515
PRKD3	Downregulated	-1.09230581	0.001740776	-1.826885715	9.79199E-05
ENOSF1	Downregulated	-1.091890305	0.005476338	-1.250917631	0.002797635
TBXAS1	Downregulated	-1.091559389	0.009162067	-1.072733809	0.009911396
FBF1	Downregulated	-1.088918057	0.008578912	-1.343553824	0.003120458
CACNA1G	Downregulated	-1.085662773	0.003954916	-1.002229092	0.005830647
EXTL1	Downregulated	-1.083817631	0.005735474	-1.199723395	0.003491755
FBXW4P1	Downregulated	-1.083147078	0.012304001	-2.270799855	0.000274892
ACCS	Downregulated	-1.073659737	0.007477892	-1.205135995	0.004306548
MMACHC	Downregulated	-1.072624805	0.00264944	-1.464353648	0.000499956
ZDHHC8	Downregulated	-1.072043223	0.00630602	-1.087508572	0.005891599
KIAA1456	Downregulated	-1.052366371	0.002647925	-1.657392552	0.00022236
UBOX5	Downregulated	-1.05228551	0.006874132	-1.320442857	0.002243887
C1QL3	Downregulated	-1.046163145	0.014142439	-2.194076111	0.000329317
LRRC56	Downregulated	-1.039357929	0.000665827	-1.123275393	0.000432185
MGC72080	Downregulated	-1.033445211	0.004386786	-1.072881572	0.003646652
WDR92	Downregulated	-1.025490312	0.004748021	-1.109821167	0.003212576
SCAND2	Downregulated	-1.020136114	0.001425491	-1.061262027	0.001154328
CBR3-AS1	Downregulated	-1.01844139	0.010372414	-1.018734965	0.010359051
SFXN2	Downregulated	-1.009512163	0.000864987	-1.169988214	0.000381527
LOC90784	Downregulated	-1.008077256	0.008872805	-1.391945859	0.001818738
FBXL19-AS1	Downregulated	-1.005520771	0.002147493	-1.506371946	0.000234434
ANO8	Downregulated	-1.003196538	0.009913184	-1.115316121	0.00607344

Appendix 2: Genes dysregulated by forced progerin expression in iPSC-derived neurons and differentially expressed in AD brains (MSBB and Mayo)

Gene	Direction in Progerin Transduction	MSBB - BA36 (PHG)				Mayo - Temporal			
		Log2 Fold Change	p value	FDR	Same direction as mDA neurons	β	p value	q value	Same direction as mDA neurons
LMNA	Upregulated	0.423845804	0.0000118	0.00046868	Yes	0.34256006	0.01693965	0.0441005	Yes
NOP10	Upregulated	-0.072788447	0.23591894	0.4588814	No	-0.0639772	0.29103487	0.39756322	No
SNHG15	Upregulated	-0.105343862	0.0902455	0.25098394	No	-0.3393466	0.0000632	0.0008818	No
ENHO	Upregulated	0.081923697	0.40191683	0.62708013	Yes	0.0131984	0.9361479	0.95539074	Yes
NDUFB6	Upregulated	-0.063492507	0.31793879	0.54814623	No	-0.1249564	0.00214915	0.01109022	No
ATP5L	Upregulated	-0.214997357	0.00236758	0.02026133	No	-0.2425125	1.05E-07	0.00000844	No
NEDD8	Upregulated	-0.176596246	0.00451516	0.03190707	No	-0.263068	2.44E-07	0.0000148	No
PPIB	Upregulated	0.105110984	0.07082175	0.21416371	Yes	0.13255107	0.01859376	0.04726513	Yes
TMSB10	Upregulated	-0.117637601	0.13777458	0.32954573	No	-0.1310355	0.23131437	0.3328086	No
PRDX4	Upregulated	0.130022718	0.09747172	0.26401953	Yes	0.25103932	0.00453958	0.01784468	Yes
FTL	Upregulated	0.308683094	0.0004565	0.00634544	Yes	0.0763038	0.08455664	0.15102107	Yes
TMSB4X	Upregulated	0.019331329	0.78417077	0.89419593	Yes	-0.1633408	0.0025676	0.01240219	No
ATOX1	Upregulated	0.004716122	0.90996364	0.96071545	Yes	-0.3345547	0.0000699	0.00094775	No
CCDC126	Upregulated	0.077867206	0.3148222	0.54513261	Yes	0.00906084	0.92030745	0.94411569	Yes
PSMB3	Upregulated	#N/A	#N/A	#N/A	#N/A	-0.1460709	0.00330187	0.01450856	No
LOC100128822	Upregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

TSNAX	Upregulated	-0.05051895	0.45798988	0.67544337	No	-0.3355095	0.000043	0.00066045	No
TCEAL7	Upregulated	-0.176309289	0.03162359	0.12549578	No	-0.3650857	0.0000283	0.00047899	No
UBC	Upregulated	0.043178469	0.50184632	0.70915414	Yes	0.22011021	0.01253951	0.03541976	Yes
ZNHIT3	Upregulated	#N/A	#N/A	#N/A	#N/A	-0.2741476	5.08E-08	0.00000529	No
PCNA	Upregulated	0.097586464	0.11329524	0.29128895	Yes	0.23790129	0.00043095	0.00366396	Yes
LOC401397	Upregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
C4orf52	Upregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
NDUFA5	Upregulated	-0.261783655	0.00163475	0.01554243	No	-0.488659	1.46E-07	0.0000106	No
EAPP	Upregulated	-0.085660709	0.1587781	0.36031473	No	-0.1109929	0.00947771	0.02903723	No
COX14	Upregulated	-0.058412285	0.36134692	0.5896232	No	-0.1237511	0.0025838	0.01243739	No
UBE2T	Upregulated	-0.428084105	0.0000188	0.0006451	No	-0.4921291	0.00339636	0.01478856	No
SVIP	Upregulated	-0.05432922	0.41413985	0.63788916	No	-0.3097413	0.00000887	0.00019854	No
CD164	Upregulated	0.250496108	0.00017038	0.00314309	Yes	0.38657707	0.00000101	0.0000408	Yes
RPL12	Upregulated	0.093451335	0.11815181	0.29911513	Yes	-0.0493845	0.4548476	0.56061372	No
SCOC	Upregulated	-0.148703305	0.06789185	0.20830777	No	-0.348943	4.12E-08	0.00000462	No
ARL6IP5	Upregulated	-0.090289386	0.1666827	0.37093862	No	0.02404268	0.68619629	0.76396886	Yes
UBL5	Upregulated	-0.088891397	0.1367227	0.32793058	No	-0.1801727	0.00000121	0.0000464	No
SEC11C	Upregulated	0.160286919	0.01238896	0.06523457	Yes	0.24041459	0.00143885	0.00854996	Yes
VPS25	Upregulated	-0.07778737	0.16418297	0.36761241	No	-0.0183928	0.77837582	0.83770769	No
ITM2C	Upregulated	0.208183514	0.00177489	0.01647452	Yes	0.62373628	0.0000184	0.00034509	Yes
TFAM	Upregulated	0.050410805	0.3373563	0.5674795	Yes	-0.0589131	0.30486625	0.41226559	No
PRDX1	Upregulated	0.166797673	0.00892902	0.05180833	Yes	0.60496455	1.2E-09	4.95E-07	Yes
ABHD10	Upregulated	0.001958963	0.97496534	0.98973165	Yes	-0.2805076	3.76E-07	0.0000199	No

BUD31	Upregulated	-0.047567726	0.51963515	0.72189724	No	-0.0643454	0.09689439	0.16808574	No
TCEB2	Upregulated	#N/A	#N/A	#N/A	#N/A	-0.1331713	0.0002566	0.00249689	No
WRB	Upregulated	0.00107958	0.98588792	0.99432822	Yes	-0.1708161	0.0000335	0.00054712	No
PFN1	Upregulated	0.128322069	0.24434807	0.46857249	Yes	0.19118107	0.00106082	0.00693401	Yes
TCEAL8	Upregulated	-0.1429176	0.0181189	0.0854795	No	-0.0058948	0.9191177	0.9433159	No
RGS2	Upregulated	0.112355332	0.39575363	0.62133634	Yes	-0.2284534	0.10407166	0.17782536	No
C5orf15	Upregulated	0.087053363	0.16285984	0.366032	Yes	0.17741455	0.02093388	0.05166384	Yes
ATP6V1G1	Upregulated	-0.091545452	0.11472838	0.2935815	No	-0.1035841	0.0256638	0.06023619	No
YPEL5	Upregulated	-0.14140961	0.02631548	0.11027686	No	-0.1066361	0.1338998	0.21705822	No
MT3	Upregulated	-0.047965235	0.60266012	0.78018153	No	0.18443302	0.08418481	0.15046186	Yes
UQCR10	Upregulated	-0.141290789	0.03198824	0.12642734	No	-0.1392557	0.00293392	0.0134792	No
TMEM14A	Upregulated	-0.143988821	0.08502484	0.24121938	No	-0.1503527	0.05662619	0.11075349	No
DNAJC8	Upregulated	-0.074459088	0.16161125	0.36428277	No	0.00696087	0.73910246	0.80660397	Yes
SUMO2	Upregulated	0.003875282	0.94225677	0.97599513	Yes	-0.0443417	0.26288035	0.36748544	No
BEX1	Upregulated	-0.362695662	0.00049029	0.00664824	No	-0.9929336	0.00000751	0.0001748	No
NDUFB11	Upregulated	-0.158295783	0.01415871	0.07163154	No	-0.1330292	0.00329139	0.01448821	No
LAMTOR1	Upregulated	0.09638795	0.10326343	0.27463109	Yes	-0.0214289	0.61747989	0.70632109	No
ATP5G3	Upregulated	-0.220177928	0.00281712	0.02285611	No	-0.3514446	0.0000268	0.00046003	No
VBP1	Upregulated	0.010559055	0.88717807	0.94901638	Yes	0.0526952	0.15142342	0.23873896	Yes
QPCT	Upregulated	-0.332417197	0.00246009	0.02084624	No	-0.3983135	0.02077513	0.05138806	No
ZCCHC10	Upregulated	-0.006555794	0.91917343	0.96488461	No	-0.0729858	0.12144862	0.20097614	No
NDUFB1	Upregulated	-0.055047466	0.3631706	0.59122316	No	-0.2701017	0.000018	0.00033898	No
MMADHC	Upregulated	-0.011167876	0.87074984	0.94047921	No	0.14746811	0.00321355	0.01426549	Yes

HSBP1	Upregulated	-0.005979385	0.91785886	0.96433859	No	-0.0820889	0.08883856	0.15706258	No
CAPZA2	Upregulated	0.044712135	0.55710644	0.74935032	Yes	0.10232038	0.12438339	0.20469054	Yes
CNO	Upregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SELT	Upregulated	0.003601443	0.95746369	0.9829743	Yes	0.0280999	0.42161951	0.52939235	Yes
CCDC72	Upregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ATF4	Upregulated	0.170412872	0.07407948	0.22043157	Yes	0.40049282	0.00013634	0.00156064	Yes
GABARAPL2	Upregulated	0.046286333	0.37153657	0.59956794	Yes	-0.032163	0.26856569	0.37377437	No
AASDHPPT	Upregulated	-0.169453784	0.01815626	0.08558237	No	-0.3162165	0.0000636	0.00088494	No
BANF1	Upregulated	-0.117454955	0.28393591	0.51318079	No	-0.001647	0.97144623	0.98078689	No
SUB1	Upregulated	-0.184953674	0.02590674	0.10914247	No	-0.4786434	3.11E-07	0.0000174	No
EID1	Upregulated	-0.116126072	0.12101816	0.30397904	No	0.09518529	0.13823411	0.2224545	Yes
SLIRP	Upregulated	-0.137997763	0.02170815	0.09668048	No	-0.2663583	0.000003	0.0000896	No
PFDN2	Upregulated	-0.314892281	0.00771591	0.04679731	No	-0.3060854	0.0000116	0.00024443	No
EIF3M	Upregulated	-0.07675987	0.12297023	0.3068919	No	-0.2981739	5.33E-10	3.23E-07	No
CYB5A	Upregulated	0.036353061	0.49250709	0.70214913	Yes	-0.004343	0.95013421	0.96567669	No
FDFT1	Upregulated	0.077679135	0.12346583	0.3077563	Yes	0.26343323	0.0003639	0.00323594	Yes
CDC42	Upregulated	-0.023713138	0.69416349	0.84163115	No	-0.0539491	0.14741992	0.23397558	No
DYNLT3	Upregulated	-0.212584399	0.02206326	0.09778014	No	-0.2981199	0.00143413	0.00853606	No
C12orf29	Upregulated	-0.055431181	0.41076853	0.63509369	No	-0.1691907	0.0005969	0.00462909	No
RG9MTD1	Upregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FOS	Upregulated	0.459450771	0.02990429	0.12073039	Yes	1.11015173	0.00029302	0.00275041	Yes
CCT3	Upregulated	-0.017692357	0.76632478	0.88442166	No	0.14135045	0.00979485	0.02973386	Yes
ZCRB1	Upregulated	0.049211935	0.44325894	0.6632312	Yes	0.00214903	0.96271108	0.97431421	Yes

TMBIM6	Upregulated	0.181631557	0.00096151	0.01066805	Yes	0.45627764	1.87E-08	0.00000269	Yes
GTF2B	Upregulated	-0.054327729	0.38775955	0.61442213	No	-0.0241818	0.53493989	0.63381757	No
ILF2	Upregulated	0.032539796	0.53070569	0.73072218	Yes	0.16201432	0.00000197	0.0000665	Yes
POMP	Upregulated	-0.081832056	0.22522228	0.4464219	No	0.02647985	0.42602024	0.53365449	Yes
ZBTB6	Upregulated	0.02768776	0.63647369	0.80233567	Yes	0.12378765	0.02449809	0.05812407	Yes
IDI1	Upregulated	-0.008373729	0.90635656	0.95877295	No	0.06012547	0.33066639	0.43898841	Yes
ISCA1	Upregulated	-0.101994905	0.07967967	0.23127578	No	-0.1691563	0.00214053	0.0110599	No
PRDX6	Upregulated	0.32140623	0.00000157	0.00011317	Yes	0.57566361	0.00000178	0.0000612	Yes
TTC33	Upregulated	-0.02136291	0.81193954	0.91030458	No	-0.0538131	0.53805181	0.63674527	No
ANAPC13	Upregulated	-0.155902296	0.01734104	0.08289009	No	-0.1346331	0.00391682	0.01623809	No
DDX24	Upregulated	#N/A	#N/A	#N/A	#N/A	-0.1412909	0.07410395	0.13650521	No
CCNG1	Upregulated	0.227731623	0.00151496	0.01470179	Yes	0.52639737	0.00000008	0.00000707	Yes
TIMM17B	Upregulated	-0.056945559	0.37098184	0.5990319	No	-0.2959365	1.25E-07	0.00000953	No
MRPS35	Upregulated	-0.064741668	0.32409272	0.55435406	No	-0.1258079	0.00168048	0.00945575	No
PGRMC1	Upregulated	-0.097551908	0.16603419	0.37011991	No	-0.1647229	0.0357406	0.07760847	No
CHMP1B	Upregulated	-0.002089077	0.96264225	0.98566075	No	0.05595367	0.25301442	0.35680683	Yes
RPS19BP1	Upregulated	0.07771453	0.2388727	0.46220619	Yes	-0.0331423	0.53865761	0.63727282	No
SRP9	Upregulated	0.031109358	0.68822322	0.83795791	Yes	0.15721766	0.01273264	0.03582927	Yes
CCDC90B	Upregulated	0.023914914	0.60999267	0.78456274	Yes	-0.0239313	0.66972532	0.75016551	No
MORF4L1	Upregulated	-0.029922724	0.5677144	0.75669835	No	-0.0789216	0.00773517	0.02532931	No
EEF1E1	Upregulated	-0.079659017	0.34399692	0.57346419	No	-0.2717687	0.00000201	0.0000675	No
PPP2R1A	Upregulated	-0.134740716	0.05120987	0.17230669	No	-0.3130535	0.0000388	0.00061033	No
PSMA7	Upregulated	0.024922469	0.61339745	0.78688862	Yes	0.04618551	0.19190028	0.28763117	Yes

PDRG1	Upregulated	-0.082139175	0.19033542	0.40301202	No	-0.0426845	0.42688167	0.53446241	No
PKIB	Upregulated	-0.101351147	0.30760804	0.53789245	No	-0.7089726	0.00000674	0.00016129	No
JKAMP	Upregulated	-0.023401349	0.62500641	0.79476977	No	0.08151875	0.1219014	0.20153538	Yes
DPM1	Upregulated	-0.052540073	0.36979838	0.59785856	No	-0.0323755	0.45384345	0.55969776	No
TAF7	Upregulated	0.001564625	0.97669071	0.99052263	Yes	0.06833783	0.23371542	0.33531495	Yes
RMRP	Downregulated	0.222833468	0.94530818	NA	No	0.35946834	0.08778368	0.15556262	No
RPPH1	Downregulated	NA	NA	NA	#N/A	0.02430364	0.9098921	0.93658397	No
MIR3648	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.0971602	0.69683959	0.7724845	Yes
MIR3687	Downregulated	#N/A	#N/A	#N/A	#N/A	0.53900062	0.00512718	0.01929083	No
C3orf72	Downregulated	0.368758815	0.03683358	0.13908883	No	0.73685889	0.00741843	0.02465119	No
TNIP3	Downregulated	-0.66247395	0.00010369	0.00221221	Yes	-0.7141404	0.00837767	0.02669785	Yes
NOSTRIN	Downregulated	#N/A	#N/A	#N/A	#N/A	0.4153297	0.00983147	0.02980896	No
MIR663A	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.3029072	0.22785669	0.32879675	Yes
GVINP1	Downregulated	-0.176262369	0.01615565	0.07884423	Yes	0.26453116	0.142112	0.22729767	No
PRDM1	Downregulated	0.267562455	0.00397887	0.02908029	No	0.23851898	0.12223045	0.20198818	No
C1orf129	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MARCO	Downregulated	0.627355053	0.00584148	0.03828486	No	1.17449251	0.00602984	0.02147829	No
TG	Downregulated	0.209297959	0.18600071	0.3969929	No	-0.2458712	0.22297717	0.32331197	Yes
PEAR1	Downregulated	0.50803347	0.00037834	0.00554853	No	1.02144371	2.27E-08	0.0000031	No
LAMC3	Downregulated	0.313996955	0.00339521	0.02604845	No	0.14691667	0.21296877	0.31223473	No
BCAS1	Downregulated	0.161966479	0.12471131	0.30978791	No	-0.1739568	0.39716138	0.50602431	Yes
LOC285084	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CDHR4	Downregulated	0.292894635	0.4161784	0.63973249	No	-0.418594	0.03240727	0.07199258	Yes

FLI1	Downregulated	0.512775442	5.56E-08	0.0000103	No	0.64527902	0.00021627	0.00219683	No
SLC14A2	Downregulated	-0.111028813	0.30949958	0.54000937	Yes	-0.5379277	0.00069864	0.00519516	Yes
BHMT2	Downregulated	0.327488604	0.00025011	0.00414582	No	0.623695	0.00023773	0.00235643	No
SH3TC2	Downregulated	0.263662965	0.01635454	0.07952854	No	0.23410503	0.30772217	0.41534509	No
OLAH	Downregulated	0.417242715	0.00326061	0.02532949	No	0.55654306	0.01420622	0.03872883	No
STAB2	Downregulated	0.039346537	0.7324005	0.86376014	No	-0.3675778	0.05776687	0.11245709	Yes
SLC5A1	Downregulated	-0.283624956	0.15424831	0.35422886	Yes	-0.8154017	0.00038694	0.00338421	Yes
SLFN11	Downregulated	0.3982178	0.00000873	0.00038228	No	0.63567626	0.0000838	0.001087	No
VIT	Downregulated	-0.168360875	0.22832083	0.45018376	Yes	-0.3207951	0.10254621	0.17577571	Yes
KIAA1755	Downregulated	0.410956631	0.0000127	0.00049235	No	0.24022008	0.12834718	0.20975863	No
SEC14L4	Downregulated	-0.16847326	0.36656163	0.59455042	Yes	0.37238985	0.05866462	0.11388416	No
LEP	Downregulated	-0.091239307	0.54451455	0.74071589	Yes	-0.1042961	0.64332877	0.72852058	Yes
SHE	Downregulated	0.365840853	0.00010849	0.0022813	No	0.65161661	0.0001037	0.00127294	No
DISC1	Downregulated	0.205805297	0.0007052	0.00853214	No	0.03307413	0.77056399	0.83145097	No
GJA5	Downregulated	0.322415974	0.03705066	0.13962032	No	1.09107625	0.00000897	0.00020042	No
SNORA53	Downregulated	0.501447188	0.00157218	0.01507477	No	0.03680082	0.74919827	0.81469657	No
LOC284801	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
APCDD1L	Downregulated	0.183200297	0.15557125	0.35595316	No	-0.2768045	0.23193441	0.33346839	Yes
LOC100507156	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TBXA2R	Downregulated	0.431187318	0.00171479	0.01605014	No	-0.0500474	0.70483274	0.77900875	Yes
FOXD2	Downregulated	0.928100855	0.0000332	0.00097475	No	0.96021954	0.00534236	0.01981694	No
EMR2	Downregulated	#N/A	#N/A	#N/A	#N/A	0.24761699	0.23220485	0.33372376	No
LOC727710	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

HOXC8	Downregulated	0.342162135	0.74234802	NA	No	-0.075058	0.70911251	0.78265003	Yes
TGM5	Downregulated	1.116534	0.00103127	0.01121513	No	0.19074957	0.51831346	0.61895664	No
MYH1	Downregulated	-1.063788964	0.0002638	0.00430161	Yes	0.13165352	0.65925394	0.74209325	No
LOC283547	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SGOL1	Downregulated	0.147224413	0.32750448	0.55750381	No	0.76296236	0.01544018	0.04121619	No
LOC100216001	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CMKLR1	Downregulated	0.520204393	0.00000223	0.00014338	No	0.35319106	0.06945337	0.12979092	No
PDGFRA	Downregulated	0.077437204	0.35388039	0.58247002	No	0.43222433	0.02386545	0.05695432	No
HMCN1	Downregulated	0.1558049	0.24049683	0.46437815	No	0.67568087	0.00732075	0.02441098	No
COL6A6	Downregulated	-0.026640174	0.75018549	0.87475929	Yes	-0.2201876	0.12836685	0.20978463	Yes
LIPJ	Downregulated	-0.262190364	0.02225345	0.09828755	Yes	-1.05033	0.0000499	0.00073808	Yes
MFAP5	Downregulated	0.367261398	0.09103322	0.25247166	No	0.8080997	0.00019766	0.00205383	No
WWTR1-AS1	Downregulated	0.251368727	0.19899386	0.41405054	No	1.11748134	3.64E-09	9.81E-07	No
LOC100292680	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GLI1	Downregulated	0.146963998	0.3110333	0.54158636	No	0.74305267	0.00273993	0.012922	No
GPRC5A	Downregulated	0.775083563	0.00021008	0.00363247	No	1.17520509	0.001203	0.00756277	No
FLT1	Downregulated	0.347195025	0.00276717	0.02256059	No	1.38719811	1.16E-07	0.00000905	No
RIPK3	Downregulated	0.50027568	0.00032268	0.00495227	No	0.27666877	0.0887088	0.15688789	No
MYOCD	Downregulated	0.36525614	0.02099735	0.09459104	No	0.75595273	0.00045894	0.00384384	No
MEFV	Downregulated	0.206428868	0.07086419	0.2142595	No	-0.0477609	0.79265852	0.84897392	Yes
DNM3OS	Downregulated	0.026734704	0.77819555	0.89086185	No	0.9740733	0.000917	0.0062693	No
MYH11	Downregulated	0.296752706	0.13850517	0.33051401	No	0.49326607	0.00696623	0.02362584	No
ATP6V0A4	Downregulated	0.067684503	0.60900147	0.78405778	No	0.04336485	0.81122818	0.86351352	No

MIR143HG	Downregulated	0.079683143	0.61257743	0.78650862	No	0.3139639	0.17778307	0.2708696	No
FXYD5	Downregulated	0.469393505	0.0000231	0.00075501	No	0.55249674	0.00047796	0.00395449	No
PIK3R5	Downregulated	0.634013571	4.6E-09	0.00000184	No	0.55296209	0.00697936	0.02364882	No
KCNA7	Downregulated	0.203463176	0.64073448	NA	No	-0.4704187	0.01272075	0.03579942	Yes
LOC642236	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ZNF662	Downregulated	0.039297023	0.48368421	0.69507973	No	0.02018909	0.80682641	0.86004308	No
C7orf58	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TRPA1	Downregulated	-0.467039498	0.0000717	0.00170636	Yes	-0.610279	0.00259565	0.01247461	Yes
LOC100505702	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TMEM154	Downregulated	0.245449038	0.01086419	0.05960273	No	0.17967377	0.32513962	0.43333297	No
IL1R1	Downregulated	0.516167073	0.0000199	0.00067012	No	1.09369416	0.0000037	0.0001047	No
GLP2R	Downregulated	-0.115762153	0.42885919	0.65108431	Yes	-0.7997998	0.0015746	0.00907329	Yes
COL17A1	Downregulated	-0.009956088	0.9111972	0.96129582	Yes	-0.6168521	0.00031551	0.00290627	Yes
SNX29P2	Downregulated	0.306850098	0.17398554	0.38112936	No	0.14959028	0.22210926	0.3223553	No
MSR1	Downregulated	0.866868018	2.35E-09	0.00000113	No	0.8121184	0.00602412	0.02146339	No
GSDMC	Downregulated	0.973009777	0.00180119	0.01663318	No	-0.1123109	0.73927023	0.80670811	Yes
APOL1	Downregulated	0.591942076	6.42E-07	0.0000606	No	0.51370083	0.00210918	0.01094381	No
TMC1	Downregulated	0.362394279	0.00019137	0.00341809	No	0.51063048	0.00984823	0.02983903	No
CYP19A1	Downregulated	0.458004009	0.00606544	0.03929949	No	0.39302594	0.13848385	0.22281138	No
CCBE1	Downregulated	-0.222606809	0.03890452	0.14433895	Yes	-0.6037902	0.00723581	0.02422333	Yes
ALPK2	Downregulated	0.162268921	0.34062062	0.57033784	No	0.02951956	0.89683256	0.92752493	No
LOC100507462	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CCDC36	Downregulated	0.168911713	0.14959806	0.34763025	No	0.30673113	0.1241189	0.20440008	No

PSG5	Downregulated	-0.208398922	0.18042545	0.38979105	Yes	-0.2417691	0.30423241	0.41163809	Yes
MLLT10P1	Downregulated	-0.181310783	0.4049997	0.63018625	Yes	-0.39278	0.06517117	0.12359889	Yes
P2RX7	Downregulated	0.195406201	0.0075313	0.04605709	No	0.8607724	0.0000375	0.00059493	No
DNAJC22	Downregulated	0.488659604	0.00000351	0.00019869	No	0.03669474	0.84118896	0.88683076	No
LOC100506874	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MYPN	Downregulated	-0.107515439	0.61949482	0.79115402	Yes	-0.6345128	0.02136066	0.05244782	Yes
CASP10	Downregulated	0.413196637	0.00000183	0.00012591	No	0.25610228	0.05234033	0.10422456	No
EXO1	Downregulated	-0.14574837	0.1727804	0.37928326	Yes	-0.746283	0.000053	0.00077399	Yes
CSNK1A1P1	Downregulated	-0.07522122	0.47959129	0.6918437	Yes	0.02018886	0.93015489	0.95110248	No
ADAMTS4	Downregulated	0.280681121	0.0493134	0.16858593	No	0.18035456	0.47593502	0.57989541	No
SKA1	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.7266636	2.49E-07	0.000015	Yes
DAND5	Downregulated	0.44033088	0.02332928	0.10150987	No	0.04342108	0.83031529	0.87859749	No
C4orf19	Downregulated	0.55973943	5.63E-10	4.27E-07	No	0.93162748	0.00000227	0.0000734	No
S1PR5	Downregulated	0.394852886	0.00370377	0.02763917	No	0.11216525	0.64574584	0.73053912	No
FLJ43879	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ROS1	Downregulated	-0.692050475	0.0000239	0.00077346	Yes	-0.5010559	0.07686594	0.1404147	Yes
IGSF10	Downregulated	-0.065129837	0.45544839	0.67342273	Yes	-0.3571971	0.00046675	0.00388767	Yes
TPRG1	Downregulated	0.146423892	0.1044159	0.27678453	No	0.1738539	0.37881556	0.48798004	No
SLC2A5	Downregulated	0.341026941	0.00996788	0.05615327	No	0.45412473	0.03677244	0.07933616	No
LOC399715	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GIPC3	Downregulated	0.56226702	0.00024666	0.00410426	No	0.5379832	0.00249362	0.01216504	No
E2F2	Downregulated	0.067524343	0.78924279	0.89731063	No	0.03620876	0.89958082	0.92926746	No
KCNQ1OT1	Downregulated	-0.02706674	0.68932144	0.83867626	Yes	-0.2679292	0.11972083	0.19868898	Yes

RAD51B	Downregulated	0.275636734	0.00018149	0.00328476	No	0.18265561	0.12357478	0.20372665	No
KDR	Downregulated	0.455047898	0.00027646	0.00445544	No	0.44620687	0.00968194	0.02947775	No
CPM	Downregulated	0.652740963	1.4E-12	6.68E-09	No	0.45474913	0.0011744	0.0074437	No
MRVI1	Downregulated	0.383768935	0.000008	0.0003603	No	0.86943502	0.00000319	0.0000936	No
SOAT2	Downregulated	0.349030284	0.41851732	NA	No	-0.4102398	0.08927614	0.15762628	Yes
NFATC2	Downregulated	0.497824481	1.38E-09	0.00000075	No	0.58270207	0.00015387	0.00171035	No
TNFRSF11A	Downregulated	-0.252266386	0.00038298	0.0055928	Yes	-0.6860064	0.0000115	0.0002416	Yes
ITGBL1	Downregulated	0.269715488	0.08112408	0.23414322	No	-0.158796	0.31190313	0.41965422	Yes
MKRN9P	Downregulated	0.005793425	0.99488263	NA	No	-0.2961327	0.1422407	0.22744478	Yes
LOC338817	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
AGTR1	Downregulated	0.51567119	0.01345984	0.06919339	No	0.73909409	0.00677856	0.02320391	No
ERG	Downregulated	0.206891968	0.04175764	0.15119916	No	0.68990482	0.0000111	0.00023716	No
MAP1LC3C	Downregulated	0.474176597	0.00157934	0.0151232	No	0.10095984	0.46757552	0.57240812	No
SP7	Downregulated	0.175808937	0.17284234	0.37939148	No	-0.9541304	0.00061224	0.004726	Yes
NOX5	Downregulated	-0.497527743	0.00098758	0.01087417	Yes	-0.3328191	0.13166589	0.21407177	Yes
EGFLAM	Downregulated	0.554694633	0.00110005	0.01172458	No	0.64138202	0.02344833	0.05619052	No
RIBC2	Downregulated	0.083388834	0.55224543	0.74595606	No	0.11555982	0.55003322	0.64728366	No
C3	Downregulated	0.673077579	8.39E-09	0.00000277	No	0.89738839	0.00028039	0.00266103	No
SEC1	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PAPPA2	Downregulated	-0.069260931	0.21926232	0.43896713	Yes	-0.4083156	0.00483706	0.01859198	Yes
ABCA4	Downregulated	0.152547374	0.22164495	0.44173032	No	0.17912757	0.28188472	0.387848	No
DNAH11	Downregulated	0.503485278	0.00077455	0.00909743	No	0.01389262	0.92457911	0.94699285	No
ACTL8	Downregulated	-0.070765551	0.86502471	NA	Yes	-0.67356	0.02369985	0.05665203	Yes

FLT3LG	Downregulated	0.238346504	0.16784013	0.37250479	No	0.2507564	0.01653987	0.04336078	No
PKP1	Downregulated	0.118279447	0.39620329	0.62167013	No	-0.7769722	0.00075811	0.00548026	Yes
LOC100130581	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LINC00311	Downregulated	0.375099437	0.07209836	0.21657468	No	-0.1818232	0.47116813	0.57571499	Yes
ATAD3C	Downregulated	0.339928471	0.01185812	0.06322	No	0.1804804	0.3548165	0.46384874	No
ITK	Downregulated	0.496776086	0.00111204	0.01179937	No	-0.4316114	0.05170602	0.10323799	Yes
C1QTNF2	Downregulated	-0.048749657	0.51941874	0.72178153	Yes	-0.718721	0.00000299	0.0000895	Yes
PAPL	Downregulated	#N/A	#N/A	#N/A	#N/A	0.12469334	0.60094315	0.69236241	No
KCNE3	Downregulated	0.547327822	2.85E-08	0.00000639	No	0.33307204	0.02469449	0.05849047	No
ADCY10	Downregulated	-0.008583484	0.93350469	0.97216503	Yes	-0.1884206	0.27588536	0.3815235	Yes
ELTD1	Downregulated	0.376562899	0.00021754	0.00373348	No	1.06142311	5.91E-07	0.0000271	No
RAET1E	Downregulated	-0.091105709	0.33962958	0.56957253	Yes	0.3487251	0.06373877	0.12144826	No
NOX4	Downregulated	-0.21383856	0.01263462	0.06613355	Yes	-0.5126441	0.0175404	0.04524555	Yes
FKBP1AP1	Downregulated	-0.087087778	0.42844415	0.65076319	Yes	#N/A	#N/A	#N/A	#N/A
TMEM106A	Downregulated	0.31580513	0.00064046	0.00803572	No	0.24428987	0.11169833	0.18802604	No
STX11	Downregulated	0.370419112	0.03797558	0.14197452	No	0.82028182	0.0000806	0.00105524	No
ADAMTSL3	Downregulated	0.386432303	0.000016	0.00058045	No	0.71973021	0.00014669	0.00164669	No
EEF1DP3	Downregulated	-0.136231603	0.07226712	0.21687565	Yes	-0.2373614	0.22289055	0.32325362	Yes
EMCN	Downregulated	0.374577583	0.00114893	0.01208603	No	0.71222655	0.00019735	0.00205274	No
MR1	Downregulated	0.220631837	0.00050755	0.00680693	No	0.44604804	0.00015616	0.00172921	No
HOXD-AS1	Downregulated	0.554670384	0.00270419	0.02222015	No	0.00588612	0.98324231	0.98871104	No
FER1L5	Downregulated	-0.191240368	0.02821494	0.11588247	Yes	-0.2614609	0.07841199	0.14265472	Yes
ADAM20	Downregulated	-0.228694257	0.00511818	0.03489409	Yes	-0.0161714	0.9314277	0.9518628	Yes

GPR183	Downregulated	0.114044996	0.31743584	0.5477785	No	0.45713386	0.17030463	0.26172835	No
PYY	Downregulated	0.202942692	0.44215211	0.66232944	No	-0.4055848	0.01387726	0.03809426	Yes
C10orf54	Downregulated	0.403025164	0.00033767	0.00510619	No	0.73077599	0.0000666	0.00091581	No
MIRLET7BHG	Downregulated	0.243002987	0.00512333	0.03491037	No	#N/A	#N/A	#N/A	#N/A
AURKB	Downregulated	0.674551593	0.07046586	NA	No	-0.4895252	0.09107817	0.16010323	Yes
GSDMA	Downregulated	0.87878291	0.00500177	0.03436592	No	-0.1045381	0.719285	0.79076533	Yes
SCIN	Downregulated	0.602250756	0.00063038	0.00794518	No	0.9838084	0.00257304	0.01241317	No
IQGAP3	Downregulated	-0.102670616	0.41856132	0.6418098	Yes	-0.8836003	0.0000145	0.00028957	Yes
C9orf84	Downregulated	0.107204321	0.35799034	0.58646258	No	0.31680368	0.09084588	0.15982088	No
NEIL3	Downregulated	0.029825471	0.89842678	0.95480531	No	-0.4095298	0.09581886	0.16666123	Yes
MME	Downregulated	-0.250788462	0.0621842	0.19638369	Yes	-0.6517315	0.0023023	0.0115734	Yes
OPN1SW	Downregulated	-0.03694373	0.73011633	0.86326589	Yes	-0.2020975	0.12489223	0.20537031	Yes
C6orf99	Downregulated	-0.207627946	0.12028544	0.30271955	Yes	0.23006397	0.12330877	0.2033723	No
LCP1	Downregulated	0.388972055	0.00059647	0.00763775	No	0.71220688	0.00193938	0.01037238	No
NCKAP1L	Downregulated	0.420413894	0.00000781	0.0003532	No	0.32278105	0.12709453	0.20809569	No
ABRA	Downregulated	-0.21079145	0.10526671	0.27814625	Yes	-1.1998782	0.00000472	0.0001251	Yes
CHI3L2	Downregulated	1.522940815	3.14E-09	0.00000137	No	1.31852213	0.00144973	0.008589	No
LILRA6	Downregulated	#N/A	#N/A	#N/A	#N/A	0.63457674	0.00690019	0.02349333	No
CIITA	Downregulated	0.47754803	3.92E-07	0.0000423	No	-0.1646574	0.02600523	0.06082957	Yes
TIE1	Downregulated	0.53552561	0.0000525	0.0013543	No	0.62355693	0.00026748	0.00257174	No
UNQ6975	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
USH2A	Downregulated	-0.085410118	0.27262405	0.50134083	Yes	-0.3965054	0.00635968	0.02224348	Yes
TAF4B	Downregulated	-0.16024291	0.02482319	0.1059048	Yes	-0.5656909	0.0000785	0.00103386	Yes

POLQ	Downregulated	-0.321057694	0.00069443	0.00843669	Yes	-0.2931091	0.05459846	0.10763708	Yes
LSP1	Downregulated	0.699865914	0.00000183	0.0001259	No	-0.445583	0.02411537	0.05741392	Yes
ZYG11A	Downregulated	0.142782241	0.39946181	0.62471357	No	-0.1034317	0.66649724	0.74770914	Yes
CD14	Downregulated	0.413500191	0.01203851	0.06396607	No	0.89638385	0.00056402	0.0044493	No
GDNF	Downregulated	0.207237781	0.17327224	0.38003868	No	-0.2607719	0.32495202	0.43317613	Yes
BDKRB1	Downregulated	-0.099043969	0.6700175	0.8256443	Yes	-0.5267704	0.05122348	0.10248373	Yes
ALOX5AP	Downregulated	0.338519476	0.00640914	0.04087212	No	1.20512522	0.0000128	0.00026259	No
GPR156	Downregulated	0.26053531	0.00229682	0.01980764	No	0.13924629	0.31209605	0.41987326	No
ZP1	Downregulated	0.051733898	0.64740716	0.81027836	No	-0.2650536	0.13117664	0.21343191	Yes
SYCP3	Downregulated	-0.043423797	0.61219785	0.78627989	Yes	0.08066582	0.44298188	0.54959719	No
TMEM217	Downregulated	0.129365475	0.27814277	0.50716457	No	0.04552542	0.60769324	0.69823484	No
UHRF1	Downregulated	0.440350502	0.00187574	0.01712165	No	0.61882255	0.00245657	0.01205389	No
GABRR2	Downregulated	0.680249183	0.00017646	0.00321992	No	1.56879553	4.23E-07	0.0000215	No
FGF18	Downregulated	-0.269891483	0.10818429	0.28284263	Yes	-0.3763223	0.04099066	0.08631237	Yes
ADAMTS14	Downregulated	0.277739576	0.09214528	0.2545898	No	-0.1432822	0.61496496	0.70431129	Yes
SLC15A3	Downregulated	0.689538796	2.26E-12	8.57E-09	No	0.12821121	0.19510179	0.29147385	No
CAV1	Downregulated	0.468429273	0.0000104	0.00042924	No	0.66883975	0.00073853	0.0053828	No
COL11A1	Downregulated	-0.11227508	0.10269114	0.27361151	Yes	0.31390528	0.00844771	0.02685349	No
COL13A1	Downregulated	-0.091671366	0.49535413	0.70401748	Yes	-0.235709	0.33373601	0.44221072	Yes
PTPRC	Downregulated	#N/A	#N/A	#N/A	#N/A	0.88007634	0.00133405	0.00813059	No
LRRC19	Downregulated	0.011480017	0.90653595	0.95879827	No	-0.0033689	0.98589746	0.99044502	Yes
ACSM5	Downregulated	0.505457733	0.0000178	0.00062195	No	0.26159844	0.17323185	0.26535807	No
LOC648987	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

C8orf46	Downregulated	-0.111186378	0.03865386	0.14375978	Yes	-0.1239907	0.07676763	0.14028108	Yes
ANKRD26P1	Downregulated	-0.117628174	0.65497295	0.81547183	Yes	-0.1996114	0.51320856	0.61441121	Yes
GTF2IRD2P1	Downregulated	0.26716323	0.20160603	0.41764942	No	-0.0637628	0.69567353	0.77160941	Yes
SLC2A4	Downregulated	0.627210839	0.00000399	0.00021578	No	0.78367659	0.00015914	0.00175531	No
TXNRD3NB	Downregulated	NA	NA	NA	#N/A	0.00670053	0.94421526	0.96145931	No
LOC100506810	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
HGF	Downregulated	0.28637717	0.02169242	0.0966558	No	0.92148999	0.00072282	0.00531193	No
HNRNPA3P1	Downregulated	0.335284013	0.78262235	NA	No	-0.1309383	0.3160097	0.42406404	Yes
SKA3	Downregulated	0.339839533	0.02920503	0.11880469	No	-0.6867612	0.0000199	0.00036704	Yes
BRIP1	Downregulated	-0.0123155	0.9057128	0.9584404	Yes	-0.807485	0.0000227	0.00040591	Yes
SVEP1	Downregulated	-0.273822131	0.00812905	0.04850337	Yes	-0.2245947	0.30979593	0.41744361	Yes
CCDC168	Downregulated	-0.220417538	0.24559132	0.47017266	Yes	0.0354198	0.88077203	0.91572173	No
GIPC2	Downregulated	-0.096035716	0.2897578	0.51951086	Yes	-0.2674136	0.01913556	0.04830982	Yes
TNS4	Downregulated	0.246506795	0.51392516	NA	No	-0.4519474	0.13668174	0.22050166	Yes
PTPRB	Downregulated	0.059208475	0.43227582	0.65383161	No	0.71127981	0.0000893	0.00113671	No
CD40	Downregulated	0.386677459	0.0000262	0.0008234	No	0.52648086	0.0000734	0.00098193	No
LOC100134368	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
EN1	Downregulated	-0.583365187	0.21674214	NA	Yes	-0.1397086	0.62897221	0.71630733	Yes
LOC148696	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FERMT1	Downregulated	0.045585775	0.63075256	0.79814038	No	0.0297457	0.86161954	0.90162642	No
ITGB2	Downregulated	0.594805276	6.11E-07	0.0000583	No	0.64993897	0.00679895	0.02325427	No
COL6A3	Downregulated	0.426841659	0.04348549	0.15523402	No	0.46499165	0.09141694	0.16058736	No
ATP8B5P	Downregulated	0.202511322	0.22751192	0.44927093	No	-0.3894864	0.00047736	0.00395118	Yes

OTOA	Downregulated	-0.132185708	0.22532523	0.44657557	Yes	-0.6196993	0.00067727	0.00508027	Yes
PCDHGA12	Downregulated	0.215043683	0.02065848	0.0936317	No	0.30184082	0.00016405	0.00179621	No
TBX15	Downregulated	0.443360636	0.00375639	0.02793009	No	1.42267542	2.32E-08	0.00000314	No
PTPN22	Downregulated	0.217508464	0.02101959	0.09461306	No	0.11287863	0.50130863	0.60341884	No
INHBA	Downregulated	1.034984552	0.00000302	0.000177	No	-0.0930317	0.5822795	0.67619712	Yes
BIRC3	Downregulated	0.300188296	0.00265124	0.02191312	No	0.37644235	0.02364544	0.05656078	No
BCL11B	Downregulated	-0.098089894	0.21924535	0.43896713	Yes	-0.6419024	0.000039	0.0006122	Yes
CASC5	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.2951085	0.10682789	0.18150584	Yes
AXDND1	Downregulated	0.23237127	0.07455108	0.22128035	No	-0.2528807	0.33146316	0.43977374	Yes
CYP27B1	Downregulated	0.059105654	0.64975188	0.81200399	No	-0.453362	0.0000317	0.00052267	Yes
LOC440028	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PIP5K1P1	Downregulated	0.091529445	0.52126082	0.72304411	No	0.00810806	0.97337897	0.982098	No
CYP11A1	Downregulated	0.229109569	0.04106134	0.14950517	No	0.01989777	0.90180183	0.93090298	No
ANKRD20A9P	Downregulated	-0.172288665	0.53645185	0.73482365	Yes	-0.119852	0.58955382	0.68249824	Yes
BCL11A	Downregulated	-0.377739047	3.77E-07	0.0000413	Yes	-0.6699523	0.00042128	0.00359979	Yes
DQX1	Downregulated	-0.023374357	0.8339513	0.92086121	Yes	-0.2465916	0.15450374	0.24262126	Yes
DPT	Downregulated	-0.063999411	0.60966979	0.78443376	Yes	-0.5406114	0.001911	0.0102748	Yes
ROR1	Downregulated	-0.149039039	0.08193364	0.23565544	Yes	0.06568377	0.66073833	0.74314902	No
SH2D4A	Downregulated	0.058361875	0.3809972	0.60819178	No	0.6910437	0.0000144	0.00028774	No
MOCOS	Downregulated	0.080252326	0.47000913	0.68520883	No	0.13287346	0.50301658	0.60499143	No
PLIN1	Downregulated	0.64050055	0.0000537	0.00137654	No	0.79749738	0.00039824	0.00345373	No
TPTE2	Downregulated	-0.130170659	0.38024027	0.60759289	Yes	-0.908342	0.0000165	0.00032015	Yes
SLC38A4	Downregulated	0.212954234	0.1731731	0.37991204	No	0.43836287	0.13569348	0.21923285	No

COL24A1	Downregulated	-0.616398085	3.32E-08	0.00000719	Yes	-0.3438051	0.14048201	0.22526452	Yes
TRIM29	Downregulated	-0.083568582	0.60979588	0.78443376	Yes	-0.5362202	0.00983189	0.02980896	Yes
CD101	Downregulated	-0.087594459	0.27374622	0.50248664	Yes	-0.7785195	5.27E-08	0.00000541	Yes
HYMAI	Downregulated	-0.145994167	0.18275435	0.39290012	Yes	#N/A	#N/A	#N/A	#N/A
SP110	Downregulated	0.210352452	0.00676469	0.04255006	No	0.35124747	0.00512436	0.01928415	No
CAGE1	Downregulated	-0.201127992	0.36158216	0.58985687	Yes	-0.0024081	0.9908263	0.99380294	Yes
HHIP	Downregulated	0.176685771	0.09215918	0.2545898	No	0.24153606	0.32421222	0.43245877	No
CYP2B7P1	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CLCF1	Downregulated	0.225185233	0.01841433	0.08640097	No	0.58699454	0.00142346	0.00849295	No
ODF3L2	Downregulated	0.229506012	0.13191366	0.32056929	No	-0.0914372	0.54387458	0.64189219	Yes
TMC2	Downregulated	-0.187943553	0.02427494	0.10423474	Yes	-0.2462453	0.08590724	0.15293992	Yes
MKX	Downregulated	-0.146263145	0.11866596	0.30001651	Yes	-0.5290396	0.00249587	0.01216872	Yes
LOC153684	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
BIRC5	Downregulated	0.531128918	0.00236244	0.02023391	No	-0.0292897	0.86659707	0.90545858	Yes
FHAD1	Downregulated	-0.154435172	0.13049421	0.31847875	Yes	-0.5336393	0.00101581	0.00674659	Yes
PSTPIP1	Downregulated	0.286732585	0.00027098	0.00438205	No	0.032336	0.80037718	0.85511392	No
EGF	Downregulated	0.177267159	0.05138887	0.17263397	No	0.63726725	0.00053319	0.00427691	No
C20orf152	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC100133985	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
KLHL10	Downregulated	-0.087339247	0.47822915	0.69106069	Yes	-0.1905404	0.13685045	0.22069723	Yes
FAM129C	Downregulated	0.188221393	0.09674401	0.26270459	No	-0.1653343	0.33306068	0.44148375	Yes
FMO4	Downregulated	0.480601834	0.0000333	0.00097632	No	0.21329164	0.23366104	0.33525038	No
EVC2	Downregulated	0.491909804	0.0000025	0.00015616	No	0.57151578	0.00282582	0.01317325	No

LYG2	Downregulated	-0.182729827	0.04878832	0.16739395	Yes	0.20418689	0.33440262	0.44286246	No
COL5A3	Downregulated	0.098074735	0.33898243	0.56911971	No	0.5371478	0.00300393	0.01368583	No
SP100	Downregulated	-0.345148712	0.24350902	0.46776705	Yes	0.54532049	0.0003242	0.00296474	No
C4orf22	Downregulated	0.058221413	0.70272423	0.84698195	No	-1.0277523	0.00026448	0.00255083	Yes
CDC25C	Downregulated	-0.136769767	0.42297992	0.64540402	Yes	-0.1059096	0.31907727	0.42727555	Yes
IL15	Downregulated	0.224086136	0.03963583	0.14607432	No	0.14761196	0.26129046	0.36570301	No
LOC100288637	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FLJ42289	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ITGB4	Downregulated	0.793239917	1.04E-08	0.00000302	No	1.22774373	7.72E-07	0.0000332	No
LOC100130872	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PLCG2	Downregulated	0.372307885	0.00000442	0.00023435	No	0.43360605	0.00283996	0.01322185	No
VEPH1	Downregulated	-0.143367925	0.14475479	0.34073807	Yes	-0.7102948	0.00132742	0.00809844	Yes
LILRB3	Downregulated	#N/A	#N/A	#N/A	#N/A	0.59489336	0.0175104	0.04518376	No
ANO3	Downregulated	-0.5221847	0.0000276	0.00085057	Yes	-1.1112537	0.00010982	0.00133313	Yes
FLJ14107	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
STAB1	Downregulated	0.379237344	0.00689669	0.0431586	No	0.93303203	0.0000243	0.00042864	No
ADH6	Downregulated	0.222462621	0.13547478	0.32574025	No	-0.0389665	0.86801773	0.90634362	Yes
FBXW10	Downregulated	-0.036297142	0.73681185	0.86659302	Yes	-0.293066	0.08978619	0.15837137	Yes
FLJ38109	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
NLRP14	Downregulated	0.052914754	0.69764951	0.8439391	No	0.26986113	0.55632563	0.65285595	No
PCDHGA9	Downregulated	-0.013284462	0.79795913	0.90294686	Yes	0.30168419	0.0001968	0.00204851	No
ABCG2	Downregulated	0.313077984	0.02134327	0.0956842	No	0.69498358	0.00562704	0.02050731	No
LRRK1	Downregulated	-0.175648699	0.00815144	0.04857136	Yes	-0.1282658	0.3004451	0.40764143	Yes

SOX7	Downregulated	0.347744553	0.00317583	0.02485778	No	0.48875498	0.00018984	0.00199334	No
KIF6	Downregulated	0.389969603	0.00000422	0.00022643	No	-0.2370383	0.19823953	0.29508618	Yes
LOC149773	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FAM176A	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
KIAA1875	Downregulated	-0.097386512	0.40868852	0.63341998	Yes	-0.0612547	0.68623184	0.76399319	Yes
SLC26A8	Downregulated	-0.213366476	0.01241596	0.06534047	Yes	-0.5651671	0.00062257	0.00478389	Yes
CDK15	Downregulated	-0.16316398	0.20491871	0.42179537	Yes	-0.6125283	0.0153362	0.04100537	Yes
TM4SF18	Downregulated	0.451307744	0.00068619	0.00836879	No	1.02084336	0.00000418	0.00011453	No
KIF4B	Downregulated	-0.12167777	0.26076164	0.48810718	Yes	-0.214905	0.31130474	0.41901089	Yes
ASB2	Downregulated	#N/A	#N/A	#N/A	#N/A	-1.0664607	0.0000034	0.0000982	Yes
KCNJ14	Downregulated	0.117565046	0.17293548	0.37953008	No	-0.0992504	0.35917404	0.46819507	Yes
LRRIQ4	Downregulated	-0.332709965	0.01591731	0.07800201	Yes	-0.1655619	0.50508758	0.60682777	Yes
LOC152742	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PAQR5	Downregulated	0.285672024	0.00713097	0.04428882	No	0.58238569	0.00247127	0.01209555	No
LOC100506655	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SND1-IT1	Downregulated	-0.071892227	0.31584216	0.54630056	Yes	#N/A	#N/A	#N/A	#N/A
NLRC5	Downregulated	0.504651342	0.00000107	0.0000884	No	0.69621221	0.00000433	0.00011743	No
GLI2	Downregulated	0.557516345	0.0000194	0.00065577	No	0.98111212	5.3E-08	0.00000543	No
DYSF	Downregulated	0.199007565	0.019059	0.08856089	No	0.092646	0.67773708	0.75693899	No
EPSTI1	Downregulated	0.307255559	0.00398871	0.02912746	No	0.24274684	0.2101863	0.30895962	No
BARD1	Downregulated	0.207161584	0.0034068	0.0261057	No	0.38248915	0.00019836	0.0020588	No
DENND2D	Downregulated	0.510838082	0.0000112	0.00045084	No	0.52094826	0.00806349	0.02599707	No
CDC45	Downregulated	0.547365461	0.00242817	0.02066336	No	0.4749377	0.0344582	0.0754586	No

FUT2	Downregulated	-0.074436811	0.2987995	0.52865483	Yes	-0.187829	0.04156035	0.0872553	Yes
OSCAR	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.0596063	0.6367262	0.72277012	Yes
TINAGL1	Downregulated	0.537970259	0.00027579	0.00444659	No	0.60669342	0.00120056	0.0075551	No
INMT	Downregulated	0.402680631	0.03205416	0.12659557	No	0.13726519	0.46618303	0.57119756	No
HNMT	Downregulated	0.294352702	0.0000478	0.00126647	No	0.2584666	0.01321737	0.03680506	No
C19orf35	Downregulated	#N/A	#N/A	#N/A	#N/A	0.52156286	0.0028233	0.01316765	No
DTL	Downregulated	0.482020882	0.00196921	0.01774442	No	-0.1918402	0.29086507	0.39744811	Yes
LOC100129931	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SATB2	Downregulated	-0.247320473	0.00041082	0.00588603	Yes	-0.3916954	0.00805798	0.02598802	Yes
PRAM1	Downregulated	0.434302145	0.0000478	0.00126647	No	0.04295825	0.78051567	0.8395245	No
SLC12A1	Downregulated	-0.410890153	0.00077395	0.00909677	Yes	-0.8565587	0.00000228	0.0000736	Yes
ALPK1	Downregulated	0.361041252	0.00033046	0.00503039	No	0.55106041	0.00023749	0.00235525	No
EMX2OS	Downregulated	0.401831855	0.000038	0.0010635	No	0.99519881	0.00000423	0.0001154	No
PRRG4	Downregulated	0.597603813	0.0000224	0.00073842	No	0.78263086	0.00068881	0.00513783	No
SPDYE5	Downregulated	-0.013495106	0.87446675	0.94220206	Yes	#N/A	#N/A	#N/A	#N/A
S1PR1	Downregulated	0.341462532	0.00047563	0.00653584	No	0.91017564	2.77E-08	0.00000355	No
SP140L	Downregulated	0.259219245	0.00041554	0.00592691	No	0.3420866	0.00175605	0.00974135	No
TDRD9	Downregulated	-0.159739789	0.11422907	0.29279733	Yes	-0.364512	0.02266481	0.05478148	Yes
ZMYND15	Downregulated	0.590610516	0.00000197	0.00013224	No	0.09170389	0.53442375	0.6333524	No
C14orf182	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.3789874	0.05673372	0.11093267	Yes
MIP	Downregulated	-0.062019773	0.71621113	0.85473312	Yes	-0.1343611	0.20588341	0.30401323	Yes
DLGAP5	Downregulated	0.947769429	0.00312569	0.02463295	No	-0.4336474	0.11660709	0.19459974	Yes
APOBEC3D	Downregulated	0.390920527	0.0240874	0.10375816	No	0.44313517	0.01077954	0.0317515	No

PSMB9	Downregulated	0.461870914	0.0000107	0.00043711	No	0.31846934	0.0150448	0.04043956	No
LOC440600	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CDRT1	Downregulated	-0.256410916	0.12741507	0.31411141	Yes	0.02488711	0.86824443	0.9064494	No
LOC400891	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MEI1	Downregulated	-0.144040059	0.08872507	0.2484302	Yes	-0.4314779	0.01179477	0.0338758	Yes
GPR39	Downregulated	-0.422965395	0.00093196	0.01044414	Yes	0.02749944	0.86684876	0.90556015	No
IGSF6	Downregulated	0.210911004	0.00180324	0.01664737	No	0.5383316	0.01515746	0.04066202	No
HOGA1	Downregulated	0.391654057	0.00000727	0.00033496	No	0.00724182	0.96031865	0.97254612	No
LOC285540	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ZBTB20	Downregulated	0.317444653	0.00000569	0.00027991	No	0.60934102	0.0000135	0.00027486	No
ZNF850	Downregulated	0.162898157	0.0011213	0.01187111	No	0.02893529	0.815255	0.86667476	No
CCDC158	Downregulated	-0.308983308	0.0000592	0.00147747	Yes	-0.3509558	0.00768386	0.02522499	Yes
ERAP2	Downregulated	0.244492211	0.0370495	0.13962032	No	0.20862883	0.4624411	0.56788903	No
KCTD19	Downregulated	0.026459879	0.85832602	0.9344085	No	-0.3304184	0.04904936	0.09909399	Yes
ITGA11	Downregulated	0.070209868	0.27154257	0.50012746	No	0.39904261	0.00117134	0.00742988	No
TMPRSS5	Downregulated	0.48271906	0.00105688	0.01140216	No	0.46205627	0.11298261	0.18971986	No
ARHGAP6	Downregulated	0.082073278	0.43655645	0.65773743	No	-0.0201481	0.87873745	0.91422013	Yes
NKX3-1	Downregulated	0.30197116	0.0027183	0.02229746	No	0.31891914	0.01451633	0.03937578	No
GREM1	Downregulated	0.1253725	0.39114028	0.61718896	No	0.14324071	0.59566204	0.68781288	No
DIAPH3	Downregulated	0.245066282	0.0303143	0.12195769	No	0.20441611	0.26957481	0.37490741	No
FRRS1	Downregulated	0.407495128	0.00729786	0.0450452	No	0.79686295	0.00633275	0.0221827	No
TLR5	Downregulated	0.550935325	0.00000324	0.00018613	No	0.68147621	0.00018896	0.00198802	No
LRTM1	Downregulated	-0.256570729	0.00803256	0.04811727	Yes	-0.0686	0.7827973	0.84134372	Yes

ALS2CR11	Downregulated	-0.01008674	0.89408389	0.95218755	Yes	-0.1882409	0.15279004	0.24043128	Yes
KIF20A	Downregulated	0.055336032	0.63053694	0.79798766	No	-0.4073967	0.0029297	0.01346869	Yes
BTBD18	Downregulated	0.00478308	0.94734016	0.97830976	No	0.01758754	0.89854461	0.92861737	No
PRR5L	Downregulated	0.396640624	0.000032	0.00094748	No	0.06660838	0.73005681	0.79934504	No
RPGRIP1	Downregulated	0.072868569	0.53843089	0.73617948	No	-0.4986569	0.00439622	0.01747205	Yes
MALAT1	Downregulated	-0.057625435	0.38853192	0.61489202	Yes	0.94415683	0.0000428	0.00065738	No
GOLGA6L10	Downregulated	-0.084543709	0.64127855	0.8063972	Yes	0.07983839	0.75177939	0.81668829	No
RERGL	Downregulated	0.178503015	0.26111324	0.48840401	No	0.1071664	0.68878474	0.76607054	No
GALM	Downregulated	0.269490151	0.00018756	0.00336571	No	0.35269737	0.00156781	0.00905007	No
PPP1R36	Downregulated	0.269388762	0.01102063	0.06008866	No	-0.1623479	0.3398001	0.44849784	Yes
COLEC11	Downregulated	-0.075355207	0.66715864	0.82377966	Yes	0.27469995	0.29506691	0.40183741	No
COX7A1	Downregulated	-0.200356781	0.02661704	0.11113566	Yes	-0.0973956	0.39273503	0.5015882	Yes
RAD21-AS1	Downregulated	-0.089708212	0.57141471	0.75889289	Yes	0.31978533	0.01671139	0.04370971	No
PRR11	Downregulated	0.06596666	0.42180604	0.64444192	No	-0.1347796	0.29055946	0.39706118	Yes
VDR	Downregulated	0.131701875	0.40963998	0.63406217	No	-0.2922441	0.1737977	0.26601144	Yes
SPTBN5	Downregulated	0.171346924	0.073004	0.21829306	No	0.04718578	0.73435921	0.80293627	No
HAS2	Downregulated	0.230452315	0.05477771	0.18050859	No	-0.0320734	0.88269174	0.91717035	Yes
NCAPH	Downregulated	0.088119496	0.40974835	0.63415843	No	-0.3116332	0.0984716	0.17017756	Yes
LOC158376	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SERPINE3	Downregulated	0.258671111	0.02819923	0.11583046	No	-0.2398837	0.00437581	0.01742574	Yes
CPS1	Downregulated	0.166424153	0.01073068	0.05912778	No	0.13840502	0.25747297	0.36158703	No
CAPN12	Downregulated	-0.116548877	0.54638777	0.74179655	Yes	-0.3933422	0.0000404	0.00062922	Yes
ACTR3C	Downregulated	-0.008853786	0.9075202	0.95932013	Yes	-0.2725822	0.01722735	0.04464872	Yes

NCF2	Downregulated	0.497638992	0.0000175	0.00061369	No	0.9204783	0.00010172	0.00125373	No
CX3CR1	Downregulated	0.242895616	0.10500521	0.27776469	No	-0.0570647	0.86347165	0.90291322	Yes
ENDOU	Downregulated	0.138436681	0.12915704	0.31656611	No	0.09054643	0.49309139	0.59592074	No
IGFN1	Downregulated	0.05338518	0.8052548	0.90698402	No	-0.2976786	0.27988021	0.38577541	Yes
ADAMTS9-AS2	Downregulated	-0.002853814	0.97289012	0.9892478	Yes	0.36930626	0.01193903	0.0341914	No
HJURP	Downregulated	0.433248258	0.11238851	0.28991175	No	-0.395252	0.08732484	0.1549465	Yes
SGCG	Downregulated	-0.126063363	0.19298634	0.40649334	Yes	-0.3447332	0.08318759	0.14910973	Yes
LOC646626	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
C6orf97	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TAT	Downregulated	-0.221576396	0.26779857	0.49616924	Yes	-0.4073237	0.01920157	0.04844355	Yes
WNK4	Downregulated	0.214217987	0.05367386	0.17780726	No	-0.2062338	0.13409284	0.21732059	Yes
GLIS1	Downregulated	0.039946226	0.719611	0.85709269	No	0.0663645	0.59518368	0.68744559	No
LOC100505826	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
RGS20	Downregulated	0.075535251	0.38690879	0.61373753	No	0.23435437	0.18638987	0.28107953	No
TMEM204	Downregulated	0.274616454	0.01509371	0.07508084	No	0.49109615	0.00481452	0.01854602	No
CPNE6	Downregulated	-0.017562876	0.8362782	0.92201469	Yes	-0.1758216	0.26425234	0.36896858	Yes
FGF7	Downregulated	-0.022040996	0.87713792	0.94401864	Yes	-0.5250586	0.00023956	0.00236947	Yes
POTEKP	Downregulated	0.379371549	0.61116789	NA	No	-0.3449001	0.10045145	0.17285797	Yes
RUNX2	Downregulated	0.045781491	0.4614996	0.67827431	No	-0.1180054	0.34905804	0.45800673	Yes
NAT1	Downregulated	0.360474873	0.00523107	0.0354599	No	0.52606391	0.00257425	0.01241411	No
CFB	Downregulated	#N/A	#N/A	#N/A	#N/A	0.68702537	0.0000969	0.00120894	No
ROCK1P1	Downregulated	-0.22348142	0.07971229	0.23135278	Yes	-0.0197184	0.84054436	0.88639339	Yes
LOC100507178	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

RSPO1	Downregulated	-0.404065482	0.17266275	0.37908497	Yes	-0.4055066	0.00190532	0.01025058	Yes
TROAP	Downregulated	0.638732314	0.07105865	0.21460697	No	-0.1125901	0.69386109	0.77014948	Yes
MCTP2	Downregulated	-0.203624959	0.03239642	0.12754914	Yes	0.51229409	0.00792696	0.02573084	No
KIF14	Downregulated	0.208969254	0.13109353	0.31929177	No	0.13276483	0.52345531	0.62357436	No
TWIST1	Downregulated	-0.11480304	0.22473345	0.44580219	Yes	-0.4420828	0.00881364	0.02766812	Yes
CRISPLD2	Downregulated	0.144715982	0.30056165	0.53051606	No	0.41247982	0.02428722	0.05773678	No
MYLK2	Downregulated	-0.024036982	0.90385628	0.95759718	Yes	-0.6299893	0.00823632	0.02636644	Yes
PXDNL	Downregulated	-0.232657732	0.00336808	0.02589267	Yes	-0.36888	0.01374066	0.03782581	Yes
C21orf7	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC100499405	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ACRV1	Downregulated	-0.407354353	0.00055396	0.00723755	Yes	-0.6769944	0.0000835	0.00108429	Yes
E2F8	Downregulated	0.076498215	0.65958071	0.81868422	No	-0.0874837	0.72431262	0.79479219	Yes
NUF2	Downregulated	-0.029852637	0.76357965	0.88265135	Yes	-0.26086	0.06257462	0.11974159	Yes
CD163	Downregulated	0.644568655	0.00279936	0.0227381	No	1.69124701	0.00020085	0.00207801	No
FGF5	Downregulated	-0.370024065	0.00881121	0.05132301	Yes	-0.749815	0.00000583	0.00014551	Yes
DNAH5	Downregulated	-0.024133321	0.81173328	0.91015337	Yes	-0.4742934	0.00430651	0.01726196	Yes
ANKRD31	Downregulated	-0.131293179	0.08458576	0.24042298	Yes	-0.425525	0.01854448	0.04717883	Yes
CC2D2B	Downregulated	-0.052801579	0.65995908	0.81904673	Yes	0.04024153	0.7854889	0.84331993	No
MFSD7	Downregulated	0.317415005	0.00063317	0.00796905	No	0.0824916	0.30944241	0.41707813	No
PTGS1	Downregulated	0.395916852	0.0000463	0.00123742	No	0.3303322	0.04901059	0.09903721	No
RAD54L	Downregulated	-0.082910119	0.41836831	0.64156569	Yes	-0.2520907	0.01199184	0.03431027	Yes
NDE1	Downregulated	0.324390134	0.00062816	0.0079365	No	0.37315317	0.03635816	0.0786364	No
ADAM32	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.6066482	3.43E-07	0.0000186	Yes

C8orf31	Downregulated	-0.093817379	0.22249056	0.44288073	Yes	-0.2840332	0.00126259	0.00781318	Yes
ANP32A-IT1	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ATP10A	Downregulated	0.255009913	0.04484816	0.15831165	No	0.56703718	0.00235343	0.01174312	No
HKDC1	Downregulated	0.406756682	0.00830721	0.04923359	No	0.00642198	0.97312914	0.98188355	No
MST1P2	Downregulated	0.1193413	0.24179377	0.46598155	No	0.05571418	0.64823045	0.73271659	No
IMPG1	Downregulated	0.067896119	0.50843655	0.71368027	No	0.10491781	0.43405134	0.54121596	No
PLAC8	Downregulated	0.079487682	0.74416802	0.87142583	No	0.34758322	0.2509576	0.35457888	No
LINC00315	Downregulated	0.213207839	0.12896253	0.31629362	No	0.73012075	0.00859673	0.02718047	No
TBX3	Downregulated	0.387099926	0.01035267	0.05759679	No	0.87432533	0.0000118	0.00024722	No
COL11A2	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.1440993	0.29677797	0.40355956	Yes
CDCP1	Downregulated	0.293855166	0.01035572	0.05760531	No	0.41369771	0.0278031	0.06395173	No
CCNB2	Downregulated	0.050581828	0.65334525	0.81429155	No	-0.1696229	0.4458062	0.55221905	Yes
EDNRA	Downregulated	0.223090763	0.00640895	0.04087212	No	0.47493487	0.00034612	0.00311514	No
LOC100132215	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
DIO2	Downregulated	-0.278281631	0.02885499	0.11783311	Yes	-0.0569324	0.82292426	0.87268131	Yes
MPL	Downregulated	0.185132194	0.10720046	0.28125856	No	0.03363988	0.83083783	0.87900029	No
FBXO43	Downregulated	0.089214575	0.59579131	0.77581444	No	-0.4375	0.07996393	0.14467094	Yes
ASPM	Downregulated	-0.06890352	0.5485589	0.74311898	Yes	-0.5114816	0.00614812	0.02175231	Yes
CAPN14	Downregulated	-0.239415286	0.01571459	0.07728337	Yes	-0.1411076	0.361531	0.47065126	Yes
EYS	Downregulated	-0.092743586	0.21053056	0.42881167	Yes	0.26800755	0.03074021	0.06911929	No
CCDC38	Downregulated	-0.138285947	0.26999975	0.49844693	Yes	-0.2994461	0.07974361	0.1444176	Yes
CDCA2	Downregulated	0.306389401	0.11716076	0.29754083	No	0.20270492	0.42336442	0.53106046	No
TLR1	Downregulated	0.342871817	0.00096157	0.01066805	No	0.79723892	0.00086305	0.0060165	No

MST1R	Downregulated	-0.039000951	0.75152813	0.87557254	Yes	-0.029796	0.83467654	0.88183626	Yes
TNFSF13B	Downregulated	0.119081032	0.19906843	0.41413305	No	0.01547748	0.90443106	0.93277086	No
HLA-F-AS1	Downregulated	#N/A	#N/A	#N/A	#N/A	0.22842747	0.05006156	0.10070833	No
GSG2	Downregulated	#N/A	#N/A	#N/A	#N/A	0.03722362	0.86853351	0.90663237	No
HOXC4	Downregulated	0.252712416	0.36970208	0.59772835	No	0.36165939	0.14328227	0.22873781	No
CCDC147	Downregulated	0.242735218	0.01748184	0.08330267	No	-0.2812533	0.05636077	0.11035049	Yes
PLAUR	Downregulated	0.150525483	0.2941201	0.52352081	No	0.43690005	0.00706908	0.02384271	No
C9orf47	Downregulated	0.151930439	0.07783465	0.22755633	No	0.49397457	0.00048265	0.00398264	No
APOBEC3F	Downregulated	0.423292772	0.00119157	0.0123972	No	0.3018453	0.06508274	0.12345217	No
CLDN11	Downregulated	0.451498937	0.00046329	0.00641037	No	0.26312519	0.2604928	0.36478806	No
LOC401074	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SSPO	Downregulated	0.165584086	0.09741594	0.26401953	No	0.25376237	0.07384167	0.13612102	No
TBX1	Downregulated	0.293097778	0.12670847	0.31303087	No	0.32564658	0.11466612	0.19199749	No
CCDC150	Downregulated	0.164604733	0.11542623	0.29463225	No	-0.3426092	0.07251817	0.1342583	Yes
SLC11A1	Downregulated	0.46291138	0.01113196	0.06051309	No	0.85706032	0.00830521	0.02651695	No
IL21R	Downregulated	0.232184997	0.2474548	0.47271489	No	-0.0870029	0.68450534	0.76257352	Yes
PODN	Downregulated	0.491678942	0.0000654	0.00159127	No	0.58709795	0.00035396	0.00316675	No
PRG4	Downregulated	0.1910818	0.2294965	0.45156877	No	-0.4162505	1.27E-07	0.00000961	Yes
FLJ12825	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MEIS1	Downregulated	0.11452587	0.11623045	0.29602809	No	-0.2389058	0.09703733	0.16823948	Yes
LOC100134713	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
XRCC2	Downregulated	-0.076650831	0.31185135	0.54244646	Yes	-0.1550928	0.14567116	0.23181326	Yes
ENAM	Downregulated	-0.34656096	0.16245548	0.36542614	Yes	-0.2776553	0.29379111	0.40038661	Yes

ABCA6	Downregulated	0.169684704	0.19912014	0.41420902	No	0.31781864	0.26624016	0.37121424	No
ITGA1	Downregulated	0.253629763	0.00799393	0.04793832	No	0.84493169	0.00000463	0.00012328	No
BRCA2	Downregulated	0.125532061	0.1169478	0.29719698	No	-0.0342477	0.82672704	0.87573457	Yes
TRPV4	Downregulated	0.34617083	0.05723992	0.18577765	No	0.35008133	0.09419453	0.16441505	No
TLCD2	Downregulated	#N/A	#N/A	#N/A	#N/A	0.62003962	0.0003479	0.00312809	No
KIF2C	Downregulated	0.25555144	0.0033276	0.02569988	No	-0.2728141	0.01173819	0.03374971	Yes
ANKRD1	Downregulated	0.005715605	0.97481874	0.98973165	No	-0.6281484	0.01177182	0.03382024	Yes
PRH2	Downregulated	0.060600551	0.54765199	0.74258096	No	-0.4690218	0.0030482	0.01381364	Yes
BHMT	Downregulated	-0.219494478	0.05084864	0.17162426	Yes	-0.4088881	0.05255489	0.10451743	Yes
NOTUM	Downregulated	0.013520039	0.92387194	0.96709369	No	0.10877871	0.49778003	0.6002211	No
C6orf132	Downregulated	-0.175871366	0.37587525	0.60359506	Yes	-0.5184683	0.0132741	0.03691878	Yes
PKD1L1	Downregulated	-0.057229187	0.52213128	0.72374897	Yes	0.10338103	0.43152601	0.53886146	No
BDKRB2	Downregulated	0.025848342	0.83552729	0.92158101	No	-0.5295624	0.0319183	0.07114278	Yes
CEP55	Downregulated	0.745833654	0.01166482	0.06249668	No	-0.1985305	0.5054676	0.60717723	Yes
C2orf65	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CCDC144A	Downregulated	-0.065981644	0.64171068	0.80671349	Yes	-0.4503984	0.00154911	0.00897278	Yes
MOV10L1	Downregulated	-0.247515979	0.00352517	0.02673561	Yes	-0.4184437	0.00034507	0.00310822	Yes
PIWIL2	Downregulated	0.149034685	0.15193784	0.35102728	No	-0.2124652	0.24621768	0.34919146	Yes
LOC100505806	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TGFBI	Downregulated	0.572398101	0.00014216	0.00275852	No	0.93922516	0.00157094	0.00905937	No
MCM10	Downregulated	0.363867767	0.06373732	0.19961471	No	-0.442283	0.02285618	0.05511738	Yes
LOC100132774	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PTPN14	Downregulated	0.00974174	0.84205285	0.92508164	No	0.03485631	0.65675077	0.73990292	No

CAV2	Downregulated	0.370307243	0.00015196	0.00289978	No	0.34879071	0.00827236	0.02645205	No
LOC388692	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FLJ35024	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FLJ12334	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PLIN4	Downregulated	0.536167092	0.0000265	0.00082989	No	0.77327694	0.00000383	0.00010756	No
CTSW	Downregulated	0.130069947	0.30971888	0.5401898	No	0.06920708	0.67638101	0.75580294	No
ABCA17P	Downregulated	-0.122197239	0.08923228	0.24915811	Yes	-0.4032236	0.00021125	0.00216147	Yes
KIAA0101	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.1424097	0.31817471	0.42632511	Yes
LDHAL6A	Downregulated	-0.210421049	0.02941932	0.11933804	Yes	0.10636575	0.51508489	0.61605117	No
FKBP9L	Downregulated	-0.249818132	0.16455213	0.36811339	Yes	-0.1022334	0.22619398	0.32693829	Yes
HTR4	Downregulated	-0.389086671	2.89E-07	0.0000343	Yes	-0.6643339	0.00206935	0.01080862	Yes
LINC00482	Downregulated	0.306321379	0.17008164	0.37562854	No	0.30832941	0.18744608	0.28231345	No
ANKFN1	Downregulated	0.396045488	0.0000184	0.0006347	No	0.5672367	0.00355126	0.01521471	No
MYH15	Downregulated	0.220584973	0.00811937	0.04846088	No	-0.2602076	0.07940958	0.14401381	Yes
TOB2P1	Downregulated	0.489579169	0.04286252	0.15384556	No	0.4850618	0.06373721	0.12144826	No
EXPH5	Downregulated	0.186937965	0.02129622	0.09551452	No	-0.0412739	0.7999335	0.85469629	Yes
AGAP11	Downregulated	0.864047275	0.0018514	0.01694835	No	0.37323727	0.00398997	0.01643262	No
ESPL1	Downregulated	0.564588644	0.00243342	0.02069876	No	0.00307416	0.98732178	0.99136094	No
METTL7A	Downregulated	0.385085579	0.0000307	0.00091956	No	0.75299568	3.76E-07	0.0000199	No
IFI44L	Downregulated	0.635962755	0.00012198	0.00247183	No	0.35317499	0.18711316	0.28196908	No
NFIB	Downregulated	0.077379656	0.12130823	0.30434509	No	0.12706723	0.12827867	0.20968965	No
COL8A1	Downregulated	0.268748804	0.10804386	0.28259228	No	1.09134822	0.000015	0.00029754	No
PI16	Downregulated	0.711770709	1.63E-08	0.00000426	No	0.4150814	0.10352372	0.17704645	No

NR5A2	Downregulated	-0.069791397	0.69385965	0.84150021	Yes	0.14330863	0.66227951	0.74453283	No
KIF23	Downregulated	-0.010873932	0.894795	0.95265083	Yes	-0.3050689	0.03635925	0.0786364	Yes
MYO15A	Downregulated	-0.119614971	0.1949478	0.40931426	Yes	-0.4882674	0.00079319	0.00566628	Yes
RFX8	Downregulated	-0.336991798	0.00890359	0.05169486	Yes	-0.6417171	0.00190484	0.01025058	Yes
BLM	Downregulated	0.050244515	0.43532268	0.6565477	No	0.03052953	0.76831195	0.82951863	No
ABI3BP	Downregulated	0.288713357	0.01170397	0.06266128	No	0.65012999	0.00119281	0.00752586	No
RAC2	Downregulated	0.26952303	0.05675885	0.18481685	No	0.62235726	0.00383128	0.01600654	No
LOC729020	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FLJ41484	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
COLEC10	Downregulated	-0.42357306	0.00349445	0.02658732	Yes	-0.5636567	0.03721447	0.08001427	Yes
ANGPT1	Downregulated	0.813578885	1.33E-08	0.0000036	No	1.10985855	4.76E-08	0.00000511	No
PRDM6	Downregulated	0.31136898	0.00787266	0.04752649	No	0.4010766	0.0616071	0.11826356	No
PRELID2	Downregulated	0.067155606	0.36778807	0.59570584	No	-0.3313952	0.00294021	0.01350031	Yes
ACSL5	Downregulated	0.308553723	0.00066197	0.00819389	No	0.94731079	0.00000234	0.0000749	No
FRK	Downregulated	0.212916905	0.02280722	0.09996825	No	0.04745613	0.78397364	0.84216693	No
HCG25	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.1515446	0.00546804	0.02011453	Yes
LRRC2	Downregulated	-0.370908864	0.0000526	0.00135501	Yes	-0.8593104	0.0000194	0.00035917	Yes
PARPBP	Downregulated	-0.141118741	0.24213889	0.46623614	Yes	-0.4110141	0.0050625	0.01914371	Yes
ACY1	Downregulated	-0.036667871	0.7264273	0.86101832	Yes	-0.2485199	0.0000547	0.00079297	Yes
GRB7	Downregulated	-0.490017319	0.00343151	0.02623149	Yes	-0.9025985	0.00055396	0.00439378	Yes
AOX1	Downregulated	0.273270371	0.00719292	0.04458601	No	0.5727228	0.00380514	0.01593865	No
FANCD2	Downregulated	-0.010997877	0.90530078	0.95821813	Yes	-0.3260548	0.00505954	0.0191358	Yes
COL12A1	Downregulated	-0.426056555	5.09E-07	0.0000512	Yes	-0.3388025	0.02849707	0.06520634	Yes

MGC23270	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CHEK2	Downregulated	0.292374489	0.00029784	0.00469661	No	0.08172569	0.33274563	0.4412025	No
BMPER	Downregulated	-0.366743485	5.86E-07	0.0000566	Yes	-0.5721475	0.00069195	0.00515777	Yes
ACRC	Downregulated	#N/A	#N/A	#N/A	#N/A	0.08552027	0.59476482	0.6871339	No
PKN3	Downregulated	0.458563883	0.00042168	0.00598738	No	0.59197088	0.0000543	0.00078917	No
CLEC14A	Downregulated	0.229789335	0.04141246	0.15033655	No	0.62907011	0.00032848	0.00299553	No
LOC100128788	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
JPH2	Downregulated	0.404560192	0.01673533	0.08074913	No	0.73579975	0.00278382	0.01305423	No
IGF1	Downregulated	-0.341887243	0.00182068	0.01674794	Yes	-1.0951469	0.0000113	0.00023956	Yes
IGFBP3	Downregulated	0.07932602	0.52638106	0.72735526	No	0.17348572	0.390947	0.49983	No
MBOAT1	Downregulated	0.580790458	0.0000826	0.00187818	No	0.22462506	0.29859251	0.40555222	No
EFCAB5	Downregulated	-0.067428958	0.35421353	0.58274036	Yes	-0.3350828	0.00034404	0.00310093	Yes
FAM160A1	Downregulated	-0.124950025	0.10709558	0.28113332	Yes	-0.4598102	0.02475754	0.05861574	Yes
KLHL30	Downregulated	0.307810715	0.13131319	0.31962167	No	0.06010002	0.80926669	0.86211689	No
ARHGAP9	Downregulated	0.136360568	0.1053994	0.27836119	No	0.21013096	0.0496282	0.10000252	No
ANPEP	Downregulated	0.543337335	0.00151542	0.01470249	No	0.61274097	0.00211331	0.01095933	No
DENND2C	Downregulated	0.101975076	0.16643883	0.3706301	No	-0.2001439	0.04732846	0.09644646	Yes
TRPC4	Downregulated	-0.039593746	0.588744	0.77055203	Yes	0.36662711	0.02508863	0.05918517	No
FLJ31813	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC100129845	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LINC00312	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.2163074	0.15522755	0.24351602	Yes
RAD51	Downregulated	0.043328661	0.66929977	0.82516172	No	-0.0180428	0.84450348	0.88934057	Yes
PABPC4L	Downregulated	0.548264576	0.00011168	0.00232521	No	0.83493972	0.00021102	0.00215958	No

CNTD2	Downregulated	-0.138167163	0.4037768	0.62879306	Yes	-0.2504342	0.14449673	0.23026464	Yes
MARK2P9	Downregulated	-0.186295393	0.34438406	0.57383233	Yes	0.09979547	0.72164853	0.79270727	No
HERC2P3	Downregulated	0.306506634	0.03550449	0.13577204	No	1.29436192	0.00000284	0.000086	No
CYP2A6	Downregulated	-0.087854716	0.39744574	0.62285042	Yes	0.1535068	0.34692272	0.45571971	No
STARD13	Downregulated	-0.072777674	0.08850343	0.24799255	Yes	0.19044641	0.02345898	0.05621122	No
GHRLOS	Downregulated	-0.056894894	0.59028096	0.77176353	Yes	-0.0335528	0.83620661	0.88288774	Yes
GSG1	Downregulated	-0.17981454	0.04100725	0.14935124	Yes	-0.9371047	1.62E-08	0.00000245	Yes
SLC26A4	Downregulated	-0.365777142	0.00017968	0.00326343	Yes	-0.5694823	0.00119418	0.00753162	Yes
SHCBP1	Downregulated	-0.098924572	0.42728364	0.64967243	Yes	-0.4333351	0.00166204	0.00939938	Yes
CXorf69	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
COL7A1	Downregulated	0.166070805	0.02431214	0.10433586	No	0.15642997	0.2522435	0.35596994	No
MYLK3	Downregulated	0.559444393	0.01177504	0.06291608	No	-0.5416361	0.02288894	0.055163	Yes
LOC731275	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
C19orf40	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.2164986	0.10481713	0.1787923	Yes
ALS2CL	Downregulated	-0.208243703	0.0163102	0.07937394	Yes	-0.0847548	0.49569155	0.59820736	Yes
ENTPD3-AS1	Downregulated	0.096112061	0.07136178	0.21516983	No	-0.0399489	0.61868087	0.70731272	Yes
CLCNKB	Downregulated	0.050879152	0.7841521	0.89419593	No	0.18239129	0.40847373	0.51681178	No
FAM53A	Downregulated	0.161296194	0.08901321	0.24885145	No	-0.1922846	0.23514231	0.33693801	Yes
LOC100133315	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SLC35F2	Downregulated	0.216627834	0.00137622	0.01374557	No	-0.022142	0.79618332	0.85164503	Yes
CLDN2	Downregulated	0.050747553	0.722733	0.85887057	No	0.01830688	0.93817083	0.95687727	No
TNFAIP8	Downregulated	0.466064102	0.0000953	0.00208039	No	0.31077337	0.09407953	0.16427089	No
FLJ32224	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

VTCN1	Downregulated	-0.039679593	0.86763035	0.93906072	Yes	-0.4921044	0.03106122	0.06969214	Yes
LYN	Downregulated	0.401002571	0.00000814	0.0003625	No	0.54309639	0.00277367	0.01302194	No
TSHZ2	Downregulated	-0.110831824	0.16629228	0.37037911	Yes	-0.4009632	0.01413423	0.0385771	Yes
TM6SF2	Downregulated	-0.271785273	0.15461781	0.3548627	Yes	-0.4032964	0.00130784	0.0080114	Yes
ETS1	Downregulated	0.262183571	0.00118522	0.01235093	No	0.66704591	0.00000138	0.0000509	No
LOC100101266	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ZNF90	Downregulated	0.089392939	0.3453455	0.57465224	No	-0.2816599	0.01008363	0.03033467	Yes
NME9	Downregulated	-0.129783577	0.00427938	0.03065096	Yes	-0.3600219	0.00000201	0.0000674	Yes
UNC13D	Downregulated	0.422641361	0.0000146	0.00054514	No	0.07069244	0.63258448	0.71923123	No
ANKRD18B	Downregulated	-0.150519202	0.16683137	0.37111228	Yes	-0.6010988	0.00036196	0.00322282	Yes
EBLN2	Downregulated	0.154952423	0.12288553	0.30674103	No	0.71585532	0.0000405	0.00063082	No
TP53TG5	Downregulated	0.040584491	0.49424934	0.70335634	No	-0.1498552	0.44994474	0.55605814	Yes
DAPK2	Downregulated	0.087722021	0.2762465	0.5049198	No	-0.4065328	0.00409842	0.01671752	Yes
HELB	Downregulated	0.169064294	0.06766727	0.20783713	No	0.83758198	0.0000079	0.00018212	No
ORC1	Downregulated	0.070151672	0.55100044	0.74512474	No	-0.1547626	0.35368005	0.46266682	Yes
SEPT7L	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
DLEU2	Downregulated	0.046979455	0.51934133	0.72175323	No	-0.1437891	0.23655906	0.338507	Yes
PPP1R13L	Downregulated	0.648254682	1.79E-07	0.0000239	No	0.34218405	0.01129987	0.03282479	No
NUDT13	Downregulated	-0.019443676	0.78139852	0.89263924	Yes	0.07331666	0.40462935	0.51327556	No
MMP12	Downregulated	0.226268555	0.60325057	NA	No	-0.2470884	0.19233488	0.28818187	Yes
NOS3	Downregulated	0.584979467	0.00027786	0.00447243	No	0.71044993	0.0000878	0.00112322	No
CEP128	Downregulated	0.130623003	0.00837742	0.04953369	No	-0.0455905	0.70601634	0.78000766	Yes
BCL2L15	Downregulated	-0.216235236	0.02823164	0.11592595	Yes	-0.3313353	0.01162118	0.03351083	Yes

RPS10P7	Downregulated	0.295860478	0.0011708	0.01225657	No	0.29141734	0.05947222	0.11515256	No
LOC100506068	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GYPC	Downregulated	0.636840646	5E-11	7.91E-08	No	0.38437616	0.0112253	0.03266927	No
AGMAT	Downregulated	-0.147012196	0.04856779	0.16687866	Yes	-0.6903174	0.0000154	0.00030276	Yes
CCRL1	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TDRD6	Downregulated	-0.111195481	0.10598714	0.27926923	Yes	-0.1289657	0.22953395	0.33081463	Yes
SLC19A3	Downregulated	0.299143906	0.00089872	0.010173	No	0.43688015	0.0054888	0.02017226	No
WDR65	Downregulated	-0.107595603	0.38300654	0.61003946	Yes	-0.3916993	0.0000703	0.00095187	Yes
MYOM3	Downregulated	0.727324554	0.01087747	0.05961713	No	0.43174182	0.1789031	0.27218929	No
SLC17A9	Downregulated	0.377195235	0.00240604	0.02053027	No	0.54820304	0.00019	0.00199461	No
DHRS3	Downregulated	0.295921536	0.00019628	0.00347133	No	0.46312062	0.00040599	0.00350731	No
MATN1	Downregulated	0.044876891	0.75140749	0.87553863	No	-0.1019114	0.58535371	0.67870696	Yes
BTN3A2	Downregulated	0.433080061	0.0000617	0.00152456	No	0.26371309	0.08164666	0.1469429	No
TBX2	Downregulated	0.576244128	0.0000374	0.00105186	No	0.48931831	0.00122721	0.00766316	No
CD37	Downregulated	0.489636458	1.33E-07	0.0000192	No	0.39612239	0.00919466	0.02843988	No
PCDHGB3	Downregulated	0.063534403	0.38188619	0.60904733	No	0.28363324	0.00034328	0.00309556	No
MKI67	Downregulated	0.772663199	0.00855287	0.05022679	No	-0.3361862	0.23890724	0.34113173	Yes
FAIM3	Downregulated	0.560660962	0.01875323	0.08754736	No	0.27217218	0.27590103	0.38152809	No
LOC100128881	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
DNAH12	Downregulated	0.341771063	0.00786908	0.04751244	No	-0.1342593	0.47818962	0.58212573	Yes
SYPL2	Downregulated	0.147439329	0.2091435	0.42714396	No	0.54465357	0.00211774	0.01097671	No
HLA-DPA1	Downregulated	#N/A	#N/A	#N/A	#N/A	0.67624782	0.00621029	0.02189405	No
ABCA10	Downregulated	-0.280749122	0.0012907	0.01315443	Yes	-0.4813228	0.00002	0.00036825	Yes

MSH5-SAPCD1	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.4169418	0.0000413	0.00063954	Yes
PCOLCE2	Downregulated	0.114704699	0.32688757	0.55701493	No	0.29679808	0.09103805	0.16004798	No
SNORA48	Downregulated	NA	NA	NA	#N/A	0.79333057	0.0000593	0.00084341	No
EFCAB6	Downregulated	-0.092362833	0.04814859	0.16583074	Yes	-0.4553084	0.0000285	0.00048186	Yes
SYNPO2	Downregulated	0.038515185	0.56495988	0.75491084	No	-0.0327629	0.74217363	0.80883159	Yes
PRO0611	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MPP4	Downregulated	-0.240247782	0.01438829	0.07261605	Yes	-0.4209466	0.00692094	0.02353096	Yes
MELK	Downregulated	0.704176886	0.00715539	0.04441138	No	-0.0852369	0.75913227	0.82242648	Yes
CASS4	Downregulated	0.278568054	0.01696439	0.08163155	No	0.62566391	0.00286929	0.01330294	No
C3orf35	Downregulated	-0.159073422	0.05135363	0.17261302	Yes	-0.2065849	0.16892076	0.26005557	Yes
ITIH2	Downregulated	0.267632537	0.02486696	0.10602119	No	0.5002047	0.01207242	0.03446366	No
SLC2A9	Downregulated	0.378856379	1.26E-07	0.0000186	No	0.44131472	0.00309033	0.01393596	No
LOC641298	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
KCNAB3	Downregulated	-0.179677391	0.05191176	0.17389753	Yes	-0.5904215	0.00040799	0.00351754	Yes
INPP4B	Downregulated	-0.052178797	0.3165664	0.54698217	Yes	-0.1182981	0.22734107	0.32818011	Yes
SYT15	Downregulated	-0.161702289	0.11005279	0.28628812	Yes	-0.1030697	0.32319711	0.43138338	Yes
ITGB3	Downregulated	0.185753531	0.16369104	0.36696572	No	0.59597938	0.00052132	0.00420647	No
CCDC33	Downregulated	0.477484604	0.07711777	0.2261573	No	-0.3382672	0.21360926	0.31298446	Yes
ENPP3	Downregulated	-0.086556043	0.30960644	0.54006816	Yes	-0.2993887	0.0132712	0.03691254	Yes
PVRL4	Downregulated	-0.496166947	0.16226278	NA	Yes	-0.4499596	0.05886646	0.11421764	Yes
NOXRED1	Downregulated	0.077452902	0.29658826	0.52638349	No	-0.0376261	0.74558259	0.81174086	Yes
SIX1	Downregulated	0.821725449	0.00060391	0.00770961	No	0.97177496	0.00399969	0.01645561	No
LOC100268168	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

LOC389641	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
COL4A3	Downregulated	0.001492851	0.98637232	0.99459722	No	0.61293923	0.00044441	0.00375148	No
SLC7A5P2	Downregulated	NA	NA	NA	#N/A	0.45014331	0.00092916	0.00632326	No
SHOX2	Downregulated	1.051705233	0.00797641	0.04789379	No	-0.3143182	0.21683387	0.31665242	Yes
MSLN	Downregulated	0.058258217	0.6933933	0.84106901	No	-0.3642396	0.15710387	0.24575606	Yes
FOXH1	Downregulated	-0.147843427	0.5090624	0.714057	Yes	-0.1891229	0.07811841	0.14220412	Yes
C1orf38	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ADAP2	Downregulated	0.327608649	0.00014828	0.00285104	No	0.12856467	0.33179095	0.44015647	No
EMP2	Downregulated	0.487815798	0.00000169	0.00012052	No	0.51067003	0.00142493	0.00849988	No
BMP3	Downregulated	-0.326703282	0.00586082	0.03832708	Yes	-0.7628843	0.00101024	0.00672168	Yes
DUOX1	Downregulated	0.105365111	0.13879676	0.33097483	No	-0.16417	0.193729	0.28978856	Yes
MYBL2	Downregulated	0.839603575	0.01428494	0.07219314	No	-0.3881085	0.19726178	0.29399182	Yes
FERMT3	Downregulated	0.425805198	0.0001062	0.00224857	No	0.42995009	0.00520852	0.01950082	No
RANBP3L	Downregulated	0.348576685	0.0000968	0.00210622	No	1.30136989	1.42E-08	0.00000227	No
USP18	Downregulated	0.131264416	0.17924935	0.38829004	No	0.15812768	0.09039374	0.15916606	No
LRRC8E	Downregulated	-0.136029462	0.70907934	NA	Yes	-0.2034865	0.31034677	0.41800793	Yes
FOXM1	Downregulated	0.275488032	0.00745506	0.04572552	No	-0.0714629	0.50463745	0.60645686	Yes
KANK4	Downregulated	0.251694246	0.05004534	0.1701685	No	0.17285231	0.44211038	0.54888235	No
ZNF587B	Downregulated	-0.005795234	0.93949943	0.97448104	Yes	-0.1413091	0.12599929	0.206703	Yes
RGPD3	Downregulated	-0.037061708	0.81868958	0.91384461	Yes	0.31770823	0.05426869	0.10714228	No
PTH1R	Downregulated	0.40631721	0.00038445	0.0056121	No	0.39323703	0.00545164	0.02007011	No
SLC28A3	Downregulated	0.135677417	0.51393882	0.7178648	No	0.14031535	0.59906434	0.69074016	No
MTMR11	Downregulated	0.258118496	0.00015527	0.00294812	No	0.38467603	0.00037407	0.00329906	No

ANKRD19P	Downregulated	-0.273231287	0.00449506	0.03179972	Yes	-0.2943972	0.05804222	0.11291308	Yes
WFIKKN1	Downregulated	0.128453185	0.32812401	0.5581212	No	-0.0443509	0.77033221	0.83126522	Yes
LOC729799	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CDH15	Downregulated	0.065038439	0.82551184	0.9168739	No	-0.6684972	0.03085305	0.0693255	Yes
ADAM12	Downregulated	0.268422465	0.00076616	0.00904187	No	0.84924591	2.57E-07	0.0000153	No
CCDC88B	Downregulated	0.303485944	0.00224333	0.01949904	No	-0.0133338	0.90932431	0.93617236	Yes
HR	Downregulated	0.015882296	0.86366571	0.93717496	No	-0.4208683	0.0000403	0.00062798	Yes
FAM194A	Downregulated	-0.156563878	0.17725388	0.38544138	Yes	-0.446269	0.00536347	0.01987013	Yes
NPEPL1	Downregulated	0.124312118	0.12308471	0.30708704	No	0.04465848	0.67452632	0.75435031	No
ATP8B4	Downregulated	0.152408537	0.06225287	0.19653513	No	-0.093771	0.53602156	0.63484118	Yes
RNF125	Downregulated	0.316569621	0.00042334	0.0060042	No	-0.02442	0.89946743	0.9292158	Yes
CASQ1	Downregulated	-0.34123449	0.00064594	0.00807268	Yes	-0.5978553	0.00061308	0.00473117	Yes
FAM65C	Downregulated	#N/A	#N/A	#N/A	#N/A	0.73024089	0.00022906	0.00229411	No
CLSPN	Downregulated	-0.400963308	0.0000554	0.00141284	Yes	-0.6005544	0.00621226	0.02189724	Yes
DMC1	Downregulated	0.065104313	0.55637545	0.74884478	No	-0.259804	0.0945241	0.16486128	Yes
POLN	Downregulated	-0.046355298	0.43365828	0.65503711	Yes	0.05803277	0.5176141	0.61835987	No
C8orf73	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
IL17RA	Downregulated	0.28084079	0.00033967	0.00513006	No	0.31475511	0.00157222	0.00906363	No
NEB	Downregulated	0.121114751	0.16450196	0.36806213	No	0.04396244	0.71556768	0.78796816	No
CASP8	Downregulated	0.103340561	0.11024716	0.28649793	No	0.0751072	0.48385934	0.58719444	No
C2	Downregulated	#N/A	#N/A	#N/A	#N/A	0.16048632	0.25838	0.36259433	No
SOX6	Downregulated	0.125726648	0.01073807	0.05914274	No	0.18641641	0.06813058	0.12792782	No
RBL1	Downregulated	0.175351835	0.00059502	0.00762699	No	0.40956481	0.0302825	0.06833263	No

SECTM1	Downregulated	0.775217907	0.00075337	0.00893821	No	0.3997135	0.15761129	0.24640465	No
RRN3P2	Downregulated	0.209806145	0.02097822	0.09455022	No	0.10099818	0.25731981	0.36141581	No
FOXP3	Downregulated	0.137267316	0.324171	0.55441537	No	-0.2879417	0.00012018	0.0014227	Yes
GINS4	Downregulated	0.28506035	0.00383393	0.02833198	No	0.05720154	0.73813256	0.80584518	No
CNTD1	Downregulated	0.059637953	0.41974605	0.6428955	No	-0.2794608	2.29E-08	0.00000312	Yes
LINC00471	Downregulated	0.065695322	0.4936506	0.70275004	No	-0.5194196	0.00095847	0.00647138	Yes
ZNF69	Downregulated	0.12171204	0.08957582	0.24967031	No	0.22973387	0.0856032	0.15250805	No
C22orf43	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.1644607	0.3560488	0.46520884	Yes
CD4	Downregulated	0.354060454	0.000012	0.00047327	No	0.27508899	0.10303593	0.17643182	No
LOC100287036	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
IFI16	Downregulated	0.348930115	0.00071205	0.00858214	No	0.71878821	0.00000812	0.00018546	No
ARHGAP10	Downregulated	0.172129351	0.00300207	0.02393344	No	-0.0578203	0.61733906	0.70621795	Yes
TBC1D3P1-DHX40P1	Downregulated	0.062151996	0.98154124	NA	No	0.25799725	0.00290103	0.01339766	No
MYBPHL	Downregulated	-0.126458862	0.19905655	0.41413305	Yes	-0.0790547	0.62950492	0.7167747	Yes
ECT2L	Downregulated	-0.01430191	0.86537636	0.93795854	Yes	-0.317914	0.00666574	0.02294165	Yes
FGF1	Downregulated	0.482027151	0.00000135	0.00010276	No	0.15412426	0.32280788	0.43096704	No
3-Mar	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PPARG	Downregulated	0.08882323	0.16681695	0.37110196	No	-0.3034448	0.00606784	0.02156802	Yes
NLRP1	Downregulated	-0.073235562	0.28270562	0.5119428	Yes	-0.468485	0.0000259	0.00044984	Yes
LOC284454	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ALDH3B1	Downregulated	0.324981488	0.0000573	0.00144816	No	-0.0073578	0.94946707	0.96522055	Yes
KL	Downregulated	-0.08735626	0.43424804	0.65556064	Yes	-0.0469274	0.72337464	0.79409948	Yes
SUSD2	Downregulated	0.377674598	0.01640525	0.07965649	No	0.21929886	0.29914498	0.40618385	No

IRF7	Downregulated	0.455836318	0.0000109	0.00044146	No	0.65147328	0.0000257	0.0004464	No
MXRA5	Downregulated	0.15439467	0.28323112	0.51255205	No	0.3798021	0.08401688	0.15023878	No
KCNJ2	Downregulated	0.372893192	0.0000213	0.00070748	No	0.33446293	0.09055791	0.15939976	No
LOC100130093	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PGM5P2	Downregulated	0.008136071	0.91514384	0.96321047	No	0.15079638	0.27622264	0.38186679	No
TMOD4	Downregulated	NA	NA	NA	#N/A	0.32736703	0.02903124	0.06613149	No
PKDREJ	Downregulated	0.214896078	0.13127594	0.31957199	No	0.24468896	0.31735036	0.42547796	No
DKFZP564C196	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
HLA-DMA	Downregulated	#N/A	#N/A	#N/A	#N/A	0.28621011	0.05489072	0.10807567	No
LRRC70	Downregulated	0.030655125	0.79494696	0.90080065	No	0.39958468	0.01305965	0.03649529	No
TMPRSS9	Downregulated	0.026125794	0.81055404	0.90965969	No	-0.6548843	1.44E-07	0.0000105	Yes
MICALCL	Downregulated	0.044083916	0.79883151	0.90336842	No	-0.221236	0.23395244	0.33560389	Yes
DEPDC1	Downregulated	-0.124614918	0.27811683	0.50715169	Yes	-0.8426	0.0000162	0.00031542	Yes
COL15A1	Downregulated	0.382672533	0.00259527	0.02162454	No	0.40931731	0.03234878	0.0718982	No
MUC5B	Downregulated	0.189010827	0.25445686	0.48105478	No	0.00931995	0.96969668	0.97944618	No
FAM18B2	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
WDR76	Downregulated	0.273214706	0.00012389	0.00249586	No	0.10329097	0.30189488	0.40916472	No
ITGA5	Downregulated	0.433714586	0.00015488	0.00294501	No	1.08198323	5.41E-08	0.00000549	No
IRF1	Downregulated	0.592340203	1.71E-07	0.0000234	No	0.45428182	0.00539366	0.01994223	No
DGKH	Downregulated	-0.171338598	0.00183602	0.01683198	Yes	-0.3233259	0.00052658	0.00423911	Yes
NUDT4	Downregulated	-0.106708144	0.04243896	0.15283232	Yes	-0.0836335	0.41882334	0.52675675	Yes
GBP1	Downregulated	0.939389988	3.25E-09	0.0000014	No	0.86957664	0.0001125	0.00135417	No
SLC28A2	Downregulated	-0.077904548	0.67021706	0.82570443	Yes	-0.2767312	0.16133544	0.25083428	Yes

TNFRSF10A	Downregulated	0.389483063	0.00474175	0.03310065	No	1.1077883	5.06E-07	0.0000244	No
BMP6	Downregulated	0.351899915	0.00783076	0.04731869	No	1.14967971	0.00000781	0.00018063	No
HLA-L	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.0898326	0.22647038	0.32719431	Yes
CSGALNACT1	Downregulated	0.085194169	0.04775217	0.1649573	No	0.3150539	0.00317365	0.01414446	No
ESCO2	Downregulated	0.118561465	0.28173764	0.51101889	No	-0.7125855	0.00018387	0.00195089	Yes
HEATR4	Downregulated	0.02659937	0.63466516	0.8010669	No	-0.1508987	0.056748	0.11094504	Yes
LOC729177	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
KIF15	Downregulated	0.054858417	0.40310401	0.62820931	No	-0.0213855	0.817423	0.8683669	Yes
DNAH17	Downregulated	0.315401933	0.00300974	0.023968	No	-0.1281589	0.44900327	0.55518997	Yes
APOL6	Downregulated	0.538399454	0.00000112	0.0000911	No	0.81002459	0.000037	0.00058891	No
LOC387723	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FAM54A	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC100129858	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CHRNA10	Downregulated	-0.123840042	0.31058549	0.54103	Yes	-0.158077	0.41304073	0.52130065	Yes
EMX2	Downregulated	0.411941141	0.02305081	0.10066394	No	0.79038801	0.0000146	0.00029194	No
LRRK2	Downregulated	-0.112319429	0.08745497	0.2459262	Yes	0.13188526	0.22076257	0.32091037	No
PCDHB19P	Downregulated	-0.145422246	0.05798182	0.18724393	Yes	0.42195841	0.00594744	0.02127628	No
LINC00173	Downregulated	0.196136696	0.03542656	0.13556963	No	-0.217778	0.15394506	0.24189999	Yes
RELL1	Downregulated	0.520003439	2.86E-08	0.00000639	No	1.48743223	1.31E-10	1.33E-07	No
ASB3	Downregulated	-0.028840076	0.53900712	0.73656931	Yes	0.37751628	2.89E-07	0.0000165	No
GALNTL2	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
AGPAT9	Downregulated	0.000115045	0.99915373	0.99968051	No	-0.5471479	0.00258286	0.012435	Yes
WDR62	Downregulated	0.115383703	0.2348258	0.45761853	No	-0.1053822	0.4121372	0.52034876	Yes

GRAMD2	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.0040292	0.97729284	0.98497749	Yes
OTOGL	Downregulated	-0.580165101	0.00000038	0.0000413	Yes	-0.5858493	0.00219045	0.01122168	Yes
ANGPTL4	Downregulated	0.245538496	0.15873988	0.36024955	No	1.22817476	0.00000634	0.00015518	No
LCNL1	Downregulated	0.290807465	0.01072671	0.05911448	No	0.47618656	0.01040342	0.03099606	No
SNORD116-20	Downregulated	NA	NA	NA	#N/A	0.55873804	0.00178452	0.00984152	No
BUB1	Downregulated	0.243430555	0.08831857	0.24762082	No	-0.3102743	0.14679484	0.23322865	Yes
DKK1	Downregulated	-0.140465983	0.29475551	0.524283	Yes	-0.4141237	0.00720049	0.02414425	Yes
DPF3	Downregulated	0.185130169	0.00561691	0.03726999	No	0.03381098	0.71232586	0.78540612	No
RGS5	Downregulated	0.196810544	0.04114975	0.14976962	No	0.36699698	0.0258652	0.06058394	No
EBF2	Downregulated	-0.176483979	0.3581613	0.58653739	Yes	-0.4066835	0.05010366	0.10076032	Yes
CENPF	Downregulated	-0.232562675	0.01385376	0.07064432	Yes	-0.5734957	0.00915908	0.02838336	Yes
PHACTR3	Downregulated	0.110815146	0.0615646	0.19515081	No	0.01113283	0.88691937	0.92025972	No
ITIH4	Downregulated	-0.016558941	0.89834904	0.95477415	Yes	-0.1597859	0.20119	0.29846609	Yes
RHBDL2	Downregulated	0.084995521	0.11048731	0.28681256	No	-0.126611	0.43080774	0.5381787	Yes
HSF4	Downregulated	-0.01154986	0.8597907	0.93532757	Yes	0.13271158	0.20973064	0.30846754	No
C21orf49	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.0095283	0.94640963	0.96291999	Yes
GTSE1	Downregulated	0.430201182	0.00955126	0.05445523	No	-0.3534848	0.07925388	0.14382993	Yes
KIAA1656	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PRIMA1	Downregulated	#N/A	#N/A	#N/A	#N/A	0.36051708	0.13029955	0.21231462	No
SLC25A34	Downregulated	0.084437555	0.32249518	0.55276982	No	0.07341905	0.50435294	0.60618027	No
COL4A4	Downregulated	0.077727694	0.33867065	0.56886042	No	0.6157636	0.00015836	0.00174871	No
C6orf163	Downregulated	-0.157040556	0.04983527	0.16968224	Yes	-0.0069783	0.95514118	0.96892185	Yes
MCM9	Downregulated	0.124200762	0.00314844	0.02471985	No	0.11102608	0.08816169	0.15611341	No

TOMM20L	Downregulated	0.051536369	0.68396993	0.83486829	No	-0.5261113	7.65E-10	3.91E-07	Yes
ZNF490	Downregulated	-0.061388592	0.18156752	0.39141278	Yes	0.02871253	0.65918444	0.74204082	No
CACNA2D3	Downregulated	-0.329683401	0.00000132	0.00010119	Yes	-0.4385997	0.00749673	0.02481109	Yes
IMPA2	Downregulated	0.23318238	0.00168323	0.01585639	No	0.47104378	0.00036473	0.00323976	No
RPL19P12	Downregulated	0.006239357	0.95463539	0.9817448	No	-0.3271435	0.00564731	0.02055442	Yes
LMOD1	Downregulated	0.38234129	0.00283249	0.02295141	No	0.33334813	0.06149514	0.11809923	No
CCDC163P	Downregulated	#N/A	#N/A	#N/A	#N/A	0.26743572	0.13260954	0.21534228	No
PHEX	Downregulated	0.365761732	0.0000105	0.00043084	No	0.43191931	0.0178325	0.04582518	No
KLRG1	Downregulated	0.046430166	0.51561536	0.71931432	No	-0.0657242	0.62959622	0.71681301	Yes
KIAA1462	Downregulated	-0.08737416	0.30552206	0.53557731	Yes	0.25241708	0.05445912	0.10745355	No
ERBB3	Downregulated	0.283495687	0.00467265	0.03270249	No	0.10528185	0.63512907	0.72137413	No
NFATC1	Downregulated	0.555632804	5.13E-08	0.00000984	No	0.18468642	0.13810807	0.22232225	No
MLN	Downregulated	0.145844942	0.51706757	0.72012266	No	0.04015723	0.88516171	0.91907758	No
OXT	Downregulated	-0.373861408	0.4429653	0.6630212	Yes	-0.4140732	0.13566738	0.21920338	Yes
TAGAP	Downregulated	-0.03335149	0.56539867	0.75513878	Yes	-0.0530247	0.65908678	0.74201354	Yes
LY6G5C	Downregulated	#N/A	#N/A	#N/A	#N/A	0.00964792	0.91860399	0.94300967	No
GP1BA	Downregulated	0.184771842	0.04188284	0.15146462	No	-0.0047399	0.96588333	0.97660325	Yes
SYCP2	Downregulated	0.03010014	0.70634016	0.84941419	No	0.07143665	0.33299409	0.44147191	No
C15orf42	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ZNF469	Downregulated	0.237432438	0.06010195	0.19181882	No	0.15018682	0.27905434	0.38495111	No
C3orf49	Downregulated	-0.184992925	0.0027127	0.0222695	Yes	-0.3376557	0.01902557	0.04808658	Yes
CCDC7	Downregulated	0.084657609	0.28234206	0.51167505	No	-0.1315434	0.10714064	0.18192635	Yes
KCNK6	Downregulated	0.170404725	0.02845041	0.11662241	No	-0.0824855	0.4553394	0.56109584	Yes

PKD1L3	Downregulated	0.055659301	0.5812002	0.76595281	No	-0.1636278	0.13356009	0.21658309	Yes
CEP152	Downregulated	0.07442241	0.33865291	0.56886042	No	0.31540776	0.0159747	0.04226801	No
KRT15	Downregulated	0.387401012	0.15704557	0.35787678	No	0.96338522	0.00180402	0.00990834	No
PLCB3	Downregulated	0.380772802	0.00015742	0.00297538	No	0.38561032	0.00026815	0.00257557	No
TAS2R20	Downregulated	0.025273886	0.82189086	0.9155869	No	0.13672415	0.45517692	0.56095762	No
KIAA1614	Downregulated	0.132682107	0.0498449	0.16969978	No	-0.1326413	0.12314313	0.20317809	Yes
MYO15B	Downregulated	0.395344742	0.0000319	0.00094696	No	0.11603289	0.4285052	0.5359415	No
ARHGAP31	Downregulated	0.360939169	0.00000867	0.00037982	No	1.01811804	3.97E-09	0.00000103	No
IZUMO4	Downregulated	0.115893195	0.11588562	0.29542738	No	-0.0564515	0.65529985	0.73865636	Yes
LOC221442	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
USP43	Downregulated	-0.208136729	0.00337534	0.02593271	Yes	-0.378239	0.00361484	0.01540423	Yes
PDE1A	Downregulated	-0.224683975	0.0232735	0.10134494	Yes	-0.7139314	0.0000381	0.00060198	Yes
ATP8B3	Downregulated	0.027496332	0.81785076	0.91321555	No	-0.2448696	0.11018545	0.18599194	Yes
BAIAP2L2	Downregulated	-0.075122797	0.39193822	0.61796375	Yes	-0.4450411	0.0000105	0.00022657	Yes
ABCC3	Downregulated	0.497113369	0.00025304	0.00418475	No	0.51022331	0.00773926	0.02533215	No
SPATA5	Downregulated	0.106608661	0.00810908	0.04842263	No	0.13754596	0.07933633	0.14394025	No
AGBL2	Downregulated	0.605367226	0.00026283	0.00429239	No	-0.0152121	0.94553017	0.96227258	Yes
FAM71F2	Downregulated	-0.124057283	0.14778496	0.34506493	Yes	0.08868885	0.50249044	0.60454369	No
CAPN3	Downregulated	0.352515986	0.00048584	0.00661628	No	0.09170644	0.66755974	0.74848096	No
RARB	Downregulated	-0.030863603	0.69901876	0.84468492	Yes	-0.2463133	0.06622645	0.12514479	Yes
PDGFRB	Downregulated	0.33239346	0.00046866	0.00646112	No	0.79196746	3.28E-07	0.000018	No
C10orf140	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GPR126	Downregulated	0.186549949	0.04666865	0.16256075	No	0.95672729	0.0000344	0.00055899	No

KRTAP5-7	Downregulated	-0.026699719	0.87108111	0.94055322	Yes	-0.6174012	0.00037955	0.00333419	Yes
RHOJ	Downregulated	0.125161563	0.09898264	0.2668409	No	0.84441656	4.41E-08	0.00000485	No
HERC2P7	Downregulated	0.147840016	0.9636985	NA	No	-0.2725465	0.18413153	0.27838922	Yes
SNX22	Downregulated	0.020063973	0.81317429	0.91104645	No	-0.1823553	0.05084702	0.10189872	Yes
RBMS3	Downregulated	0.172235925	0.00422651	0.03037551	No	0.31981112	0.00227015	0.0114807	No
NLRC3	Downregulated	-0.001359319	0.98074868	0.99199089	Yes	-0.2041104	0.02862357	0.06541929	Yes
GRIN2C	Downregulated	0.144035757	0.14489781	0.34087847	No	0.2508739	0.13067208	0.21281344	No
FAM129A	Downregulated	0.296353169	0.01106458	0.06027232	No	0.68981958	0.00082502	0.00582054	No
SH3D21	Downregulated	-0.111265254	0.22644981	0.44794268	Yes	0.16894712	0.10872803	0.18409475	No
TPTE2P1	Downregulated	-0.271923329	0.00044174	0.00619633	Yes	-0.676956	4.78E-07	0.0000233	Yes
NMI	Downregulated	0.369134525	0.0000428	0.00115891	No	0.54250185	0.0000292	0.00048991	No
UCP3	Downregulated	-0.068992023	0.47247131	0.68703024	Yes	-0.1446557	0.26552945	0.37041783	Yes
ADAMTS6	Downregulated	-0.081688342	0.293487	0.52298774	Yes	0.18017694	0.30769425	0.41533435	No
CFD	Downregulated	#N/A	#N/A	#N/A	#N/A	0.07013129	0.66196868	0.74426969	No
ARAP3	Downregulated	0.034783583	0.76663801	0.88467556	No	0.33552441	0.00228983	0.0115389	No
LOC439949	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CLMP	Downregulated	-0.008793316	0.91679584	0.96406698	Yes	0.12848643	0.520076	0.62055636	No
AFAP1L1	Downregulated	0.381750928	0.00028418	0.00454331	No	0.83429866	0.0000106	0.00022743	No
ABCA9	Downregulated	-0.020875033	0.8102376	0.90951932	Yes	0.00616761	0.95763035	0.97070457	No
LOC100506746	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
THSD4	Downregulated	0.30652174	0.01000556	0.05630948	No	0.90869582	0.00045632	0.00382593	No
RAB41	Downregulated	0.162300434	0.0409559	0.14920839	No	0.28301065	0.00590856	0.02117891	No
DUSP19	Downregulated	0.029658733	0.70100971	0.84603544	No	-0.2387369	0.05072685	0.10168349	Yes

DLC1	Downregulated	0.125692131	0.02283025	0.1000461	No	0.50406935	7.27E-08	0.0000067	No
LDB3	Downregulated	0.076118994	0.49088924	0.70068484	No	-0.6255398	0.01590602	0.04213314	Yes
LOC648809	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GSTM2P1	Downregulated	0.110325533	0.79297811	NA	No	0.09942957	0.71239963	0.78545687	No
PCDHB11	Downregulated	-0.005203989	0.92389656	0.96709369	Yes	0.55140166	0.00023632	0.00234741	No
LOC728377	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
RASA4	Downregulated	0.177449678	0.0942867	0.25817454	No	0.02326318	0.79148272	0.84801611	No
NPHP3	Downregulated	0.094104975	0.23257124	0.454917	No	0.09474061	0.43037906	0.53779057	No
LOC388849	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
E2F7	Downregulated	0.128112719	0.3023599	0.53223469	No	0.09509735	0.64555802	0.73040713	No
LOC619207	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
EHBP1L1	Downregulated	0.265457068	0.00162505	0.01547696	No	0.33135643	0.00036444	0.00323853	No
ABCA1	Downregulated	0.560290503	6.94E-10	4.47E-07	No	0.92564657	3.44E-08	0.00000414	No
MUC1	Downregulated	0.54352099	0.00016229	0.00304182	No	0.856342	0.00000298	0.0000894	No
PHACTR2	Downregulated	0.090467394	0.10718643	0.28125856	No	0.0763726	0.42813123	0.53560593	No
FMN1	Downregulated	-0.257498643	0.00423288	0.03040978	Yes	-0.4682806	0.00661431	0.02282776	Yes
CARNS1	Downregulated	0.27275724	0.04901262	0.16781461	No	-0.2367648	0.40023139	0.50906421	Yes
ATP2C2	Downregulated	-0.117558723	0.14685399	0.34371585	Yes	-0.3318028	0.00156086	0.00902252	Yes
STL	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
COL16A1	Downregulated	0.281475848	0.00072936	0.00873251	No	0.06113058	0.67485341	0.75459504	No
LAMA4	Downregulated	0.259961946	0.00071816	0.00863931	No	0.36880364	0.00067577	0.0050724	No
MND1	Downregulated	0.308071873	0.01387392	0.07069963	No	-0.1863143	0.41562726	0.52369974	Yes
GLI3	Downregulated	0.225125425	0.00902305	0.05221423	No	0.53300465	0.00071079	0.0052507	No

NFKBIZ	Downregulated	0.276688066	0.0056581	0.03746465	No	0.51008826	0.00020956	0.00214702	No
LOC100505894	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LMOD3	Downregulated	0.027834785	0.77134594	0.88718902	No	-0.4792226	0.00099882	0.00666949	Yes
CATSPER3	Downregulated	-0.040695533	0.77795179	0.89068339	Yes	0.05469229	0.56383797	0.65974166	No
LINC00174	Downregulated	0.066195349	0.37750421	0.60518162	No	-0.175358	0.20651005	0.30476097	Yes
DOCK5	Downregulated	0.322721403	0.00043478	0.00613221	No	0.47128832	0.03225996	0.07173225	No
NRXN3	Downregulated	-0.323079056	0.00010587	0.00224609	Yes	-0.945232	1.23E-08	0.00000209	Yes
ITGA10	Downregulated	0.417138799	0.00019453	0.003455	No	1.15305859	3.28E-09	9.39E-07	No
TTN	Downregulated	-0.059141683	0.4389731	0.65956393	Yes	-0.3061261	0.07982538	0.1444906	Yes
MYOZ3	Downregulated	-0.350792452	0.0000532	0.00136918	Yes	-0.8948707	0.00000161	0.0000569	Yes
TAS2R31	Downregulated	0.036384067	0.734245	0.86496787	No	0.17137179	0.42176231	0.52953926	No
IL27RA	Downregulated	0.187804038	0.06068417	0.19318964	No	0.20754234	0.0456256	0.09368339	No
SCARNA12	Downregulated	0.096502798	0.97629945	NA	No	0.47527579	0.00655083	0.02267152	No
PDE6C	Downregulated	0.025238137	0.79376968	0.90002667	No	0.07470008	0.57856177	0.67286074	No
OPLAH	Downregulated	0.377174701	0.00012398	0.00249632	No	0.32634581	0.01418904	0.03869299	No
NPR3	Downregulated	-0.124644127	0.22037528	0.4401808	Yes	-0.9469944	0.00020417	0.00210458	Yes
PRSS36	Downregulated	-0.019293503	0.86955027	0.93987899	Yes	-0.5928245	0.00000476	0.00012595	Yes
DPH3P1	Downregulated	NA	NA	NA	#N/A	-0.0572301	0.74137002	0.8083192	Yes
TAF1L	Downregulated	-0.255484617	0.19048272	0.40321905	Yes	-0.023757	0.87263751	0.90980352	Yes
KIAA1530	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
DOK3	Downregulated	0.234891143	0.01807751	0.08533753	No	0.26891431	0.03420798	0.07503366	No
LOC387646	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MIR940	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.4715933	0.00011118	0.00134439	Yes

HSPB6	Downregulated	0.374233693	0.00920827	0.05296116	No	0.22868352	0.09091297	0.15990862	No
P2RX5-TAX1BP3	Downregulated	-0.036537255	0.61376273	0.78712747	Yes	0.04837748	0.54402178	0.64202516	No
CENPN	Downregulated	0.121677787	0.0254719	0.10786127	No	-0.0153895	0.82047183	0.87080941	Yes
FBXO32	Downregulated	0.265662808	0.00019138	0.00341809	No	0.06917344	0.53001271	0.62936892	No
LOC285593	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
APOLD1	Downregulated	0.499569856	0.0021638	0.01897962	No	0.79266842	0.00000484	0.00012766	No
LRGUK	Downregulated	-0.217776887	0.00135864	0.01361655	Yes	0.0295223	0.8654702	0.90448458	No
CDCA7	Downregulated	0.201624921	0.0759586	0.22391709	No	0.01597874	0.91918059	0.94333574	No
IL1RAP	Downregulated	-0.031019416	0.6548608	0.81535951	Yes	0.20871929	0.16172016	0.25128527	No
NID1	Downregulated	0.286169079	0.00844441	0.0497992	No	1.04888786	1.34E-07	0.0000099	No
ATP2A1	Downregulated	0.018568665	0.86545945	0.93799848	No	-0.1785132	0.14019561	0.22494235	Yes
PCDH12	Downregulated	-0.00222126	0.96925577	0.98775497	Yes	0.01337384	0.8660876	0.90501106	No
EFNA4	Downregulated	0.315146705	0.00759512	0.04634486	No	0.52085652	0.00027495	0.00262366	No
SAMD9	Downregulated	0.195661647	0.04425223	0.15690854	No	0.68927488	0.00031214	0.00288287	No
ASF1B	Downregulated	0.26665871	0.03380027	0.1315181	No	0.01300431	0.94987631	0.96553095	No
ULK4	Downregulated	0.043272117	0.53359102	0.73267659	No	-0.1169679	0.30901893	0.41666886	Yes
CDC6	Downregulated	-0.167558695	0.05699423	0.18529714	Yes	-0.4670642	0.00036982	0.00326936	Yes
HSF2BP	Downregulated	-0.113502907	0.13815326	0.33011011	Yes	-0.1273549	0.30427434	0.41167484	Yes
RFTN2	Downregulated	0.351497372	0.0000409	0.00111803	No	0.59066739	0.00018321	0.00194458	No
MCC	Downregulated	0.235827456	0.00012082	0.00245747	No	0.3826532	0.00605981	0.02154651	No
C3orf32	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
HAR1A	Downregulated	-0.135821196	0.16069845	0.36294809	Yes	-0.7690718	0.00019738	0.00205274	Yes
TNFRSF25	Downregulated	-0.004819936	0.96340641	0.9860308	Yes	0.10694237	0.60119932	0.6926003	No

LOC100506649	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FLJ39653	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ADM2	Downregulated	0.116318103	0.66348338	0.82116507	No	0.67335449	0.0045327	0.0178228	No
KLHL34	Downregulated	-0.14898524	0.08972948	0.24995112	Yes	-0.0174338	0.92890223	0.95012421	Yes
MGC16275	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LTBR	Downregulated	0.543917387	0.00000126	0.000098	No	0.50408858	0.00013494	0.00155092	No
LAMA3	Downregulated	0.073080263	0.26307439	0.49096353	No	0.50276872	0.0000143	0.00028612	No
CORO6	Downregulated	-0.221308603	0.02437012	0.10449584	Yes	-0.165726	0.32000964	0.42819501	Yes
LOC100288846	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
C9orf100	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
JAK3	Downregulated	-0.040339956	0.70312196	0.84701398	Yes	-0.2125791	0.12395014	0.20417644	Yes
ANGPTL6	Downregulated	-0.156174761	0.13627758	0.32717307	Yes	-0.0931163	0.09084354	0.15982088	Yes
HSD17B11	Downregulated	-0.009361026	0.88525754	0.94820074	Yes	0.1664435	0.01926844	0.04858249	No
C16orf74	Downregulated	0.190360561	0.10270773	0.27363254	No	-0.2869981	0.03866416	0.08244873	Yes
CHDH	Downregulated	0.396704611	4.3E-08	0.00000872	No	0.54736641	0.00015577	0.00172669	No
ZHX2	Downregulated	0.277011111	0.00043778	0.00616123	No	0.42216977	0.0003206	0.00294142	No
ENPEP	Downregulated	0.167062188	0.21594376	0.43500502	No	0.47334036	0.03993073	0.08455027	No
LOC100507501	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MAK	Downregulated	-0.058097599	0.47428028	0.68836841	Yes	-0.016333	0.89228736	0.92417844	Yes
SLC39A11	Downregulated	#N/A	#N/A	#N/A	#N/A	0.49745423	0.00000995	0.00021709	No
LOC100506451	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ATG9B	Downregulated	-0.246302773	0.01960653	0.09035379	Yes	-0.0611253	0.50262964	0.60462542	Yes
UCKL1-AS1	Downregulated	0.246377866	0.04344544	0.15513484	No	#N/A	#N/A	#N/A	#N/A

MMS22L	Downregulated	0.149736614	0.0358685	0.1367644	No	-0.1713982	0.09411361	0.16430256	Yes
TMC3	Downregulated	-0.136077485	0.3102228	0.54067118	Yes	-0.7792366	0.0000315	0.00052043	Yes
GPR179	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.4325144	0.00456073	0.01789502	Yes
CCNE1	Downregulated	-0.107931747	0.10126165	0.27095916	Yes	-0.3913584	0.0000431	0.00066103	Yes
SARDH	Downregulated	0.074196404	0.45396324	0.67235262	No	0.13255598	0.33051544	0.43881935	No
ATHL1	Downregulated	0.508651728	0.00000963	0.00041057	No	0.66315224	0.0000854	0.00110149	No
PLEKHG4B	Downregulated	0.140514726	0.35324879	0.58175842	No	-0.2903796	0.18929211	0.28457872	Yes
ARHGEF26	Downregulated	0.339946552	1.38E-07	0.0000198	No	0.62616339	0.0000674	0.00092314	No
ALDH8A1	Downregulated	-0.145285907	0.19126252	0.40434932	Yes	-0.2795216	0.0759616	0.13914564	Yes
AMH	Downregulated	0.300286559	0.03160134	0.12544685	No	-0.2103727	0.26934213	0.37463989	Yes
MIR137HG	Downregulated	-0.34667905	0.00113611	0.01197776	Yes	-0.4760836	0.01378783	0.0379142	Yes
PIWIL4	Downregulated	0.02273285	0.66990131	0.82555472	No	-0.0233481	0.74401343	0.81044061	Yes
C5	Downregulated	0.208303272	0.00213787	0.01883493	No	0.04393463	0.70918851	0.7827058	No
CATSPER2	Downregulated	-0.216145635	0.01084281	0.05952957	Yes	-0.2506824	0.04319264	0.08989692	Yes
RNF144B	Downregulated	0.273934386	0.00259638	0.02162454	No	0.54128267	0.00036008	0.00320973	No
AIFM3	Downregulated	0.330873021	0.00048396	0.00660492	No	0.38284361	0.00450232	0.0177474	No
FAM186B	Downregulated	0.084735169	0.28015333	0.50940411	No	0.21831789	0.12302276	0.20300266	No
RAPGEF3	Downregulated	0.320882509	0.00026206	0.00428162	No	0.53667768	0.0003158	0.002908	No
TUBD1	Downregulated	0.101444744	0.04310135	0.15435995	No	0.02915807	0.6942227	0.7704895	No
GALNT6	Downregulated	0.280066994	0.02555708	0.10810136	No	-0.0193405	0.93681192	0.95589345	Yes
LOC389791	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ERBB4	Downregulated	-0.04935812	0.34308847	0.57242746	Yes	-0.0753755	0.42787479	0.53534517	Yes
LRP5L	Downregulated	0.116975913	0.10491207	0.27767312	No	0.0518963	0.63963142	0.72530587	No

C7orf10	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TPX2	Downregulated	-0.299467302	0.00037486	0.00551022	Yes	-0.5588601	0.0000177	0.00033583	Yes
C8orf51	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PFN1P2	Downregulated	-0.131315794	0.17435725	0.38167927	Yes	-0.146932	0.50057773	0.60278632	Yes
CCDC102B	Downregulated	-0.121310997	0.03772499	0.14138583	Yes	-0.3835596	0.0000615	0.00086447	Yes
PLB1	Downregulated	-0.011761703	0.8883715	0.94954102	Yes	-0.2379299	0.03905738	0.08310216	Yes
SNORD22	Downregulated	NA	NA	NA	#N/A	-0.4469963	0.00418091	0.01692643	Yes
SPHK1	Downregulated	0.724332644	9.18E-09	0.0000028	No	0.81006994	0.00016534	0.00180686	No
LGALS3	Downregulated	0.297107757	0.00182779	0.01677664	No	0.58997524	0.00057864	0.00453448	No
CYP20A1	Downregulated	0.298088974	0.00000136	0.00010282	No	0.16959982	0.08380111	0.14994431	No
FBXO36	Downregulated	0.084030246	0.13094677	0.31920179	No	0.08058832	0.38013396	0.48930532	No
ANO9	Downregulated	0.206240453	0.22002887	0.4397012	No	-0.0079032	0.9691654	0.97908043	Yes
GNN	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
AIM1	Downregulated	0.025722478	0.70361858	0.84748626	No	0.14668564	0.14798926	0.23465829	No
CD27	Downregulated	0.111501435	0.38133906	0.60850716	No	0.0395904	0.68418552	0.76226292	No
RPL23AP64	Downregulated	0.02706184	0.78765964	0.89647744	No	0.02281981	0.86384976	0.90312965	No
PNPLA7	Downregulated	0.12991212	0.09297192	0.25616379	No	-0.0897572	0.39538608	0.50428065	Yes
SERPINF2	Downregulated	#N/A	#N/A	#N/A	#N/A	0.15350222	0.35199595	0.46095042	No
ZNF563	Downregulated	-0.046915409	0.47337673	0.68771635	Yes	-0.0466423	0.47169595	0.57615385	Yes
MDM4	Downregulated	0.118628212	0.01803565	0.08519291	No	0.03707858	0.74463452	0.81100623	No
CDH23	Downregulated	0.472673667	0.0000119	0.00047164	No	0.66229011	0.00058057	0.00454422	No
TAF8	Downregulated	0.09178026	0.10218573	0.27258626	No	0.07925858	0.13547354	0.21899173	No
DCHS2	Downregulated	-0.253249226	0.00064229	0.00804002	Yes	0.06383825	0.65464479	0.73819733	No

LOC100132247	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC646214	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
HAPLN3	Downregulated	0.511177237	0.00114033	0.01200557	No	0.35685524	0.03280137	0.07268625	No
ISPD	Downregulated	-0.045675602	0.43305086	0.65460774	Yes	-0.1841837	0.08207498	0.14754232	Yes
FBLN2	Downregulated	-0.052828058	0.66107429	0.81952961	Yes	0.2122113	0.22944445	0.33071129	No
DHRS4L1	Downregulated	0.311455698	0.00599308	0.03893555	No	#N/A	#N/A	#N/A	#N/A
P2RX5	Downregulated	-0.298961859	0.00251347	0.02118184	Yes	-0.5514858	0.000397	0.00344786	Yes
ATG16L2	Downregulated	0.220931036	0.00138491	0.01381783	No	0.10658678	0.13503412	0.21844607	No
SH2D3A	Downregulated	0.623748164	0.00341648	0.02616408	No	0.66248622	0.00609643	0.02163322	No
ARRDC2	Downregulated	0.365966681	0.00090819	0.01024966	No	0.44188221	0.01450519	0.03935338	No
GHR	Downregulated	-0.113816224	0.11120749	0.28804812	Yes	-0.14623	0.15302152	0.24072023	Yes
BRCA1	Downregulated	0.247276879	0.0001578	0.00298119	No	0.00933827	0.94518237	0.96204019	No
NRG4	Downregulated	-0.193218376	0.04603522	0.16111131	Yes	-0.3733103	0.00143474	0.00853606	Yes
LPIN3	Downregulated	0.293557157	0.01040786	0.05781906	No	0.23465936	0.09587241	0.16672787	No
LOC645166	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
B3GNT7	Downregulated	0.307937563	0.01259249	0.06599347	No	0.23071862	0.17246329	0.26446268	No
SLCO2A1	Downregulated	0.08109819	0.43351016	0.65494166	No	0.11078106	0.48153401	0.58506015	No
MYLK4	Downregulated	-0.051114525	0.45515705	0.67330218	Yes	-0.3714316	0.00055201	0.00438303	Yes
LOC400680	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MYLK	Downregulated	0.320098238	0.0000158	0.00057723	No	0.42710762	0.00576432	0.02082924	No
SCNN1D	Downregulated	0.057579525	0.44250784	0.66257942	No	-0.0271719	0.73099197	0.80008615	Yes
CA13	Downregulated	-0.056931728	0.29578546	0.52552389	Yes	-0.3612571	0.0000252	0.00043946	Yes
CENPL	Downregulated	0.125342198	0.01780552	0.08432446	No	-0.0906501	0.17861762	0.27189181	Yes

FST	Downregulated	0.004635856	0.97922038	0.99153904	No	-0.8405434	0.00023303	0.0023218	Yes
PCSK5	Downregulated	0.049283685	0.394859	0.62062785	No	0.45555215	0.0000144	0.00028875	No
VWCE	Downregulated	0.112810535	0.21327428	0.43201859	No	0.05792963	0.64481255	0.72981544	No
NR6A1	Downregulated	-0.077946241	0.08128982	0.2344255	Yes	-0.1136548	0.19649928	0.29310924	Yes
FHOD1	Downregulated	0.125768981	0.0564512	0.18417119	No	0.06132119	0.36835619	0.47750733	No
XPNPEP3	Downregulated	0.098188987	0.06284877	0.19785684	No	-0.2092179	0.00013388	0.00154228	Yes
MAP7D3	Downregulated	0.240486164	0.00066384	0.00819867	No	0.15973241	0.13490905	0.21833243	No
TMOD1	Downregulated	-0.209838476	0.00100535	0.01100573	Yes	-0.1316001	0.1117905	0.18816008	Yes
NEK8	Downregulated	0.201267597	0.05267222	0.17556175	No	-0.1521933	0.23584181	0.337706	Yes
ESR2	Downregulated	-0.170565856	0.01636088	0.07953092	Yes	0.18821058	0.15503096	0.24329157	No
DMKN	Downregulated	-0.264395945	0.00557535	0.03711056	Yes	-0.5752633	0.0000141	0.0002842	Yes
PLCE1	Downregulated	0.428686087	1.98E-11	3.96E-08	No	0.68053176	7.53E-08	0.00000685	No
C18orf56	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.2318951	0.25828083	0.36247892	Yes
SLC25A35	Downregulated	0.233122513	0.02140295	0.09583853	No	-0.2019536	0.0000189	0.00035286	Yes
FANCI	Downregulated	-0.072887916	0.27122256	0.49980487	Yes	-0.2497506	0.00148575	0.00873284	Yes
CCDC154	Downregulated	0.207749865	0.06524004	0.20282768	No	0.06278145	0.6975962	0.77315629	No
LOC100506023	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PTGIS	Downregulated	0.159964769	0.21721982	0.43664854	No	-0.1446032	0.28646976	0.39282853	Yes
PRRX1	Downregulated	0.388580089	0.00013878	0.00270399	No	0.73133553	0.0000285	0.00048232	No
C9orf3	Downregulated	0.028290222	0.58233898	0.76642256	No	-0.2049669	0.06806163	0.12782848	Yes
DNAH7	Downregulated	-0.040905836	0.6101027	0.78457132	Yes	0.20514362	0.26357095	0.36820159	No
FBXO17	Downregulated	0.036538759	0.53230706	0.73176074	No	-0.0330029	0.64623689	0.73091805	Yes
MIR149	Downregulated	-0.245939867	0.19891576	0.41404237	Yes	0.11488728	0.52462044	0.62466872	No

CD44	Downregulated	0.975681759	9.07E-08	0.0000146	No	2.06106114	1.23E-08	0.00000209	No
FGFR4	Downregulated	0.223533025	0.0668593	0.20624008	No	0.19352662	0.23308061	0.33466697	No
TEP1	Downregulated	0.353589776	3.25E-07	0.0000372	No	0.57692153	1.37E-07	0.00001	No
GNL3L	Downregulated	-0.05869916	0.2121501	0.43074653	Yes	0.49123885	6.01E-08	0.00000591	No
TRIM38	Downregulated	0.427117209	3.85E-07	0.0000417	No	0.51944296	0.00082073	0.00579611	No
CLMN	Downregulated	0.30154039	0.00134212	0.01349152	No	0.75396037	0.00055042	0.00437283	No
CHST5	Downregulated	-0.193805011	0.06825198	0.20905784	Yes	-0.3294015	0.00181996	0.0099572	Yes
LTB4R	Downregulated	0.140363041	0.09579302	0.26103736	No	-0.044095	0.70521303	0.77932092	Yes
HMBOX1	Downregulated	0.277823216	1.85E-10	1.82E-07	No	0.40376655	0.0000821	0.00107091	No
ZNF573	Downregulated	0.004385385	0.9181642	0.96445717	No	0.16118628	0.01775877	0.04566728	No
PLEKHG6	Downregulated	0.349202705	0.03847934	0.14332138	No	0.77112017	0.00013427	0.00154551	No
MACROD2	Downregulated	-0.261244114	0.00056217	0.00731698	Yes	-0.6905671	0.00000055	0.0000259	Yes
LOC344967	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GMEB1	Downregulated	0.044636103	0.21641726	0.43570447	No	-0.1663726	0.0024572	0.01205486	Yes
GATSL2	Downregulated	#N/A	#N/A	#N/A	#N/A	0.11523193	0.19356884	0.28964157	No
ZNF221	Downregulated	-0.015021498	0.74218341	0.87016029	Yes	0.23519904	0.01522579	0.04079897	No
C10orf103	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SGK494	Downregulated	#N/A	#N/A	#N/A	#N/A	0.05669384	0.67487331	0.75460215	No
HYAL1	Downregulated	0.087093634	0.24910046	0.47469114	No	0.31529603	0.01093007	0.03208808	No
LOC100507053	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC283440	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ITGB1BP2	Downregulated	0.020855351	0.87961511	0.94541539	No	-0.1115244	0.55141115	0.64856299	Yes
LOC100131067	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

DNAH1	Downregulated	-0.050982511	0.52935593	0.72960653	Yes	-0.139684	0.25597444	0.35999775	Yes
C20orf132	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
MMP25	Downregulated	0.211431862	0.07687044	0.2258508	No	0.41551874	0.00084142	0.00590485	No
CDCA8	Downregulated	-0.021261367	0.79375762	0.90002667	Yes	-0.1326934	0.16790611	0.25880555	Yes
EDARADD	Downregulated	0.209401119	0.39017594	0.61618348	No	0.09269227	0.46737791	0.57221235	No
EFNA5	Downregulated	-0.266583376	0.00181621	0.01672367	Yes	-0.4496951	0.00204802	0.01073914	Yes
BNC2	Downregulated	0.623022272	0.00000475	0.00024484	No	0.99444348	0.00011955	0.00141616	No
NEK2	Downregulated	-0.134520492	0.50643494	0.71242519	Yes	-1.18221	0.0000122	0.00025264	Yes
PDE11A	Downregulated	0.200534489	0.02689017	0.11195583	No	-0.2941528	0.07313077	0.13514458	Yes
RYR3	Downregulated	0.243430865	0.00095674	0.0106377	No	0.76690183	0.0000225	0.00040203	No
DDR2	Downregulated	0.576008207	7.4E-12	2.2E-08	No	0.95599569	1.33E-07	0.00000985	No
JMJD7	Downregulated	-0.065717599	0.54012923	0.73743892	Yes	0.11275345	0.14727484	0.23383416	No
ZAK	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CCDC18	Downregulated	0.100469175	0.1646442	0.36827568	No	0.29886617	0.0000291	0.00048972	No
COL9A2	Downregulated	0.411246385	0.0000297	0.00089998	No	0.07444639	0.66218669	0.74447767	No
MYL3	Downregulated	0.45853089	0.00000797	0.00035953	No	0.43931488	0.01360842	0.03757309	No
LOC100131655	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
SRCRB4D	Downregulated	0.08962184	0.36558938	0.59362839	No	-0.3440951	0.00335286	0.01466557	Yes
DDX60L	Downregulated	0.334855933	0.00017043	0.00314309	No	0.45309899	0.00141729	0.00847364	No
MTL5	Downregulated	-0.238173998	0.02979964	0.1204361	Yes	-0.5440372	0.00870013	0.02740881	Yes
MOB3B	Downregulated	0.25231695	0.00502288	0.0344496	No	0.38670624	0.03373748	0.07424775	No
C4orf47	Downregulated	-0.075476365	0.44243664	0.66254647	Yes	0.09338214	0.53861234	0.63723278	No
DSCR6	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

YJEFN3	Downregulated	-0.167638537	0.08581072	0.24282235	Yes	-0.2550571	4.21E-07	0.0000215	Yes
KIFC1	Downregulated	0.044909445	0.81773317	0.91321142	No	-0.0908353	0.62318769	0.7114052	Yes
PILRB	Downregulated	0.307226518	0.0240563	0.10367125	No	0.23187939	0.0812454	0.14644859	No
LOC100288198	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PROC	Downregulated	-0.016506641	0.88975954	0.95000798	Yes	-0.1773825	0.18975266	0.2850943	Yes
ACACB	Downregulated	0.376138557	0.00012328	0.00248745	No	0.47429897	0.00137249	0.00828454	No
SSPN	Downregulated	0.447084242	0.00000108	0.0000884	No	0.90434523	4.51E-07	0.0000225	No
SLC26A1	Downregulated	0.091901272	0.26366216	0.49152522	No	0.22081262	0.00604428	0.02150638	No
IBA57	Downregulated	0.116415605	0.02969137	0.1201905	No	0.05657948	0.34293552	0.45164193	No
C17orf53	Downregulated	0.017158313	0.8605847	0.93557902	No	-0.1894481	0.07061778	0.13151994	Yes
LOC728989	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GRHL1	Downregulated	-0.269432121	0.00031975	0.00492395	Yes	-0.6170886	0.00000691	0.00016422	Yes
CYP2D6	Downregulated	#N/A	#N/A	#N/A	#N/A	0.24044112	0.08569466	0.15261735	No
TTLL3	Downregulated	0.113736997	0.08109129	0.23408419	No	-0.0345075	0.7377199	0.80556156	Yes
FAM46C	Downregulated	0.18079951	0.13324212	0.32234204	No	0.31852129	0.07984098	0.14451323	No
CPT1A	Downregulated	0.245587063	0.0010493	0.01135244	No	0.63471738	0.0000154	0.00030276	No
ZSCAN22	Downregulated	0.035729507	0.48311597	0.69460503	No	-0.0507676	0.46432279	0.56949738	Yes
PIEZO1	Downregulated	0.452325348	0.00000774	0.00035127	No	0.74374698	9.68E-11	1.15E-07	No
AKR7A3	Downregulated	0.070170885	0.37391607	0.60156022	No	-0.058301	0.51998801	0.6204912	Yes
C1orf101	Downregulated	-0.004482511	0.94758494	0.97841664	Yes	-0.1101544	0.2974558	0.40431364	Yes
TONSL	Downregulated	0.072378064	0.38835512	0.61478139	No	-0.0938698	0.17441295	0.26676272	Yes
LOC285456	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CILP2	Downregulated	-0.18470829	0.17701449	0.38513093	Yes	-0.6453283	0.00020655	0.00212397	Yes

ASB14	Downregulated	-0.024880332	0.72633214	0.86101628	Yes	0.06974298	0.25806573	0.36223536	No
RTDR1	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.3184838	0.0000443	0.00067373	Yes
TIAM2	Downregulated	-0.201462166	0.00279421	0.02270908	Yes	-0.3703509	0.0008811	0.006108	Yes
POLR2J3	Downregulated	-0.02680313	0.80951435	0.90912669	Yes	-0.0476549	0.68314897	0.76134596	Yes
CCDC77	Downregulated	0.057356068	0.21941233	0.43917472	No	-0.0649564	0.47997822	0.58362772	Yes
LOC728758	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ARHGEF1	Downregulated	0.261059503	0.00059294	0.00761571	No	0.07232343	0.57767722	0.67210542	No
PRR16	Downregulated	-0.227240978	0.00446805	0.03167622	Yes	-0.6320689	0.00000301	0.0000899	Yes
TEN1-CDK3	Downregulated	0.358318715	0.01272391	0.0664726	No	-0.068438	0.41446979	0.52258596	Yes
LOC100131208	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FAM13A-AS1	Downregulated	-0.003842656	0.96165751	0.9852012	Yes	0.10775372	0.21568307	0.31534353	No
NPAS2	Downregulated	-0.150880607	0.01411691	0.07150584	Yes	-0.1014949	0.26311251	0.36774544	Yes
PION	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FMNL3	Downregulated	0.326204927	0.00000201	0.00013376	No	0.21480392	0.01490049	0.04014651	No
NOXO1	Downregulated	0.541497221	0.65760205	NA	No	-0.0099513	0.92263869	0.94578841	Yes
ASPRV1	Downregulated	0.226843815	0.00048233	0.00659445	No	0.09621377	0.40176885	0.51056465	No
SIRT4	Downregulated	-0.061448469	0.49460494	0.70353724	Yes	-0.1512273	0.23541776	0.33719405	Yes
DCDC2B	Downregulated	0.049785723	0.58882607	0.77057805	No	-0.0282346	0.81437716	0.8659562	Yes
MYO7A	Downregulated	0.063597716	0.48003729	0.69219849	No	0.0609865	0.55008394	0.64732968	No
C10orf68	Downregulated	-0.058975171	0.38286707	0.6098685	Yes	#N/A	#N/A	#N/A	#N/A
RRM2	Downregulated	0.598089468	0.0358733	0.13676899	No	-0.1697891	0.54219812	0.64032022	Yes
OBSCN	Downregulated	-0.02226612	0.7878957	0.89661169	Yes	-0.0315747	0.7847688	0.84271733	Yes
RGS11	Downregulated	0.015861481	0.83658773	0.92216874	No	-0.2168438	0.06407319	0.12197708	Yes

LOC440300	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FAM70B	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ATAD5	Downregulated	-0.048745042	0.47967248	0.69192437	Yes	-0.2375694	0.00660235	0.02279385	Yes
LENG8	Downregulated	#N/A	#N/A	#N/A	#N/A	0.18262899	0.12678004	0.20766004	No
NBEAL2	Downregulated	0.264946014	0.00151631	0.01470361	No	0.59922496	4.55E-07	0.0000226	No
C8orf77	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
POLE	Downregulated	0.102444223	0.21507777	0.43409899	No	0.02821976	0.83409607	0.88136035	No
LINC00085	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
C15orf52	Downregulated	0.445414907	0.00000218	0.00014221	No	0.21717882	0.06420138	0.12217106	No
LOC401010	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC642846	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CYP27C1	Downregulated	0.331035744	0.10930999	0.28494879	No	-0.4902762	0.02861127	0.06540632	Yes
ANKRD36	Downregulated	-0.076718195	0.29260486	0.52231293	Yes	-0.0263561	0.76377845	0.82600503	Yes
TMC7	Downregulated	0.324785797	0.0000561	0.0014257	No	0.09586365	0.6041704	0.69523301	No
PDZD2	Downregulated	-0.113688023	0.07633466	0.2245896	Yes	0.21410216	0.03843521	0.08204423	No
GAL3ST4	Downregulated	0.246229817	0.01943088	0.08980512	No	0.29413867	0.03333712	0.07357866	No
HYDIN	Downregulated	0.154847181	0.0605904	0.19290731	No	0.14161641	0.26392841	0.36859936	No
CSMD2	Downregulated	-0.111439752	0.09349942	0.257076	Yes	0.02319527	0.7856584	0.84342523	No
RNF112	Downregulated	-0.161492776	0.01713528	0.0822502	Yes	-0.3935327	0.0008972	0.0061781	Yes
LAMP3	Downregulated	0.30426589	0.0378137	0.1416204	No	0.04784476	0.82750535	0.87638384	No
LOC100130987	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
LOC100289019	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
OAF	Downregulated	0.158901366	0.19839996	0.41349032	No	0.34431189	0.0309317	0.06945743	No

LEPREL1	Downregulated	0.177677336	0.00162627	0.0154801	No	0.3855077	0.00150587	0.00880835	No
AGER	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.106306	0.37447064	0.4836233	Yes
ROBO3	Downregulated	0.208245645	0.00614874	0.03966167	No	0.18241157	0.10082695	0.1734185	No
FDXACB1	Downregulated	-0.118867981	0.07896095	0.22987528	Yes	-0.1982208	0.00529096	0.01970016	Yes
CDKN3	Downregulated	-0.226061312	0.0113016	0.06117241	Yes	-0.5679776	0.0000104	0.0002242	Yes
LOC100132832	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
RREB1	Downregulated	0.457585912	5.75E-09	0.00000208	No	0.66393682	8.13E-07	0.0000346	No
LOC100507577	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
EML3	Downregulated	0.410991174	0.0000105	0.00042954	No	0.30945121	0.0109659	0.03215435	No
TRPC3	Downregulated	-0.033376913	0.72469468	0.86004701	Yes	-0.0518921	0.71707162	0.78908862	Yes
LOC646851	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FZD4	Downregulated	-0.001038855	0.98725115	0.99478182	Yes	0.41723329	0.00037677	0.00331759	No
NPIPL3	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
TMEM30B	Downregulated	0.608970998	0.00238622	0.02040184	No	0.70732007	0.05970968	0.11550805	No
MEGF6	Downregulated	0.3506892	0.0015054	0.01465023	No	0.12115435	0.36746069	0.476557	No
HIF3A	Downregulated	0.368475576	0.0011762	0.01229449	No	0.84200277	0.000087	0.00111749	No
PCSK4	Downregulated	0.00930976	0.91684211	0.9640872	No	-0.0682113	0.37919923	0.48835018	Yes
CENPE	Downregulated	-0.017396876	0.8274149	0.91794174	Yes	-0.4522563	0.00656178	0.0226875	Yes
SSC5D	Downregulated	0.518436121	0.00010043	0.00215723	No	0.46913853	0.00082657	0.00582778	No
DEPDC4	Downregulated	-0.070005316	0.44428538	0.66442363	Yes	-0.1724353	0.09652784	0.16759066	Yes
FRMPD4	Downregulated	-0.385620487	0.00000525	0.00026366	Yes	-0.721726	0.00135052	0.00820702	Yes
B3GALT5	Downregulated	0.126970815	0.14630031	0.34282163	No	0.09735449	0.39857933	0.50741351	No
TMEM51	Downregulated	0.300379579	0.00051405	0.0068602	No	0.2526007	0.05623203	0.11015991	No

SLC12A8	Downregulated	-0.136771486	0.12858591	0.31581891	Yes	-0.3941542	0.00047378	0.00392746	Yes
ETV6	Downregulated	0.076039406	0.20818544	0.42590934	No	0.22780564	0.02900303	0.06608471	No
LOC283922	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
NTN3	Downregulated	0.221755066	0.06470009	0.20160313	No	0.71602449	0.0000021	0.0000698	No
ARID3A	Downregulated	0.139812625	0.04613083	0.16134765	No	-0.1031814	0.1839918	0.27823763	Yes
FES	Downregulated	0.370358919	0.0001027	0.00219589	No	0.55696955	0.0000198	0.00036477	No
LRRC16A	Downregulated	-0.022987915	0.62979025	0.79748638	Yes	0.50800966	0.00010656	0.00130003	No
CLCNKA	Downregulated	0.400060197	0.07453888	0.22126143	No	0.62708921	0.0151262	0.04060745	No
UTRN	Downregulated	0.311322444	9.43E-08	0.000015	No	0.52948867	0.00000596	0.00014806	No
MACC1	Downregulated	0.122006758	0.27134261	0.499929	No	-0.2542246	0.06026237	0.11629253	Yes
ARHGAP25	Downregulated	0.214281819	0.0051208	0.03489941	No	-0.0331636	0.78505238	0.84298938	Yes
NRIP2	Downregulated	0.225580944	0.0029419	0.02357124	No	0.14200876	0.32188622	0.43000427	No
GPLD1	Downregulated	-0.234044474	0.0000647	0.00158229	Yes	-0.10905	0.28199744	0.3879648	Yes
BMP8A	Downregulated	0.021674161	0.81065519	0.90969213	No	-0.2478264	0.00870899	0.02742917	Yes
MAF	Downregulated	0.324244955	0.0000118	0.00046868	No	0.30056947	0.02297003	0.0553098	No
TTF2	Downregulated	0.270834093	0.0003885	0.00565592	No	0.05642121	0.60655509	0.69715699	No
SGK1	Downregulated	0.306848779	0.00186003	0.0170028	No	0.55544222	0.00457063	0.01791495	No
TRMT2B	Downregulated	0.038872252	0.32578906	0.55575522	No	0.08687225	0.18181156	0.27559908	No
MCM8	Downregulated	0.131126268	0.01496275	0.07462497	No	0.25718725	0.04308185	0.08973333	No
ZNF276	Downregulated	0.23031857	0.00033055	0.00503039	No	-0.0033672	0.97117907	0.98061073	Yes
PDE7B	Downregulated	0.035244422	0.5788198	0.76430876	No	-0.0791829	0.50810227	0.60954343	Yes
MAP3K5	Downregulated	0.111992188	0.00535211	0.03608703	No	0.54005366	0.00000277	0.0000844	No
LIPT1	Downregulated	0.046151566	0.43855251	0.65924866	No	0.00252915	0.97758728	0.9851852	No

TENC1	Downregulated	#N/A	#N/A	#N/A	#N/A	0.15618287	0.24334967	0.34611883	No
BCO2	Downregulated	-0.065392569	0.29201724	0.52173527	Yes	-0.0971849	0.37442731	0.48357854	Yes
KCNMB3	Downregulated	0.09167546	0.24790009	0.47335111	No	-0.3156601	0.00063354	0.00484348	Yes
CNIH3	Downregulated	-0.259466187	0.00000284	0.00017053	Yes	-0.7266843	0.00000875	0.00019658	Yes
RTKN2	Downregulated	-0.424268773	0.00120432	0.01248187	Yes	-0.9476606	0.0000066	0.00015914	Yes
KNTC1	Downregulated	-0.048028146	0.49590322	0.70432493	Yes	-0.1756903	0.02465217	0.05841258	Yes
HRC	Downregulated	0.412088908	0.01028996	0.05738113	No	-0.0350798	0.84093397	0.88668627	Yes
SLC16A4	Downregulated	0.120218118	0.04704418	0.16334413	No	0.65210338	7.02E-07	0.000031	No
SYTL2	Downregulated	-0.319830343	0.0000392	0.00108865	Yes	0.07805478	0.6308553	0.71776284	No
CCDC84	Downregulated	-0.108052825	0.1117113	0.28891931	Yes	-0.2864699	0.00546157	0.02009604	Yes
PLAGL1	Downregulated	-0.18782868	0.01214572	0.0643286	Yes	-0.0386539	0.69485414	0.77096668	Yes
PPFIBP2	Downregulated	0.283847884	0.00029077	0.00461679	No	0.26231266	0.07750071	0.14128726	No
NFIA	Downregulated	0.291925404	0.0000408	0.00111803	No	0.36194972	0.00041732	0.00357586	No
HSPG2	Downregulated	0.517071023	0.00054351	0.00713542	No	0.64777682	0.0000369	0.00058804	No
SERINC4	Downregulated	NA	NA	NA	#N/A	0.28160757	0.00013933	0.00158699	No
ADAMTS16	Downregulated	0.048563896	0.65834511	0.81787188	No	-0.5217318	0.00193447	0.01035604	Yes
VAMP8	Downregulated	0.394665508	0.00035616	0.00531352	No	0.41550551	0.01660517	0.043493	No
MGC27345	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PPIEL	Downregulated	-0.089049075	0.26246876	0.49020443	Yes	-0.2003847	0.0757451	0.13885823	Yes
CNKSR1	Downregulated	0.209000876	0.04133698	0.15010595	No	-0.2441019	0.10696702	0.18170648	Yes
OIP5	Downregulated	0.273620756	0.02934717	0.11916576	No	0.01241942	0.91515491	0.94057729	No
CROCC	Downregulated	0.203034358	0.01968222	0.09057443	No	0.02354717	0.79617634	0.85164503	No
MYOM1	Downregulated	0.426008709	4.26E-07	0.0000454	No	0.13548793	0.30665125	0.4142775	No

LOC146880	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
BDNF-AS1	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
BUB1B	Downregulated	-0.051431011	0.68103194	0.83288929	Yes	-0.5903783	0.00548213	0.02015308	Yes
LOC441454	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ZNF530	Downregulated	-0.00399578	0.95293123	0.98082881	Yes	-0.371304	0.0000748	0.0009963	Yes
RCN3	Downregulated	0.191269955	0.03398365	0.13197745	No	-0.0371076	0.65919406	0.74204082	Yes
CCDC142	Downregulated	0.0932367	0.13024552	0.3180632	No	-0.0179761	0.70349961	0.77793626	Yes
DDX58	Downregulated	0.267784296	0.00000466	0.00024246	No	0.42381252	0.00000213	0.0000703	No
LOC286437	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
AP1G2	Downregulated	-0.020365222	0.81976853	0.91432292	Yes	0.2105537	0.15006727	0.23704472	No
IKBKB	Downregulated	0.218578326	0.00000669	0.00031518	No	0.2746935	0.00395816	0.01634508	No
CTAGE1	Downregulated	-0.13943346	0.82242594	NA	Yes	-0.3337281	0.13786538	0.22201668	Yes
HSPBAP1	Downregulated	0.052920719	0.33535229	0.56556147	No	-0.1726569	0.04108944	0.08647176	Yes
KCND1	Downregulated	-0.00142534	0.98416396	0.99353545	Yes	0.02127699	0.8177366	0.86865039	No
PPARGC1B	Downregulated	-0.149462203	0.00259598	0.02162454	Yes	-0.2804207	0.00912729	0.0283209	Yes
NEXN	Downregulated	0.077751357	0.33742897	0.56755058	No	0.27399899	0.01778409	0.04571763	No
MSS51	Downregulated	-0.295912257	0.00015137	0.00289102	Yes	-0.074877	0.55804189	0.65449806	Yes
RTTN	Downregulated	0.189862161	0.0072585	0.04485329	No	0.09380687	0.34332146	0.45201967	No
GSDMB	Downregulated	-0.123963884	0.13566832	0.3261023	Yes	0.01241468	0.93805515	0.95682929	No
FBLN1	Downregulated	0.37221779	0.00067646	0.00829013	No	0.80640395	0.00000804	0.00018406	No
FBXL13	Downregulated	0.02217509	0.67640402	0.83007346	No	0.11055129	0.16233337	0.2519923	No
CCDC69	Downregulated	0.235812844	0.01755947	0.08358864	No	0.37423944	0.00395681	0.01634191	No
FAM72B	Downregulated	-0.019520924	0.91895032	0.96488461	Yes	-0.283869	0.09620212	0.16715727	Yes

SLC25A45	Downregulated	0.00878475	0.89776458	0.95454183	No	-0.6121878	0.00000028	0.0000162	Yes
FRZB	Downregulated	0.398660907	0.00431369	0.0308327	No	0.49012205	0.0297506	0.06742326	No
POLE2	Downregulated	0.128495473	0.10048623	0.26958749	No	-0.2394336	0.0209857	0.05175737	Yes
LOC100131691	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
PLK4	Downregulated	-0.141064414	0.21462064	0.43358236	Yes	-0.4466962	0.00606137	0.02154931	Yes
LOC401321	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
RAD9A	Downregulated	-0.051286088	0.42591039	0.64810372	Yes	-0.3286741	0.00000208	0.0000692	Yes
CASP6	Downregulated	0.172591318	0.01456953	0.07323159	No	0.47235994	0.0000359	0.00057681	No
TPK1	Downregulated	-0.07891343	0.1675499	0.37217546	Yes	-0.3670639	0.00000219	0.0000716	Yes
LRRC37A4	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
GLDC	Downregulated	0.010403634	0.85360411	0.93175006	No	0.16718487	0.11620035	0.19404196	No
MTBP	Downregulated	-0.097637414	0.338829	0.569048	Yes	-0.1528791	0.06666133	0.12576197	Yes
CHRD	Downregulated	-0.110237007	0.07323298	0.21870207	Yes	-0.2435492	0.03002282	0.06788127	Yes
C9orf169	Downregulated	0.216116936	0.06359109	0.19932739	No	-0.2532235	0.01049926	0.03118457	Yes
B3GNTL1	Downregulated	#N/A	#N/A	#N/A	#N/A	-0.4691573	2.83E-08	0.0000036	Yes
TOM1L1	Downregulated	-0.2157498	0.00021071	0.00364176	Yes	-0.4022265	1.18E-07	0.00000914	Yes
SLC26A5	Downregulated	0.296287479	0.02068526	0.09370833	No	0.63511784	0.0044153	0.01752668	No
IFIT3	Downregulated	0.208742537	0.0046425	0.03253351	No	0.46155087	0.00015382	0.00171016	No
DNAH10	Downregulated	0.063985638	0.31731695	0.54762857	No	0.08151467	0.40837382	0.51674733	No
SCUBE3	Downregulated	0.066357648	0.28744873	0.51679879	No	0.47618747	0.00183001	0.01000336	No
PROM2	Downregulated	0.059173501	0.45014826	0.66947207	No	0.01077917	0.93069914	0.95136238	No
ERN1	Downregulated	0.168996568	0.00069842	0.00847419	No	0.18381851	0.01065255	0.03150225	No
MIR210HG	Downregulated	-0.1437565	0.32648475	0.55654176	Yes	-0.0349329	0.85872407	0.89954193	Yes

HEATR7A	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
BAHCC1	Downregulated	0.24118401	0.00735068	0.0452388	No	#N/A	#N/A	#N/A	#N/A
H1FX-AS1	Downregulated	0.108216224	0.1849162	0.39555038	No	-0.1895586	0.00710626	0.02393768	Yes
CLEC16A	Downregulated	-0.002177424	0.95381581	0.98131514	Yes	-0.0043064	0.92895263	0.95013452	Yes
ATP8B1	Downregulated	0.00349904	0.95653836	0.98266225	No	0.00055917	0.99496546	0.99648993	No
SNTB2	Downregulated	0.036267057	0.48230325	0.69412976	No	0.27465971	0.00109082	0.0070622	No
FAM26F	Downregulated	0.383224982	0.02037458	0.09266384	No	0.02351201	0.9088529	0.93594625	No
EDA	Downregulated	0.228186502	0.00288971	0.02324958	No	0.24064749	0.02642215	0.06154718	No
TRPS1	Downregulated	0.231307334	0.0000342	0.00098946	No	0.74029642	2.03E-08	0.00000287	No
STC2	Downregulated	0.022524985	0.91386838	0.96276335	No	0.20205389	0.42235556	0.53009528	No
C19orf57	Downregulated	0.11883447	0.07714473	0.22620143	No	-0.0521027	0.34089423	0.44958012	Yes
FUT4	Downregulated	0.082783123	0.05394065	0.17843873	No	0.02867935	0.72738841	0.79700248	No
SLC13A3	Downregulated	0.242424131	0.00173132	0.01616897	No	0.13850655	0.35833471	0.46737415	No
PRKD3	Downregulated	0.171279286	0.00140081	0.01394712	No	0.66305146	1.79E-08	0.00000261	No
ENOSF1	Downregulated	0.1909921	0.09973281	0.26830782	No	-0.4270017	0.07365584	0.13588063	Yes
TBXAS1	Downregulated	0.500726846	2.04E-08	0.00000506	No	0.28415185	0.09207582	0.16145992	No
FBF1	Downregulated	0.105436687	0.09271799	0.25566831	No	0.01875794	0.78107387	0.83998125	No
CACNA1G	Downregulated	-0.047527631	0.63448427	0.80094513	Yes	-0.3536526	0.02843016	0.06507192	Yes
EXTL1	Downregulated	-0.280366102	0.00102699	0.01118779	Yes	-0.414019	0.01308338	0.03654282	Yes
FBXW4P1	Downregulated	0.10448103	0.262858	0.49070447	No	0.09514819	0.46611711	0.57113278	No
ACCS	Downregulated	-0.06690486	0.48872664	0.6990176	Yes	-0.0260879	0.86823998	0.9064494	Yes
MMACHC	Downregulated	0.035325388	0.40751176	0.63247416	No	-0.138218	0.06711608	0.12645302	Yes
ZDHHC8	Downregulated	0.033940386	0.67637674	0.83007346	No	-0.0612258	0.14037939	0.22515299	Yes

KIAA1456	Downregulated	-0.216562422	0.0040566	0.02951203	Yes	-0.5116997	0.00059429	0.00461749	Yes
UBOX5	Downregulated	0.018889138	0.73704848	0.86681761	No	-0.238729	0.0011244	0.00720434	Yes
C1QL3	Downregulated	-0.405249888	0.00061965	0.00786296	Yes	-0.5533329	0.11145808	0.18768556	Yes
LRRC56	Downregulated	0.07039551	0.49598667	0.70437877	No	-0.2882218	0.00852371	0.02702465	Yes
MGC72080	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
WDR92	Downregulated	-0.075241687	0.08108551	0.23408419	Yes	-0.2231766	0.000119	0.00141196	Yes
SCAND2	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CBR3-AS1	Downregulated	-0.098803761	0.15238238	0.35164267	Yes	-0.417409	0.000011	0.00023461	Yes
SFXN2	Downregulated	0.01957112	0.77731055	0.89030524	No	-0.2640373	0.0043636	0.01739821	Yes
LOC90784	Downregulated	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
FBXL19-AS1	Downregulated	0.115779008	0.24465802	0.46890625	No	-0.1676507	0.14838371	0.23510989	Yes
ANO8	Downregulated	0.192230789	0.01231402	0.06495417	No	0.39642087	0.00000131	0.0000488	No

Appendix 3: Common variants near LMNA and ZMPSTE24 are not associated with risk for AD in IGAP Stage 1

Gene	# Variant ID	IGAP P value Stage 1
LMNA	rs71630614	0.05618
LMNA	rs75088561	0.094
LMNA	rs74116482	0.09867
LMNA	rs138130536	0.09987
LMNA	rs6669212	0.1016
LMNA	rs12144377	0.1061
LMNA	rs116755477	0.1178
LMNA	rs77778388	0.1298
LMNA	rs56106339	0.1757
LMNA	rs41310120	0.196
LMNA	rs116394986	0.197
LMNA	rs11584621	0.1994
LMNA	rs74610158	0.2004
LMNA	rs114427537	0.2058
LMNA	rs76017998	0.2235
LMNA	rs12035654	0.24
LMNA	rs11264435	0.2407
LMNA	rs11578696	0.2654
LMNA	rs12035615	0.2673
LMNA	rs547915	0.2725
LMNA	rs11590832	0.2731
LMNA	rs35997354	0.2745
LMNA	rs6700693	0.2762
LMNA	rs9919256	0.2791
LMNA	rs584025	0.2797
LMNA	rs520973	0.3095
LMNA	rs581342	0.3103
LMNA	rs509551	0.3125
LMNA	rs665979	0.3139

LMNA	rs553016	0.3193
LMNA	rs693671	0.3196
LMNA	rs6657367	0.3224
LMNA	rs594028	0.3264
LMNA	rs471679	0.3274
LMNA	rs2485666	0.3281
LMNA	rs577492	0.332
LMNA	rs671728	0.3321
LMNA	rs2485665	0.3391
LMNA	rs28653480	0.3394
LMNA	rs610918	0.3434
LMNA	rs7531942	0.3439
LMNA	rs1962065	0.3504
LMNA	rs2485668	0.3537
LMNA	rs2485676	0.3573
LMNA	rs78261031	0.3576
LMNA	rs505058	0.3578
LMNA	rs955383	0.3637
LMNA	rs2430415	0.3661
LMNA	rs2430416	0.3664
LMNA	rs609625	0.3696
LMNA	rs2993267	0.3756
LMNA	rs543235	0.3817
LMNA	rs500940	0.387
LMNA	rs528636	0.3879
LMNA	rs513043	0.3932
LMNA	rs4661147	0.3972
LMNA	rs520910	0.4008
LMNA	rs672200	0.4027
LMNA	rs2993269	0.4035
LMNA	rs675661	0.4061
LMNA	rs501791	0.4064

LMNA	rs6691659	0.4065
LMNA	rs544627	0.4083
LMNA	rs10159320	0.4087
LMNA	rs2485667	0.4093
LMNA	rs116251020	0.4105
LMNA	rs2485675	0.4111
LMNA	rs503815	0.4117
LMNA	rs517606	0.4162
LMNA	rs6686943	0.4164
LMNA	rs569025	0.4189
LMNA	rs623189	0.419
LMNA	rs653969	0.4218
LMNA	rs2485674	0.423
LMNA	rs521354	0.4231
LMNA	rs7339	0.4262
LMNA	rs2475758	0.428
LMNA	rs545731	0.4288
LMNA	rs568036	0.429
LMNA	rs593987	0.4297
LMNA	rs538089	0.4313
LMNA	rs2993266	0.4328
LMNA	rs2430417	0.4361
LMNA	rs10158206	0.4385
LMNA	rs2485664	0.4413
LMNA	rs140762385	0.4466
LMNA	rs646840	0.4505
LMNA	rs666869	0.4507
LMNA	rs508641	0.4515
LMNA	rs534807	0.452
LMNA	rs111340905	0.4536
LMNA	rs476000	0.4539
LMNA	rs582690	0.4625

LMNA	rs9427236	0.4658
LMNA	rs16837187	0.4669
LMNA	rs141257912	0.4756
LMNA	rs2485672	0.4836
LMNA	rs573739	0.492
LMNA	rs573735	0.4924
LMNA	rs56702163	0.499
LMNA	rs7542186	0.5
LMNA	rs11264443	0.5056
LMNA	rs11264442	0.5057
LMNA	rs74116489	0.5191
LMNA	rs2430414	0.5238
LMNA	rs622834	0.5292
LMNA	rs12063072	0.5563
LMNA	rs12073543	0.5609
LMNA	rs2485662	0.5691
LMNA	rs11264434	0.5698
LMNA	rs915180	0.5841
LMNA	rs113487506	0.5991
LMNA	rs112941217	0.601
LMNA	rs11803917	0.6141
LMNA	rs139860915	0.6255
LMNA	rs12063564	0.643
LMNA	rs6661281	0.6609
LMNA	rs12076700	0.6623
LMNA	rs10737170	0.6802
LMNA	rs6691151	0.6925
LMNA	rs6691151	0.6925
LMNA	rs11264437	0.7089
LMNA	rs12565130	0.7168
LMNA	rs4661146	0.7549
LMNA	rs4641	0.7577

LMNA	rs12131777	0.7593
LMNA	rs61813324	0.8164
LMNA	rs915179	0.8994
LMNA	rs11264447	0.8997
LMNA	rs536857	0.9264
LMNA	rs72708262	0.9336
LMNA	rs682267	0.9519
LMNA	rs480886	0.952
ZMPSTE24	rs114052415	0.03941
ZMPSTE24	rs80160325	0.09068
ZMPSTE24	rs60640112	0.1034
ZMPSTE24	rs77081740	0.1166
ZMPSTE24	rs111781530	0.1595
ZMPSTE24	rs11207778	0.174
ZMPSTE24	rs71648511	0.242
ZMPSTE24	rs12725815	0.256
ZMPSTE24	rs79638111	0.2903
ZMPSTE24	rs12757549	0.2974
ZMPSTE24	rs16827109	0.302
ZMPSTE24	rs11811980	0.3261
ZMPSTE24	rs16827106	0.3302
ZMPSTE24	rs7517840	0.3339
ZMPSTE24	rs3765483	0.3367
ZMPSTE24	rs2284447	0.3367
ZMPSTE24	rs7548758	0.3372
ZMPSTE24	rs6691598	0.4041
ZMPSTE24	rs6676644	0.4346
ZMPSTE24	rs149885289	0.4351
ZMPSTE24	rs1579150	0.4822
ZMPSTE24	rs74938879	0.4935
ZMPSTE24	rs6600324	0.5127
ZMPSTE24	rs6600323	0.514

ZMPSTE24	rs6682701	0.5423
ZMPSTE24	rs12134085	0.5513
ZMPSTE24	rs10889220	0.5567
ZMPSTE24	rs2092735	0.5685
ZMPSTE24	rs9326050	0.6201
ZMPSTE24	rs12121804	0.6311
ZMPSTE24	rs11589157	0.6575
ZMPSTE24	rs140585118	0.688
ZMPSTE24	rs55674553	0.6906
ZMPSTE24	rs7516571	0.7033
ZMPSTE24	rs720793	0.7253
ZMPSTE24	rs6664294	0.7535
ZMPSTE24	rs6677717	0.7756
ZMPSTE24	rs7556313	0.7848
ZMPSTE24	rs11207771	0.8402
ZMPSTE24	rs74763199	0.8579
ZMPSTE24	rs2284446	0.8593
ZMPSTE24	rs12144229	0.8622
ZMPSTE24	rs6698320	0.8727
ZMPSTE24	rs10489432	0.8789
ZMPSTE24	rs926830	0.8862
ZMPSTE24	rs7514099	0.8873
ZMPSTE24	rs11580085	0.8908
ZMPSTE24	rs11207716	0.8943
ZMPSTE24	rs10489430	0.9341
ZMPSTE24	rs10489431	0.9423
ZMPSTE24	rs2076697	0.9428
ZMPSTE24	rs12117796	0.9766

Curriculum Vitae

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PhD Candidate

Department of Psychiatry

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Citizenship: USA

Education:

Washington University, St Louis, MO, US

PhD Candidate, Molecular Cell Biology

Mentor: Dr. Celeste M Karch

Luther College, Decorah, Iowa, USA

BA, *cum laude*, Biology, May 2015

Positions:

2018-present	Doctoral student in the laboratory of Celeste Karch, St Louis, MO
2016-2018	Doctoral student in the laboratory of Zhongsheng You, St Louis, MO
2015-present	PhD Student in the Division of Biology and Biomedical Sciences at Washington University, St. Louis, MO
2014	Undergraduate research intern in the laboratory of Bryan Phillips, Iowa City, IA
2013	Undergraduate research intern in the laboratory of Thomas Rutkowski, Iowa City, IA

Selected Honors:

2021	Travel Fellowship, Alzheimer's Association International Conference
2016-2018	Cell and Molecular Biology Training Grant Recipient

2014 University of Iowa Summer Undergraduate Research Program Intern

Supervising, Teaching, and Science Outreach:

2019 Summer Mentor for the Biomed RAP Undergraduate Research Program, Madhavi Jere

2017 Teaching Assistant for General Biology, Washington University in St. Louis, St Louis, MO

2014 Undergraduate Lab Assistant, Molecular Biology, Luther College, Decorah, IA

Conference Abstracts

2021 Defining the role of phospholipase D3 in Alzheimer disease pathogenesis (Talk), AAIC Next Virtual Conference

2021 Defining the role of phospholipase D3 in Alzheimer disease pathogenesis (Talk), Alzheimer's Association International Conference, Denver, CO

2021 LMNA-mediated nucleoskeleton dysregulation in Alzheimer's disease (Poster), Alzheimer's Association International Conference, Denver, CO

2021 Defining the role of phospholipase D3 in Alzheimer disease pathogenesis (Talk), Chan-Zuckerberg Initiative Neurodegenerative Challenge Network Virtual Conference

2021 LMNA-mediated nucleoskeleton dysregulation in Alzheimer's disease (Poster), Washington University Virtual Psychiatry Residency Research Education Program Research Day Symposium

2020 LMNA-mediated nucleoskeleton dysregulation in Alzheimer's disease (Poster), Cold Springs Harbor Laboratory Virtual Conference for Neurodegenerative Diseases: Biology and Therapeutics

2020 LMNA-mediated nucleoskeleton dysregulation in Alzheimer's disease (Poster), Chan-Zuckerberg Initiative Neurodegenerative Challenge Network Virtual Conference

2014 Prevalence of Multi-Drug Resistant (MDR) Bacteria in North East Iowa Streams (Talk), Iowa Academy of Sciences Research Symposium, Fort Dodge, IA

Professional Service:

2020-Present Member of the LouHealth Advocacy group Criminal Justice Reform Team

2019 Poster Judge, Biomed RAP Summer Symposium

Societal Membership:

βββ Biological Honor Society

Technical Skills:

Molecular Biology: SDS-PAGE, Western blotting, protein purification, PCR, RNA purification, reverse transcription and quantitative PCR, plasmid construction and cloning, DNA radiolabeling

Cell and Tissue Biology: Mammalian cell culture, stable and transient transfections, virus production and transduction, immunocytochemistry, confocal and fluorescence microscopy

Animals: *Xenopus laevis* handling, extract preparation from *Xenopus laevis* eggs, *Caenorhabditis elegans* handling, *mus musculus* handling, *Mus musculus* brain tissue harvesting

Peer-Reviewed Publications:

Matthew J. Rosene, Natalie Wen, Zeran Li, Logan Brase, Simon Hsu, Carlos Cruchaga, Sally Temple, Oscar Harari, Celeste M. Karch. *LMNA*-mediated nucleoskeleton dysregulation in Alzheimer disease. In Revision.

Matthew J. Rosene, Simon Hsu, Shih Feng You, Logan Brase, Anthony Verbeck, Rita Martinez, Clare E. Wallace, Zeran Li, Ping Yan, Nina M. Dräger, Sydney M. Sattler, Abhirami K. Iyer, Shannon L. Macauley, David Holtzman, Bruno A. Benitez, Martin Kampmann, Carlos Cruchaga, Oscar Harari, John Cirrito, Jin-Moo Lee, Alison Goate, Celeste M. Karch. Phospholipase D3 contributes to Alzheimer's disease risk via disruption of Aβ clearance and inflammatory response. In Revision. medRxiv: https://doi.org/10.1101/2022.01.31.22270175

Simon Hsu, Anna A. Pimenova, Kimberly Hayes, Juan A. Villa, **Matthew J. Rosene**, Madhavi Jere, Alison M Goate, Celeste M. Karch (2020). Systematic Validation of Variants of Unknown Significance in APP, PSEN1 and PSEN2. *Neurobiology of Disease* (In Press. DOI: https://doi.org/10.1016/j.nbd.2020.104817)

Justina P. Tavana*, **Matthew Rosene ***, Nick O. Jensen, Perry G. Ridge, John S.K. Kauwe, Celeste M. Karch (2019). RAB10: an Alzheimer's disease resilience locus and potential drug target. Clinical Interventions in Aging 14: 73-79.