Identification of candidate biomarkers and pathways associated with multiple sclerosis using bioinformatics and next generation sequencing data analysis

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Abstract

Multiple sclerosis (MS) is an autoinflammatory disease that might lead to severe disability. The diagnosis of MS is defined due to the urgency for biomarkers with both reliability and efficiency. Demyelination of axons are deeply involved in the pathogenesis of MS. Our study aims to identify the underlying molecular mechanism and screening for related biomarkers and signaling pathways. We obtained next generation sequencing (NGS) dataset (GSE138614) from the GEO database. Differentially expressed genes (DEGs) were screened by the DESeq2 package in R bioconductor with considering specific criteria. Gene Ontology (GO) enrichment analysis, REACTOME pathway enrichment analysis were performed; a protein-protein interaction (PPI) network was constructed; significant modules were analyzed and hub genes were identified by Human Integrated Protein-Protein Interaction rEference (HiPPIE). Subsequently, miRNA-hub gene regulatory network, TF-hub gene regulatory network and drug-hub gene interaction network were built by Cytoscape to predict the underlying microRNAs (miRNAs), transcription factors (TFs) and drugs associated with hub genes. Receiver operating characteristic (ROC) curves analysis was performed to calculate diagnostic value of hub genes. Finally, we performed molecular docking study for prediction of drug molecules against protein targets. A total of 959 DEGs (479 up-regulated and 480 down-regulated genes) were identified in the MS samples and compared with normal control samples. The DEGs were predominantly enriched in an ensemble of genes encoding the immune system process, developmental process, immune system and regulation of cholesterol biosynthesis by SREBP (SREBF). A PPI network was obtained through HiPPIE analysis, and the results were imported into Cytoscape software. The DEGs were sequenced by the Network Analyzer plug-in by various calculation methods, and 10 hub genes (LCK, PYHIN1, SLAMF1, DOK2, TAB2, CFTR, RHOB, LMNA, EGLN3 and ERBB3) were finally selected. Based on the miRNA-hub gene regulatory network and TF-hub gene regulatory network construction, miRNAs including hsa-mir-6794-3p, hsa-mir-3689a-3p, hsa-mir-4651, hsa-mir-548q, BRCA1, HNF4A, TFAP2C and NR2F1 were determined to be potential key biomarkers. Drug-hub gene interaction network constructed from DrugBank, which identified targeted therapeutic drugs (Palivizumab, Cu-Bicyclam, Lumacaftor and Zonisamide) for the hub genes. From molecular docking study we showed good drug - protein bind affinity and amino

acid interactions. This study identified novel biomarkers for MS and established a reliable diagnostic model as well as predicted novel drug molecules. The transcriptional changes identified may help to reveal the pathogenesis and molecular mechanisms of MS.

Keywords: multiple sclerosis; differentially expressed genes; protein-protein interaction network; bioinformatics; hub genes

Introduction

Multiple sclerosis (MS) is the commonest autoimmune inflammatory disorder of CNS white matter [1]. MS is one of leading causes of disability in children's, young aged adults and middle aged adults in many developed countries [2-4] and it affects 2.3 million people worldwide with an expected increase in the number of cases in future [5]. Main features of MS include selective primary demyelination with partial preservation of axons and reactive astrocytic gliosis [6]. It might affect many other organs and cause other MS associated complications include spasticity [7], paralysis [8], bladder, bowel and sexual dysfunction [9], psychiatric disorders [10], cardiovascular diseases [11], neurodegenerative diseases [12], spinal cord injury [13], obesity [14], diabetes mellitus [15] and hypertension [16]. Autoimmune inflammation is triggered by both genetic susceptibility [17] and environmental factors [18]. However, the etiology and symptoms of MS are complex in clinical practice, making its diagnosis challenging.

Correct early diagnosis assessment of MS is very difficult, even though much disease related genes and cellular pathways related to MS have appeared [19]. The common treatments of MS are interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine and monoclonal antibodies [20], but there are no valid treatment tactics available to treat MS. Therefore, it is vitally important to explore potential diagnostic and prognostic biomarkers, and therapeutic targets of MS.

The fast development of next generation sequencing (NGS) technology and bioinformatics analysis based on high-throughput data provide new tactics to identify differentially expressed genes (DEGs) and discover therapeutic targets for the initiation and evolution of MS [21]. Altered expression of key genes plays an essential role in the initiation and progression of MS, so mastering the alteration in

the characteristics of critical genes and signaling pathways promotes to comprehensively understanding of MS progression [22]. Several biomarkers including CLEC16A (C-type lectin domain containing 16A) [23], IL2RA (interleukin 2 receptor subunit alpha), RPL5 (ribosomal protein L5) and CD58 (CD58 molecule) [24], SLC9A9 (solute carrier family 9 member A9) [25], IL22RA2 (interleukin 22 receptor subunit alpha 2) [26] and ANKRD55 (ankyrin repeat domain 55) [27] were identified for the MS. Indeed, some researchers found signaling pathways include mTOR signaling pathway [28], Keap1/Nrf2/ARE signaling pathway [29], NF-κB signaling pathways [30], wnt signaling pathway [31] and Nogo-A/NgR signaling pathway [32] have been shown to be associated with MS. The identification of novel biomarkers and signaling pathway might be helpful to improve the clinical outcome of MS patients.

However, the use of bioinformatics analysis method to find the relevant genes and signaling pathways of MS has not yet been confirmed. In the current study, we downloaded NGS dataset GSE138614 [33] from the NCBI Gene Expression Omnibus (GEO) [https://www.ncbi.nlm.nih.gov/geo/] [34] database, including NGS data from 73 patients with MS brain white matter samples and 25 normal control brain white matter samples. We identified DEGs using the DESeq2 in R bioconductor tool. The GO term and REACTOME pathway enrichment analyses were performed via g:Profiler. Moreover, protein-protein interaction (PPI) network and modules, and the hub genes were identified according to toplogical properties include node degree, betweenness, stress and closeness scores. Subsequently, miRNA-hub gene regulatory network, TF-hub gene regulatory network and drug-hub gene interaction network were constructed and analyzed according to the screened hub genes. Subsequently, ten hub genes were subject to receiver operating characteristic curve (ROC) analysis to determine diagnostic value of hub genes. Finally, molecular docking study was performed for prediction of possible binding affinity of selected ligand molecules. This approach will enhance our understanding of the role of key genes and signaling pathways in MS and help to elucidate the specific molecular mechanisms of damage of white matter in brain. Additionally, the identification of these genes and signaling pathways might provide novel targets for intervention in the treatment of

Methods and materials

Next generation sequencing data source

GEO is a public functional genomics data repository of high throughput NGS data (RNA-Sequencing). The GSE138614 [33] NGS dataset generated using the GPL21697 NextSeq 550 (Homo sapiens). The GSE138614 dataset contained 73 MS brain white matter samples and 25 normal brain white matter control samples.

Identification of DEGs

Determining DEGs between MS and normal control samples was performed using DESeq2 package [35] in R bioconductor tool.The adjusted P-values (adj. P) and Benjamini and Hochberg false discovery rate were applied to strike a balance between finding statistically important genes and limiting false positives [36]. |log FC (fold change)| > 2.2 for up regulated genes, |log FC (fold change)| < -0.866 for down regulated genes and adj. P-value < 0.05 were considered statistically significant. DEGs were visualized by the "volcano" and "heatmap" by using ggplot2 and gplot packages in R software.

GO and pathway enrichment analyses of DEGs

Online tool g:Profiler (http://biit.cs.ut.ee/gprofiler/) [37] was used to perform the GO functional annotation (http://www.geneontology.org) [38] and REACTOME (https://reactome.org/) [39] pathway enrichment analyses. GO enrichment analysis is a premier bioinformatics analysis for identifying high-quality functional gene annotation based on biological process (BP), cellular component (CC) and molecular function (MF). The REACTOME is a resource of pathway database for the clarification of high-level features and effects of biological systems. Adj. P-value <0.05 was considered as the threshold.

Construction of the PPI network and module analysis

Information of DEGs' protein experimental interactions and prediction was obtained by Human Integrated Protein-Protein Interaction rEference (HiPPIE, http://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/index.php) [40]. Subsequently, a specific PPI network of DEGs was constructed by cytoscape (version 3.10.1, http://www.cytoscape.org/) [41] based on the interactions retrieved from HiPPIE. To screen the hub genes that might be involved in MS, we applied the Network Analyzer plug-in, using various topological parameters such as node

degree (refers to the number of connections (edges) a given protein (node) has within the network) [42], betweenness (measure that identifies the extent to which a node (protein) serves as a bridge or intermediary for communication between other nodes (proteins) in the network) [43], stress (network metric that measures how much a node (protein) is involved in "stress" or bottleneck situations within the network) [44] and closeness (measure that indicates how close a node (protein) is to all other nodes in the network) [45]. In addition, PEWCC analysis [46] in cytoscape was used to identify the significant modules of the PPI network

Construction of the miRNA-hub gene regulatory network

miRNet database (https://www.mirnet.ca/) [47] is used to explore miRNA- hub gene interactions for the input hub genes from PPI network and assess the effect of the miRNA on the expression of the hub gene. The parameters used were as follows: specify organism: H. sapiens (human); set ID type: Official Gene Symbol; hub gene - miRNA interaction database: TarBase, miRTarBase, miRecords, miRanda (S mansoni only), miR2Disease, HMDD, PhenomiR, SM2miR, PharmacomiR, EpimiR, starBase, TransmiR, ADmiRE and TAM 2. Cytoscape (v. 3.10.1) [41] software was used to visualize the miRNA-hub gene regulatory network.

Construction of the TF-hub gene regulatory network

NetworkAnalyst (https://www.networkanalyst.ca/) [48] is used to explore TF- hub gene interactions for the input hub genes from PPI network and assess the effect of the TF on the expression of the hub gene. The parameters used were as follows: specify organism: H. sapiens (human); set ID type: Official Gene Symbol; hub gene -TF interaction database: JASPER. Cytoscape (v. 3.10.1) [41] software was used to visualize the TF-hub gene regulatory network.

Receiver operating characteristic curve (ROC) analysis

ROC curve analysis, which shows indicators of accuracy such as the area under the curve (AUC), provides the fundamental principle and rationale for distinguishing between the specificity and sensitivity of diagnostic performance of hub genes. The diagnostic utility of hub genes in MS was then assessed using a pROC package in R bioconductor tool [49]. Expressions of hub genes within the training

and validating datasets were illustrated for assessment. When the area under the curve (AUC) exceeds 0.9, the hub gene will be regarded as good diagnostic value for MS.

Molecular docking study

Insilico molecular docking studies

Software tools:

Swiss-model, RCSBPDB, Prank web, ChemDraw, Avogadro tool, Autodock 1.7.1, and Autodock Vina tools, Biovia Discovery Studio client 2021.

Receptor and ligand preparation

The 3D crystal structure of the respective proteins was obtained from the respective genes by using the PDB IDs were downloaded from the RCSB Protein Data Bank (PDB) [50] (Table 1). The missing residues were remodelled by the Swiss-Model web server and downloaded in the pdb format [51]. Then the binding sites were identified by using the server Prank web [52], the pdb format of protein was inserted in the Software Auto Dock Tools 1.7.1, water molecules and hat atoms were removed. The receptor has also been screened for them issuing aminoacid residues, repaired missing residues, Kollman charges, and only Polar hydrogens were added. The grid was fixed using the Autogrid utilityin such a way that to covered the whole receptor, and later saved the grid dimension file [53].The structures of ligands were drawn by using ChemDraw (Fig.1) and copied as SMILES, followed by loading them into Avogadro software for converting them from 2D to 3D structures in pdb format, then pdb format of the ligand was inserted in Auto Dock Tools 1.7.1, then the root of the ligand molecule was detected and chosen. Finally, the ligand molecule was saved in the pdbqt format.

Performing AutodockVina

There are two ways to run Auto Dock Vina: from the Autodock tool or the command line (cmd). For running Autodock Vina, the configuration file was prepared, the grid dimension file saved previously consists of active site, x, y, and z coordinates, and n-pointsof the protein. That data was inserted into the config file; aconfig file was created which included the information of the active site of

the protein, also it includes the log file in the form of .txt format and output file in the form of pdbqt. Autodock Vinawas run on the command line. The command "vina.exe -- config config.txt" was given to run Auto Dock Vina once the run was completed, docked coordinates were out in the pdbqt format, the file was used to visualize the receptor-ligand interactions, and the log.txt file was used to find binding affinity [53].

Visualization

The docking results have been visualized by using the Biovia Discovery Studio Client 2021software. The output pdbqt file and the receptor pdbqt file format were inserted into the Discovery Studio Client2011software. The 3D image of the docked ligand in the PNG format, and the 2D image of the docked, which is bound to the different amino acids, are then saved in the form of PNG format [54].

Results

Identification of DEGs

Data from an overall 73 MS and 25 normal control samples from NGS datasets (GSE138614) was studied in a retrospective manner in the present research. The DEGs of the metadata were studied via the DESeq2 R bioconductor package. A threshold of adj. P-value <0.05, logFC (fold change) > 2.2 for up regulated genes and logFC (fold change) < -0.866 for down regulated genes were utilized to screen DEGs in the dataset of GSE138614. An overall 959 DEGs were identified: 479 genes were remarkably regulated upward and 480 genes were distinctly regulated downward (Table 2). In the volcano plot, every plot indicated a gene and the green plots were up regulated genes, the red plots were down regulated genes (Fig. 2). Then, heatmap (Fig. 3) identified that the expression difference of DEGs between MS samples and normal control samples was very decided.

GO and pathway enrichment analyses of DEGs

The DEGs were submitted to g:Profiler online tool for REACTOME pathway enrichment and GO enrichment analysis involving BP, CC and MF. Eligible terms for GO enrichment analysis of up and down regulated genes were shown in Fig. 4 and Fig. 5, and the number of enriched genes and adjusted P-value were shown in Table 3. From the figures and tables, it is evident that the DEGs were

primarily enriched in immune system process, response to stimulus, developmental process and multicellular organismal process (BP); membrane, protein-containing complex, cellular anatomical entity and cytoplasm (CC); antigen binding, signaling receptor binding, molecular function regulator activity and molecular function activator activity (MF). Eligible terms for pathway enrichment analysis of up and down regulated genes were shown in were shown in Fig. 4 and Fig. 5, and the number of enriched genes and adjusted P-value were shown in Table 4. From the figures and tables, it is evident that the DEGs were primarily enriched in immune system, TCR signaling, regulation of cholesterol biosynthesis by SREBP (SREBF) and degradation of the extracellular matrix.

Construction of the PPI network and module analysis

To explore the interactions between the proteins expressed by the DEGs, we constructed a PPI network using the HiPPIE online PPI database. Cytoscape (version 3.10.1) was used for visualization of PPI network. The PPI network of DEGs contained 4247 nodes (genes) and 6403 edges (interactions) (Fig 6). The hub genes include LCK, PYHIN1, SLAMF1, DOK2, TAB2, CFTR, RHOB, LMNA, EGLN3 and ERBB3 had relatively highest node degree, betweenness, stress and closeness scores (Table 5). Furthermore, PEWCC application results were indicative of two significant modules. Module 1 and module 2 were significant modules in the PPI network. The GO term and REACTOME pathway enrichment analyses of genes involved in two significant modules were analyzed. A total of 47 nodes and 54 edges were included in Module 1 (Fig. 7). Results showed that hub genes in module 1 was mainly enriched in immune system process, immune system and signaling by interleukins (Fig. 8). A total of 28 nodes and 32 edges were included in module 2 (Fig. 9). Results showed that hub genes in module 2 was mainly enriched in cellular anatomical entity (Fig. 10).

Construction of the miRNA-hub gene regulatory network

For the hub genes we identified, a miRNA-hub gene regulatory network was constructed including 8791 edges (interaction pairs among the selected hub genes) and 2203 nodes (miRNA: 1973; Hub Gene: 230) (Fig. 11). While IKZF3 was found to be regulated by 147 miRNAs (ex: hsa-mir-6794-3p); TAB2 was found to be regulated by 118 miRNAs (ex: hsa-mir-3689a-3p); C6orf141 was

found to be regulated by 59 miRNAs (ex: hsa-mir-4449); SDC1 was found to be regulated by 47 miRNAs (ex: hsa-mir-146a-5p); CCR4 was found to be regulated by 45 miRNAs (ex: hsa-mir-4695-5p); RHOB was found to be regulated by 216 miRNAs (ex: hsa-mir-4651); LGALS3BP was found to be regulated by 99 miRNAs (ex: hsa-mir-548q); SFN was found to be regulated by 91 miRNAs (ex: hsa-mir-8485); CDH1 was found to be regulated by 75 miRNAs (ex: hsa-mir-195-5p); POLR2F was found to be regulated by 68 miRNAs (ex: hsa-mir-4739) (Table 6).

Construction of the TF-hub gene regulatory network

For the hub genes we identified, a TF-hub gene regulatory network was constructed including 1809 edges (interaction pairs among the selected hub genes) and 312 nodes (TF: 80; Hub Gene: 232) (Fig. 12). While LTF was found to be regulated by 15 TFs (ex: BRCA1); CD79A was found to be regulated by 10 TFs (ex: HNF4A); LCK was found to be regulated by 10 TFs (ex: NFKB1); IKZF3 was found to be regulated by 9 TFs (ex: TEAD1); TAB2 was found to be regulated by 8 TFs (ex: ELK4); MAP1LC3A was found to be regulated by 14 TFs (ex: TFAP2C); CFTR was found to be regulated by 10 TFs (ex: NR2F1); LLGL2 was found to be regulated by 8 TFs (ex: FOXO3); POLR2F was found to be regulated by 8 TFs (ex: NRF1); FOXE1 was found to be regulated by 8 TFs (ex: NFYA) (Table 6).

Construction of the drug-hub gene interaction network

Drug-hub gene interaction network was constructed. For up regulated genes or targets (Fig. 13 and Table 7), 20 drugs (ex: Palivizumab) targeted FCGR2B, 15 drugs (ex: Cu-Bicyclam) targeted LYZ, 14 drugs (ex: Nintedanib) targeted LCK, 7 drugs (ex: Goserelin) targeted LHCGR and 5 drugs (ex: Ofatumumab) targeted MS4A1, while down regulated genes or targets (Fig. 14 and Table 6), 8 drugs (ex: Lumacaftor) targeted CFTR, 6 drugs (ex: Zonisamide) targeted CA9, 5 drugs (ex: Bentiromide) targeted HPN, 4 drugs (ex: Tamoxifen) targeted PRKCQ and 4 drugs (ex: Urokinase) targeted LRP2.

Receiver operating characteristic curve (ROC) analysis

To access the potential prediction function of hub genes in MS, ROC curves were established to evaluate the diagnostic specificity and sensitivity of hub genes using the “pROC” R bioconductor package. The AUC was calculated for each hub gene. The results are as follows: LCK (AUC□=□0.931), PYHIN1 (AUC□=□0.902), SLAMF1 (AUC□=□0.912), DOK2 (AUC□=□0.933), TAB2 (AUC□=□0.916), CFTR (AUC□=□0.920), RHOB (AUC□=□0.935), LMNA (AUC□=□0.921), EGLN3 (AUC□=□0.927) and ERBB3 (AUC□=□0.925) (Fig. 15). All hub genes exhibited high diagnostic value for MS.

Insilico molecular docking studies

The ligands were obtained from network analysis and used to find the best suitable fit for their respective receptors and the data were described belowMolecular docking study of selected ligands were performed well, and results analysis was carried out, it was indicative of all molecule was bound well, Nintedanib with LCK (Pdb id: 2go8), Glyburide with CFTR (Pbd id: 2pzg), Glyburide with CFTR (Pdb id: 2bbs), Caffeine with CA9 (Pdb id: 5dvx), Goserelin with LHCGR (1qfw), Caffeine with CA14 (Pdb id: 4lu3), Glucosamine 6-sulfate with HGF (Pdb id: 3hms), Phosphoserine with PRKCQ (Pdb id: 1xjd), receptor with binding affinity of -9.7, -8.5, -7.5, -6.7, -6.6, -5.6, and -5.2 Kcal/mol respectively (Table 8). Among all the screened compounds, Ninatanib and Glyburide exhibited the highest negative binding energy with -9.7 and -8.5 kcal/mol, and also exhibited electrostatic, hydrogen bonding, hydrophobic, and ionic bonding interactions with the amino acids of the receptors, as depicted in Fig. 16 and Fig. 17. Other molecules exhibited moderate to good binding affinity with respective receptors, and 2D and 3D images are given below Fig. 18 to Fig. 23**.**

Discussion

MS is a high-incidence autoimmune inflammatory and non-traumatic disabling disease, often resulting in heterogeneous array of symptoms and signs because of differential involvement of motor, sensory, visual and autonomic systems [55]. However, in most cases, the clinical results are suboptimal. Therefore, understanding the pathological changes and molecular mechanisms of MS is essential for clinical diagnosis and treatment. Efficient bioinformatics analyses of NGS data help us understand the molecular mechanisms of the disease onset and

advancement, which is invaluable for diagnostic and prognostic biomarkers, and therapeutic target identification [56-57]. In our study, 959 DEGs (479 up-regulated and 480 down-regulated genes) were identified between MS brain white matter samples and normal control brain white matter samples based on NGS dataset. Recent studies have shown that IGHV4-39 [58] play important roles in MS. Previous studies have demonstrated that PLAC8 [59] was shown to be involved in the obesity. Studies have shown that PLAC8 [59] might contribute to the pathogenesis of diabetes mellitus and could be a potential biomarkers for predicting disease progression and therapeutic effects in diabetes mellitus patients.. These findings might contribute to a better understanding of the molecular mechanisms underlying the pathogenesis of MS and its associated complications.

GO and REACTOME pathway enrichment analyses were used to explore the molecular mechanisms of the genes involved in the occurrence and development of MS and its associated complications. It is well known that the signaling pathways include immune system [60], TCR signaling [61], cytokine signaling in immune system [62], degradation of the extracellular matrix [63], extracellular matrix organization [63], metabolism of lipids [64] and metabolism [65] plays an important role only in MS. Recent studies have found that genes include CCL18 [66], FCRL3 [67], EOMES (eomesodermin) [68], CCR2 [69], IL2RB [70], CCL4 [71], FASLG (Fas ligand) [72], CD24 [73], IKZF3 [74], CD2 [75], CD28 [76], IL7R [77], HLA-DRB5 [78], ICOS (inducible T cell costimulator) [79], CCL5 [80], CTLA4 [81], IRF4 [82], C6 [83], NCR1 [84], CHIT1 [85], CD52 [86], CD163 [87], HGF (hepatocyte growth factor) [88], DIO3 [89], SIGLEC1 [90], TTR (transthyretin) [91], IL9 [92], VEGFA (vascular endothelial growth factor A) [93], CR2 [94], ANGPTL4 [95], CHI3L1 [96], MAG (myelin associated glycoprotein) [97], CNP (2',3'-cyclic nucleotide 3' phosphodiesterase) [98], CMTM5 [99], SEMA4D [100], NGFR (nerve growth factor receptor) [101], TF (transferrin) [102], MYRF (myelin regulatory factor) [103], MOG (myelin oligodendrocyte glycoprotein) [104], ADAMTS4 [105], BMP2 [106], HTRA1 [107], PNPLA3 [108], DYSF (dysferlin) [109], NINJ2 [110], LRP2 [111], ADAMTS14 [112] and DHCR7 [113] participates in the pathophysiological progression of MS. Recent evidence indicates that genes include CCL18 [114], SLAMF7 [115], GPR174 [116], CCR4 [117], POU4F2 [118]. CCR2 [119], IL2RB [120], CCL4 [121], CCL24 [122], FASLG (Fas ligand)

[123], CD24 [124], TDGF1 [125], CD28 [126], IL7R [127], CYP11B1 [128], CCL5 [129], CCL3 [130], LTF (lactotransferrin) [131], GPNMB (glycoprotein nmb) [132], CD209 [133], IL2RG [134], CHIT1 [135], TAB2 [136], CD163 [137], ALOX15B [138], NMRK2 [139], HGF (hepatocyte growth factor) [140], TRPM8 [141], DIO3 [142], SIGLEC1 [143], TTR (transthyretin) [144], IL24 [145], F13A1 [146], IL9 [147], VEGFA (vascular endothelial growth factor A) [148], RASAL1 [149], ADM (adrenomedullin) [150], ANGPTL4 [151], CHI3L1 [152], LDB3 [153], CNP (2',3'-cyclic nucleotide 3' phosphodiesterase) [154], HES6 [155], CMTM5 [156], PLXNB3 [157], KLK8 [158], CDKN1C [159], INSIG1 [160], GREM1 [161], ATF3 [162], HK2 [163], MCAM (melanoma cell adhesion molecule) [164], SEMA4D [165], GLUL (glutamate-ammonia ligase) [166], S1PR5 [167], FN3K [168], MEIS1 [169], ADAMTS4 [170], BIN1 [171], BMP2 [172], LMNA (lamin A/C) [173], ERBB3 [174], DLL1 [175], THBS2 [176], GADD45B [177], MYH6 [178]. PNPLA3 [179], ACTN2 [180], MMP15 [181], SVEP1 [182], CPB2 [183], DYSF (dysferlin) [184], ADAMTSL2 [185], NINJ2 [186], LRP2 [111], PHLDA3 [187], LIPC (lipase C, hepatic type) [188], CARNS1 [189], PRODH (proline dehydrogenase 1) [190], TRPV6 [191], CNDP1 [192], DHCR7 [193], KCNE5 [194] SAA1 [195], ADSS1 [196], ACADS (acyl-CoA dehydrogenase short chain) [197], ADAP1 [198], KLK10 [199], HCN2 [200], F11 [201], RNASE1 [202], GNLY (granulysin) [203], EVA1A [204], CIRBP (cold inducible RNA binding protein) [205], EDIL3 [206], NOXA1 [207], ANGPTL2 [208], CYP2A6 [209] and CTNNA3 [210] might be implicated in the cardiovascular diseases progression. Gene include CCL18 [211], EOMES (eomesodermin) [212], GZMA (granzyme A) [213], HLA-DRB5 [214], GPNMB (glycoprotein nmb) [215], PRPH (peripherin) [216], HGF (hepatocyte growth factor) [217], TTR (transthyretin) [218], VEGFA (vascular endothelial growth factor A) [219], CHI3L1 [220], AATK (apoptosis associated tyrosine kinase) [221], SREBF1 [222], OLIG2 [223], ATF3 [224], NGFR (nerve growth factor receptor) [225], ADAMTS4 [226], LMNA (lamin A/C) [227], MT3 [228], DAO (D-amino acid oxidase) [229] and LGALS3BP [230] might be related to the progression of amyotrophic lateral sclerosis. SLAMF7 [231], GPR174 [232], FCRL3 [233], SLAMF6 [234], EOMES (eomesodermin) [235], CCR4 [236], CCR2 [237], CD48 [238], CD3E [239], CCL26 [240], CCL4 [241], SLAMF1 [242], CD24 [243], IKZF3 [244], CD2 [245], CD28 [246], IL7R [247], FCGR2B [248], UBASH3A [249], CD1C [250], ICOS (inducible T cell costimulator) [251],

CD3G [252], CCL3 [253], LTF (lactotransferrin) [254], GPNMB (glycoprotein nmb) [255], CTLA4 [256], IRF4 [257], TNFRSF9 [258], FCRL5 [259], LAIR2 [260], TAB2 [261], CD52 [232], CD163 [263], MSR1 [264], HGF (hepatocyte growth factor) [265], SIGLEC1 [266], TTR (transthyretin) [267], IL24 [268], IL9 [269], CHI3L1 [270], CDH1 [271], OLIG2 [272], NKX6-2 [273]. HK2 [274], PNPLA3 [275], CPB2 [276], SEMA4C [277], LRP2 [278], SLC5A11 [279], F11 [280], ANGPTL2 [281] and CYP2A6 [282] might serve as molecular markers for autoimmune disease. Recent studies have found that genes include SLAMF7 [283], FCRL3 [284], CCR4 [285], GZMA (granzyme A) [286], CCR2 [287], CD48 [288], CD3E [289], CCL4 [290], FASLG (Fas ligand) [291], SLAMF1 [292], CD28 [293], IL7R [294], UBASH3A [295], CD3D [296], ICOS (inducible T cell costimulator) [297], CCL5 [298], CCL3 [299], LTF (lactotransferrin) [300], CTLA4 [301], TNFRSF9 [258], C6 [302], IL5RA [303], IL2RG [304], NPY2R [305], DRD3 [306], CD52 [307], CD163 [308], IQGAP2 [309], PRPH (peripherin) [310], MSR1 [311], HGF (hepatocyte growth factor) [312], TTR (transthyretin) [313], IL9 [314], ADM (adrenomedullin) [315], ANGPTL4 [316], CHI3L1 [317], CDH1 [318], SREBF1 [319], CDKN1C [320], TSC22D4 [321], CFTR (CF transmembrane conductance regulator) [322], INSIG1 [323], HSD17B3 [324], GREM1 [325], ATF3 [326], HK2 [327], TF (transferrin) [328], GLUL (glutamate-ammonia ligase) [329], DMRT2 [330], FN3K [331], TREH (trehalase) [332], ADAMTS4 [333], BMP2 [334], LMNA (lamin A/C) [335], ERBB3 [336], HSD11B1 [337], DLL1 [338], NKX2-2 [339], FGF11 [340], ASPA (aspartoacylase) [341], FASN (fatty acid synthase) [342], PNPLA3 [343], ADORA1 [344], WNT7A [345], LIPC (lipase C, hepatic type) [346], GPR142 [347], GPD1 [348], LIPE (lipase E, hormone sensitive type) [349], CNDP1 [192], DHCR7 [350], SAA1 [351], TKTL1 [352], ACADS (acyl-CoA dehydrogenase short chain) [353], SCD (stearoyl-CoA desaturase) [354], FFAR1 [355], HCN2 [200], F11 [356], GPIHBP1 [357], ANGPTL2 [208], MAPK8IP1 [358], CYP2A6 [359] and CTNNA3 [360] have been reported its expression in the diabetes mellitus. Studies have revealed that genes include MS4A2 [361], CD48 [362], HLA-DRB5 [363], FCGR2B [364], CCL5 [365], CCL3 [366], LTF (lactotransferrin) [367], GPNMB (glycoprotein nmb) [368], CTLA4 [369], TRIML2 [370], PTGDR (prostaglandin D2 receptor) [371], DRD3 [372], LHCGR (luteinizing hormone/choriogonadotropin receptor) [373], CD163 [374], PRPH (peripherin) [216], MSR1 [375], HGF (hepatocyte growth factor) [376], TTR

(transthyretin) [377], IL9 [378], ADM (adrenomedullin) [379], CHI3L1 [380], CNP (2',3'-cyclic nucleotide 3' phosphodiesterase) [381], CDH1 [382], OLIG2 [383], KLK8 [384]. CFTR (CF transmembrane conductance regulator) [385], ABCA2 [386], HK2 [387], NGFR (nerve growth factor receptor) [388], TF (transferrin) [389], GLUL (glutamate-ammonia ligase) [329], ADAMTS4 [390], BIN1 [391], HSPA2 [392], LMNA (lamin A/C) [393], HSD11B1 [394], HTRA1 [395], APLP1 [396], MT3 [397], ADORA1 [398], DYSF (dysferlin) [399], SLC24A4 [400], RHOB (ras homolog family member B) [401], NINJ2 [402], LRP2 [403], LIPC (lipase C, hepatic type) [404], DHCR7 [405], SCD (stearoyl-CoA desaturase) [406], F11 [407], PFKL (phosphofructokinase, liver type) [408], ALDH1A1 [409], SPON1 [410] and CTNNA3 [411] plays a role in diagnosis of Alzheimer's Disease. The abnormal activation of genes include CCR4 [412], CCR2 [413], CD48 [414], CD28 [415], CCL3 [416], CTLA4 [417], C6 [418], MICB (MHC class I polypeptide-related sequence B) [419], DRD3 [420], HGF (hepatocyte growth factor) [421], DIO3 [422], TTR (transthyretin) [423], GRHL3 [434], VEGFA (vascular endothelial growth factor A) [425], ADM (adrenomedullin) [426], CHI3L1 [427], SOX3 [428], MAG (myelin associated glycoprotein) [429], CNP (2',3'-cyclic nucleotide 3' phosphodiesterase) [430], SREBF1 [431], OLIG2 [432], ATF3 [433], NGFR (nerve growth factor receptor) [434], TF (transferrin) [435], GLUL (glutamate-ammonia ligase) [329]. MOG (myelin oligodendrocyte glycoprotein) [436], ERBB3 [437], NHLH2 [438], GADD45B [439], PADI2 [440], ADORA1 [441], NINJ2 [442], WNT7A [443], DAO (D-amino acid oxidase) [444], PRODH (proline dehydrogenase 1) [445] and HCRTR1 [446] in psychiatric disorders and are a significant cause of disease progression. Some researchers have reported that altered CCR2 [447], FASLG (Fas ligand) [448], GPNMB (glycoprotein nmb) [449], NPY2R [450], TRPM8 [451], TTR (transthyretin) [452], ADM (adrenomedullin) [453], CHI3L1 [380], CDH1 [382], HIP1R [454], SEMA4D [455], HAPLN2 [456], MYRF (myelin regulatory factor) [457], BIN1 [458], BMP2 [459], APLP1 [396], SEPTIN4 [460], DAO (D-amino acid oxidase) [461], TKTL1 [352], ADAP1 [462], HPDL (4-hydroxyphenylpyruvate dioxygenase like) [463], NME3 [464], SPON1 [465] and LGALS3BP [230] expression in the neurodegenerative diseases. Some studies have shown that genes include CCR2 [466], FASLG (Fas ligand) [467], CD28 [468], LYZ (lysozyme) [469], CCL5 [470], CCL3 [471], C6 [472], MSR1 [473],

HGF (hepatocyte growth factor) [474], VEGFA (vascular endothelial growth factor A) [475], ADM (adrenomedullin) [476], CR2 [477], MAG (myelin associated glycoprotein) [478], CDH1 [479], OLIG2 [480], SEMA4D [481], ADAMTS4 [482], BMP2 [483], ERBB3 [484] and NKX2-2 [485] plays a certain role in spinal cord injury. The altered expression of genes include CCR2 [486], FASLG (Fas ligand) [291], CD24 [487], CD28 [488], LYZ (lysozyme) [489], IL7R [490], CCL5 [491], LTF (lactotransferrin) [492], GPNMB (glycoprotein nmb) [493], CTLA4 [494], IRF4 [495], CHIT1 [496], NPY2R [497], TAB2 [136], CD52 [307], CD163 [498], MSR1 [311], HGF (hepatocyte growth factor) [499], TRPM8 [500], TTR (transthyretin) [501], F13A1 [502], ADM (adrenomedullin) [503], COL9A3 [504], ANGPTL4 [505], CHI3L1 [506], BMP8A [507], SREBF1 [508], CDKN1C [509], INSIG1 [510], ATF3 [511], HK2 [512], TF (transferrin) [513], MOG (myelin oligodendrocyte glycoprotein) [514], ADAMTS4 [515], BMP2 [516], HSPA2 [517], LMNA (lamin A/C) [335], HSD11B1 [518], NKX2-2 [519], NHLH2 [438], FGF11 [520], ASPA (aspartoacylase) [341], FASN (fatty acid synthase) [521], PNPLA3 [522], MMP15 [523], CBR1 [524], LRP2 [525], WNT7A [345], GPR142 [526], GPD1 [348], LIPE (lipase E, hormone sensitive type) [527], CNDP1 [528], SAA1 [529], ACADS (acyl-CoA dehydrogenase short chain) [353], SCD (stearoyl-CoA desaturase) [530], GPIHBP [531], LMF1 [532], IGSF1 [533], LSS (lanosterol synthase) [534], ALDH1A1 [535], ANGPTL2 [536], NENF (neudesin neurotrophic factor) [537] and CYP2A6 [538] promotes occurrence and progression of obesity. A previous study reported that the genes include CCR2 [539], CCL4 [540], TNFRSF13B [541], FASLG (Fas ligand) [542], CD28 [543], CYP11B1 [544], CCL5 [545], LTF (lactotransferrin) [546], CTLA4 [547], DRD3 [548], HGF (hepatocyte growth factor) [499], TRPM8 [549], IL9 [550], NPPC (natriuretic peptide C) [551], ANGPTL4 [552], CHI3L1 [553], SREBF1 [554], GDF2 [555], CFTR (CF transmembrane conductance regulator) [556], ATF3 [557], HK2 [558], NGFR (nerve growth factor receptor) [559], MEIS1 [560], MOG (myelin oligodendrocyte glycoprotein) [561], BMP2 [562], LMNA (lamin A/C) [563], ERBB3 [336], HSD11B1 [564], THBS2 [565], FASN (fatty acid synthase) [566], PNPLA3 [567], SLC45A3 [568], WNT7A [569], SCNN1G [570], TRPV5 [571], ACADS (acyl-CoA dehydrogenase short chain) [572], GNLY (granulysin) [573], NOXA1 [574], ANGPTL2 [575], SPON1 [576], CYP2A6 [577] and RASA3 [578] were associated with hypertension. Altered expression of genes include FASLG (Fas ligand) [579], GJC2 [580] and GJB1

[581] have been demonstrated to be regulated in spasticity. Genes include CD24 [582], CD28 [583], HLA-DRB5 [584], LTF (lactotransferrin) [585], GPNMB (glycoprotein nmb) [586], TNFRSF9 [587], LRRC37A2 [588], DRD3 [589], CD163 [374], HGF (hepatocyte growth factor) [590], TRPM8 [451], TTR (transthyretin) [591], VEGFA (vascular endothelial growth factor A) [592], CHI3L1 [593], MAG (myelin associated glycoprotein) [594], SREBF1 [222], HIP1R [595], HK2 [596], GPR37 [597], NGFR (nerve growth factor receptor) [598], TF (transferrin) [599], HAPLN2 [456], MOG (myelin oligodendrocyte glycoprotein) [600], BIN1 [601], BMP2 [602], GADD45B [603], UNC5B [604], ADORA1 [605], SEPTIN4 [606], DHCR7 [607], SCD (stearoyl-CoA desaturase) [608], GIPC1 [609], ALDH1A1 [610] and CTNNA3 [611] have been shown to influence the genetic risk of Parkinson's disease. However, further investigations are needed to explore and confirm the potentially significant GO terms and signaling pathways for MS and to achieve a comprehensive understanding of this process.

Based on the PPI network constructed and modules analyzed by the online PPI database HiPPIE, we identified hub genes. Previous studies have proven that the hub genes include SLAMF1 [242], TAB2 [261] and HGF (hepatocyte growth factor) [265] as a genetic locus associated with autoimmune disease susceptibility. Recent studies have shown that hub genes include SLAMF1 [292], CFTR (CF transmembrane conductance regulator) [322], LMNA (lamin A/C) [335], ERBB3 [336], HGF (hepatocyte growth factor) [312] and CCL5 [298] are genetic risk factors have been shown to increase susceptibility to diabetes mellitus. Hub genes include TAB2 [136], LMNA (lamin A/C) [173], ERBB3 [174], HGF (hepatocyte growth factor) [140] and CCL5 [129] have been reported its expression in the cardiovascular diseases. Altered levels of hub genes include TAB2 [136], LMNA (lamin A/C) [335], HGF (hepatocyte growth factor) [499] and CCL5 [491] have been detected in the obesity. Hub genes include CFTR (CF transmembrane conductance regulator) [385], RHOB (ras homolog family member B) [401], LMNA (lamin A/C) [393], HGF (hepatocyte growth factor) [376], CCL5 [365] and NGFR (nerve growth factor receptor) [388] expression was shown to be regulated in a Alzheimer's Disease. Altered level of hub genes include CFTR (CF transmembrane conductance regulator) [556], LMNA (lamin A/C) [563], ERBB3 [336], HGF (hepatocyte growth factor) [499], CCL5 [545] and NGFR (nerve

growth factor receptor) [559] can facilitate hypertension progression. Hub Genes include LMNA (lamin A/C) [227], HGF (hepatocyte growth factor) [217] and NGFR (nerve growth factor receptor) [225] have been identified the involvement in amyotrophic lateral sclerosis. Hub genes include ERBB3 [437], HGF (hepatocyte growth factor) [421] and NGFR (nerve growth factor receptor) [434] could potentially play a role in the onset of psychiatric disorders. Hub genes include ERBB3 [484], HGF (hepatocyte growth factor) [474] and CCL5 [470] were found to be linked with spinal cord injury. Hub genes include HGF (hepatocyte growth factor) [88], CCL5 [80] and NGFR (nerve growth factor receptor) [101] were recently found to be a promoter of MS. Hub genes include HGF (hepatocyte growth factor) [590] and NGFR (nerve growth factor receptor) [598] plays a crucial role in establishing Parkinson's disease. Our findings suggest that hub genes include LCK (LCK proto-oncogene, Src family tyrosine kinase), PYHIN1, DOK2, EGLN3, SDC1 and FSCN1 served as a novel biomarkers for MS. However, the exact molecular mechanism of MS progression remains unknown. This investigation might provide reference for research the connection between MS and its associated complication.

MiRNA-hub gene regulatory network analyses and TF-hub gene regulatory network are formed from the interactions of hub genes, miRNAs and TFs, and participate in all steps of the MS advancement. Recent research indicated that biomarkers include IKZF3 [74], hsa-mir-146a-5p [612], BRCA1 [613] and NFKB1 [614] might be considered as a pathogenic genetic factors for MS. Previous studies have shown that biomarkers include IKZF3 [244], TAB2 [261], CCR4 [236], LTF (lactotransferrin) [254], CDH1 [271], BRCA1 [615], NFKB1 [616] and FOXO3 [617] might have a significant role in the development of autoimmune disease. Several studies suggested that biomarkers include TAB2 [136], CCR4 [117], LTF (lactotransferrin) [131], hsa-mir-146a-5p [618], hsa-mir-8485 [619], BRCA1 [620], NFKB1 [621], TEAD1 [622], TFAP2C [623], FOXO3 [624] and NRF1 [625] might serve as therapeutic targets for cardiovascular diseases. A recent study showed that biomarkers include TAB2 [136], LTF (lactotransferrin) [492], BRCA1 [626], NFKB1 [627], TEAD1 [628], FOXO3 [629] and NRF1 [630] improves progression of obesity. The dysregulation of cellular processes that involve biomarkers include CCR4 [285], LTF (lactotransferrin) [300], CDH1 [318], CFTR (CF transmembrane conductance regulator) [322], hsa-mir-146a-5p [631], hsa-mir-

195-5p [632], hsa-mir-4739 [633], HNF4A [634], NFKB1 [635], NR2F1 [636], FOXO3 [637] and NRF1 [638] have been linked to the development of diabetes mellitus. A previous study reported that the biomarkers include CCR4 [412], hsa-mir-146a-5p [639] and NFKB1 [640] were associated with psychiatric disorders. LTF (lactotransferrin) [367], RHOB (ras homolog family member B) [401], CDH1 [382], CFTR (CF transmembrane conductance regulator) [385], hsa-mir-146a-5p [641], hsa-mir-195-5p [642], BRCA1 [643], ELK4 [644] and FOXO3 [645] were associated with Alzheimer's disease. Biomarkers include LTF (lactotransferrin) [546], CFTR (CF transmembrane conductance regulator) [556], hsa-mir-195-5p [632], BRCA1 [646], NFKB1 [647], TFAP2C [648], FOXO3 [649] and NRF1 [650] might be a potential therapeutic targets for hypertension. In many clinical studies, biomarkers include LTF (lactotransferrin) [585], hsa-mir-146a-5p [651], hsa-mir-195-5p [642], HNF4A [652], NFKB1 [643], NR2F1 [654], FOXO3 [655] and NRF1 [656] were alerted expression in Parkinson's disease. Findings have shown that biomarkers include LGALS3BP [230] and BRCA1 [657] expression is regulated in amyotrophic lateral sclerosis. Studies have shown that biomarkers include LGALS3BP [230], CDH1 [382], hsa-mir-146a-5p [658], BRCA1 [659], HNF4A [660], FOXO3 [661] and NRF1 [662] plays an important role in the development of neurodegenerative diseases. A previous study found that biomarkers include CDH1 [479] and FOXO3 [663] have been linked to the development of spinal cord injury. Hence, the results of these regulatory networks analysis were in accordance with experimental results on MS. The roles of novel biomarkers in the these networks were determined and still not reported in MS and its associated complications, such as C6orf141, SDC1, CD79A, LCK (LCK proto-oncogene, Src family tyrosine kinase), SFN (stratifin), POLR2F, MAP1LC3A, LLGL2, FOXE1, hsa-mir-6794-3p, hsa-mir-3689a-3p, hsa-mir-4449, hsa-mir-4695-5p, hsa-mir-4651, hsa-mir-548q and NFYA (nuclear transcription factor Y subunit alpha). The intricate interaction between MSs, TFs and hub genes made great improvement to the advancement of MS.

All the screened molecules were very well bound with respective protein molecules, and some of them showed potential binding affinity Nintedanib to LCK and Glyburide to CFTR genes, Nintedanib and Glyburide might be the potential lead molecule to bring breakthrough in the field of medicine in future. All the data

needs further research on these two molecules in the future to combat the burden of MS on humankind.

Nevertheless, our study has some limitations. Firstly, due to the fact that the data we used were obtained from brain white matter, derived from of MS patients are desired for clinical application. Secondly, although we have validated the hub gene in ROC analysis, the validity of the hub genes, miRNAs and TFs for MS diagnosis must be confirmed in in-vitro cell culture experiments and in-vivo animal or human experiments as possible in the future. In addition, due to the lack of comprehensive clinical data, we were inadequate to check the relationship between patients with distinct clinical symptoms and complications, and hub genes, miRNAs and TFs. Future investigation could expand the sample size and execute comprehensive phenotyping of patients, to superior understand the potential molecular mechanisms underlying MS and its associated complications. We hope that future investigation can overcome these limitations and progresses deeper into the molecular pathogenesis of MS and its associated complications, providing more scientific confirmation for the growth of better treatment options.

Conclusions

To summarize, a total of 959 DEGs, hub genes (LCK, PYHIN1, SLAMF1, DOK2, TAB2, CFTR, RHOB, LMNA, EGLN3 and ERBB3), miRNAs (hsa-mir-6794-3p, hsa-mir-3689a-3p, hsa-mir-4651and hsa-mir-548q) and TFs (BRCA1, HNF4A, TFAP2C and NR2F1) were identified, which could be considered as MS biomarkers. However, further investigations are needed to clarify the biological roles of these genes in MS.

Abbreviations

MS: Multiple sclerosis

DEGs: Differentially expressed genes

NGS: Next generation sequencing

GEO: Gene expression omnibus

GO: Gene 0ntology

PPI: Protein-protein interaction

miRNA: Micro ribonuclic acid

TF: Transcription factor

ROC: Receiver operating characteristic curve

LCK: LCK proto-oncogene, Src family tyrosine kinase

PYHIN1: Pyrin and HIN domain family member 1

SLAMF1: Signaling lymphocytic activation molecule family member 1

DOK2: Docking protein 2

TAB2: TGF-beta activated kinase 1 (MAP3K7) binding protein 2

CFTR: CF transmembrane conductance regulator

RHOB: Ras homolog family member B

LMNA: Lamin A/C

EGLN3: Egl-9 family hypoxia inducible factor 3

ERBB3: Erb-b2 receptor tyrosine kinase 3

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

No informed consent because this study does not contain human or animals participants.

Availability of data and materials

The datasets supporting the conclusions of this article are available in the GEO (Gene Expression Omnibus) (https://www.ncbi.nlm.nih.gov/geo/) repository. [(GSE138614) https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE138614]

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author Contributions

B. V. - Writing original draft, and review and editing

S.P. - Formal analysis and validation

C. V. - Software and investigation

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Reference

1. Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. Am J Med. 2020;133(12):1380-1390.e2. doi:10.1016/j.amjmed.2020.05.049
2. Brenton JN, Kammeyer R, Gluck L, Schreiner T, Makhani N. Multiple Sclerosis in Children: Current and Emerging Concepts. Semin Neurol. 2020;40(2):192-200. doi:10.1055/s-0040-1703000

3. Ow N, Kuspinar A, Mayo NE; for MSOAC. Age differences in trajectories of self-rated health of young people with Multiple Sclerosis. Mult Scler Relat Disord. 2022;57:103322. doi:10.1016/j.msard.2021.103322
4. Lynch SG, Rose JW. Multiple sclerosis. Dis Mon. 1996;42(1):1-55. doi:10.1016/s0011-5029(96)90012-7
5. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, Sormani MP, Thalheim C, Traboulsee A, Vollmer T. Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord. 2016;9 Suppl 1:S5-S48. doi:10.1016/j.msard.2016.07.003
6. Lassmann H. Multiple Sclerosis Pathology and its Reflection by Imaging Technologies: Introduction. Brain Pathol. 2018;28(5):721-722. doi:10.1111/bpa.12649
7. Etoom M, Khraiwesh Y, Lena F, et al. Effectiveness of Physiotherapy Interventions on Spasticity in People With Multiple Sclerosis: A Systematic Review and Meta-Analysis. Am J Phys Med Rehabil. 2018;97(11):793-807. doi:10.1097/PHM.0000000000000970
8. Di Stadio A, Dipietro L, Ralli M, Greco A, Ricci G, Messineo D, Bernitsas E. Clinical and radiological findings of facial paralysis in multiple sclerosis. Mult Scler Relat Disord. 2020;37:101456. doi:10.1016/j.msard.2019.101456
9. Wang G, Marrie RA, Fox RJ, Tyry T, Cofield SS, Cutter GR, Salter A. Treatment satisfaction and bothersome bladder, bowel, sexual symptoms in multiple sclerosis. Mult Scler Relat Disord. 2018;20:16-21. doi:10.1016/j.msard.2017.12.006
10. Menculini G, Mancini A, Gaetani L, Bellingacci L, Tortorella A, Parnetti L, Di Filippo M. Psychiatric symptoms in multiple sclerosis: a biological perspective on synaptic and network dysfunction. J Neurol Neurosurg Psychiatry. 2023;94(5):389-395. doi:10.1136/jnnp-2022-329806
11. Yang F, Hu T, He K, Ying J, Cui H. Multiple Sclerosis and the Risk of Cardiovascular Diseases: A Mendelian Randomization Study. Front Immunol. 2022;13:861885. doi:10.3389/fimmu.2022.861885
12. Inglese M, Petracca M. Imaging multiple sclerosis and other neurodegenerative diseases. Prion. 2013;7(1):47-54. doi:10.4161/pri.22650
13. Yorkston KM, Bamer A, Johnson K, Amtmann D. Satisfaction with participation in multiple sclerosis and spinal cord injury. Disabil Rehabil. 2012;34(9):747-753. doi:10.3109/09638288.2011.619615

14. Lutfullin I, Eveslage M, Bittner S, Antony G, Flaskamp M, Luessi F, Salmen A, Gisevius B, Klotz L, Korsukewitz C, et al. Association of obesity with disease outcome in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2023;94(1):57-61. doi:10.1136/jnnp-2022-329685
15. Hou WH, Li CY, Chang HH, Sun Y, Tsai CC. A population-based cohort study suggests an increased risk of multiple sclerosis incidence in patients with type 2 diabetes mellitus. J Epidemiol. 2017;27(5):235-241. doi:10.1016/j.je.2016.06.006
16. Conway DS, Briggs FB, Mowry EM, Fitzgerald KC, Hersh CM. Racial disparities in hypertension management among multiple sclerosis patients. Mult Scler Relat Disord. 2022;64:103972. doi:10.1016/j.msard.2022.103972
17. Goris A, Vandebergh M, McCauley JL, Saarela J, Cotsapas C. Genetics of multiple sclerosis: lessons from polygenicity. Lancet Neurol. 2022;21(9):830-842. doi:10.1016/S1474-4422(22)00255-1
18. Jörg S, Grohme DA, Erzler M, Binsfeld M, Haghikia A, Müller DN, Linker RA, Kleinewietfeld M. Environmental factors in autoimmune diseases and their role in multiple sclerosis. Cell Mol Life Sci. 2016;73(24):4611-4622. doi:10.1007/s00018-016-2311-1
19. Zheng W, Chen Y, Chen H, Xiao W, Liang Y, Wang N, Jiang X, Wen S. Identification of key target genes and biological pathways in multiple sclerosis brains using microarray data obtained from the Gene Expression Omnibus database. Neurol Res. 2018;40(10):883-891. doi:10.1080/01616412.2018.1497253
20. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA. 2021;325(8):765-779. doi:10.1001/jama.2020.26858
21. Salehi Z, Talebi S, Maleknia S, Palizban F, Naser Moghadasi A, Kavousi K, Sahraian MA, Izad M. RNA Sequencing of CD4+ T Cells in Relapsing-Remitting Multiple Sclerosis Patients at Relapse: Deciphering the Involvement of Novel genes and Pathways. J Mol Neurosci. 2021;71(12):2628-2645. doi:10.1007/s12031-021-01878-8
22. Hecker M, Rüge A, Putscher E, Boxberger N, Rommer PS, Fitzner B, Zettl UK. Aberrant expression of alternative splicing variants in multiple sclerosis - A systematic review. Autoimmun Rev. 2019;18(7):721-732. doi:10.1016/j.autrev.2019.05.010

23. Berge T, Leikfoss IS, Harbo HF. From Identification to Characterization of the Multiple Sclerosis Susceptibility Gene CLEC16A. Int J Mol Sci. 2013;14(3):4476-4497. doi:10.3390/ijms14034476
24. Rubio JP, Stankovich J, Field J, Tubridy N, Marriott M, Chapman C, Bahlo M, Perera D, Johnson LJ, Tait BD, et al. Replication of KIAA0350, IL2RA, RPL5 and CD58 as multiple sclerosis susceptibility genes in Australians. Genes Immun. 2008;9(7):624-630. doi:10.1038/gene.2008.59
25. Liu G, Zhang F, Hu Y, Jiang Y, Gong Z, Liu S, Chen X, Jiang Q, Hao J. Genetic Variants and Multiple Sclerosis Risk Gene SLC9A9 Expression in Distinct Human Brain Regions. Mol Neurobiol. 2017;54(9):6820-6826. doi:10.1007/s12035-016-0208-5
26. Laaksonen H, Guerreiro-Cacais AO, Adzemovic MZ, Parsa R, Zeitelhofer M, Jagodic M, Olsson T. The multiple sclerosis risk gene IL22RA2 contributes to a more severe murine autoimmune neuroinflammation. Genes Immun. 2014;15(7):457-465. doi:10.1038/gene.2014.36
27. Lopez de Lapuente A, Feliú A, Ugidos N, Mecha M, Mena J, Astobiza I, Riera J, Carrillo-Salinas FJ, Comabella M, et al. Novel Insights into the Multiple Sclerosis Risk Gene ANKRD55 [published correction appears in J Immunol. 2016 Nov 15;197(10):4177]. J Immunol. 2016;196(11):4553-4565. doi:10.4049/jimmunol.1501205
28. Vakrakou AG, Alexaki A, Brinia ME, Anagnostouli M, Stefanis L, Stathopoulos P. The mTOR Signaling Pathway in Multiple Sclerosis; from Animal Models to Human Data. Int J Mol Sci. 2022;23(15):8077. doi:10.3390/ijms23158077
29. Michaličková D, Hrnčíř T, Canová NK, Slanař O. Targeting Keap1/Nrf2/ARE signaling pathway in multiple sclerosis. Eur J Pharmacol. 2020;873:172973. doi:10.1016/j.ejphar.2020.172973
30. Leibowitz SM, Yan J. NF-κB Pathways in the Pathogenesis of Multiple Sclerosis and the Therapeutic Implications. Front Mol Neurosci. 2016;9:84. doi:10.3389/fnmol.2016.00084
31. Yuan S, Shi Y, Tang SJ. Wnt signaling in the pathogenesis of multiple sclerosis-associated chronic pain. J Neuroimmune Pharmacol. 2012;7(4):904-913. doi:10.1007/s11481-012-9370-3
32. Nheu D, Ellen O, Ye S, Ozturk E, Pagnin M, Kertadjaja S, Theotokis P, Grigoriadis N, McLean C, Petratos S. Modulation of the Microglial Nogo-

A/NgR Signaling Pathway as a Therapeutic Target for Multiple Sclerosis. Cells. 2022;11(23):3768. doi:10.3390/cells11233768

33. Elkjaer ML, Frisch T, Reynolds R, Kacprowski T, Burton M, Kruse TA, Thomassen M, Baumbach J, Illes Z. Molecular signature of different lesion types in the brain white matter of patients with progressive multiple sclerosis. Acta Neuropathol Commun. 2019;7(1):205. doi:10.1186/s40478-019-0855-7
34. Clough E, Barrett T. The Gene Expression Omnibus Database. Methods Mol Biol. 2016;1418:93-110. doi:10.1007/978-1-4939-3578-9_5
35. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 2014;15(12):550. doi:10.1186/s13059-014-0550-8
36. Solari A, Goeman JJ. Minimally adaptive BH: A tiny but uniform improvement of the procedure of Benjamini and Hochberg. Biom J. 2017;59(4):776-780. doi:10.1002/bimj.201500253
37. Reimand J, Kull M, Peterson H, Hansen J, Vilo J. g:Profiler--a web-based toolset for functional profiling of gene lists from large-scale experiments. Nucleic Acids Res. 2007;35(Web Server issue):W193-W200. doi:10.1093/nar/gkm226
38. Thomas PD. The Gene Ontology and the Meaning of Biological Function. Methods Mol Biol. 2017;1446:15□24. doi:10.1007/978-1-4939-3743-1_2
39. Fabregat A, Jupe S, Matthews L, Sidiropoulos K, Gillespie M, Garapati P, Haw R, Jassal B, Korninger F, May B et al The Reactome Pathway Knowledgebase. Nucleic Acids Res. 2018;46(D1):D649–D655. doi:10.1093/nar/gkx1132
40. Schaefer MH, Lopes TJ, Mah N, Shoemaker JE, Matsuoka Y, Fontaine JF, Louis-Jeune C, Eisfeld AJ, Neumann G, Perez-Iratxeta C, et al. Adding protein context to the human protein-protein interaction network to reveal meaningful interactions. PLoS Comput Biol. 2013;9(1):e1002860. doi:10.1371/journal.pcbi.1002860
41. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13(11):2498-2504. doi:10.1101/gr.1239303

42. Luo X, Guo L, Dai XJ, Wang Q, Zhu W, Miao X, Gong H. Abnormal intrinsic functional hubs in alcohol dependence: evidence from a voxelwise degree centrality analysis. Neuropsychiatr Dis Treat. 2017;13:2011-2020. doi:10.2147/NDT.S142742
43. Li Y, Li W, Tan Y, Liu F, Cao Y, Lee KY. Hierarchical Decomposition for Betweenness Centrality Measure of Complex Networks. Sci Rep. 2017;7:46491.. doi:10.1038/srep46491
44. Gilbert M, Li Z, Wu XN, Rohr L, Gombos S, Harter K, Schulze WX. Comparison of path-based centrality measures in protein-protein interaction networks revealed proteins with phenotypic relevance during adaptation to changing nitrogen environments. J Proteomics. 2021;235:104114. doi:10.1016/j.jprot.2021.104114
45. Li G, Li M, Wang J, Li Y, Pan Y. United Neighborhood Closeness Centrality and Orthology for Predicting Essential Proteins. IEEE/ACM Trans Comput Biol Bioinform. 2020;17(4):1451-1458. doi:10.1109/TCBB.2018.2889978
46. Zaki N, Efimov D, Berengueres J. Protein complex detection using interaction reliability assessment and weighted clustering coefficient. BMC Bioinformatics. 2013;14:163. doi:10.1186/1471-2105-14
47. Fan Y, Xia J. miRNet-Functional Analysis and Visual Exploration of miRNA-Target Interactions in a Network Context. Methods Mol Biol 2018; 1819:215-233. doi:10.1007/978-1-4939-8618-7_10
48. Zhou G, Soufan O, Ewald J, Hancock REW, Basu N, Xia J. NetworkAnalyst 3.0: a visual analytics platform for comprehensive gene expression profiling and meta-analysis. Nucleic Acids Res 2019, 47:W234-W241. doi:10.1093/nar/gkz240
49. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Müller M. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011;12:77. doi:10.1186/1471-2105-12-77
50. Goodsell DS, Zardecki C, Di Costanzo L, Duarte JM, Hudson BP, Persikova I, Segura J, Shao C, Voigt M, Westbrook JD, Young JY. RCSB Protein Data Bank: Enabling biomedical research and drug discovery. Protein Sci. 2020;29(1):52-65. doi:10.1002/pro.3730.
51. Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, Heer FT, de Beer TA, Rempfer C, Bordoli L, Lepore R. SWISS-MODEL:

homology modelling of protein structures and complexes. Nucleic Acids Res. 2018;46(1):296-303.doi:10.1093/nar/gky427

52. Jendele L, Krivak R, Skoda P, Novotny M, Hoksza D. PrankWeb: a web server for ligand binding site prediction and visualization. Nucleic Acids Res. 2019;47(1):345-9. doi:10.1093/nar/gkz424
53. Morris GM, Huey R, Lindstrom W, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J Comput Chem*. 2009;30(16):2785-2791. doi:10.1002/jcc.21256
54. Baroroh U, Biotek M, Muscifa ZS, Destiarani W, Rohmatullah FG, Yusuf M. Molecular interaction analysis and visualization of protein-ligand docking using Biovia Discovery Studio Visualizer. Indo J Comp Biol (IJCB). 2023;2(1):22-30. doi:10.24198/ijcb.v2i1.46322.
55. Katz Sand I. Classification, diagnosis, and differential diagnosis of multiple sclerosis. Curr Opin Neurol. 2015;28(3):193-205. doi:10.1097/WCO.0000000000000206
56. Ganekal P, Vastrad B, Kavatagimath S, Vastrad C, Kotrashetti S. Bioinformatics and Next-Generation Data Analysis for Identification of Genes and Molecular Pathways Involved in Subjects with Diabetes and Obesity. Medicina (Kaunas). 2023;59(2):309. doi:10.3390/medicina59020309
57. Alur V, Raju V, Vastrad B, Vastrad C, Kavatagimath S, Kotturshetti S. Bioinformatics Analysis of Next Generation Sequencing Data Identifies Molecular Biomarkers Associated With Type 2 Diabetes Mellitus. Clin Med Insights Endocrinol Diabetes. 2023;16:11795514231155635. doi:10.1177/11795514231155635
58. Watson CT, Ramagopalan SV, Morrison KM, Ebers GC, Breden F. IGHV4-39 deletion polymorphism does not associate with risk or outcome of multiple sclerosis. J Neuroimmunol. 2010;225(1-2):164-166. doi:10.1016/j.jneuroim.2010.04.012
59. Sasaki D, Kotoh J, Watadani R, Matsumoto K. New animal models reveal that coenzyme Q2 (Coq2) and placenta-specific 8 (Plac8) are candidate genes for the onset of type 2 diabetes associated with obesity in rats. Mamm Genome. 2015;26(11-12):619-629. doi:10.1007/s00335-015-9597-4
60. Tavassolifar MJ, Vodjgani M, Salehi Z, Izad M. The Influence of Reactive Oxygen Species in the Immune System and Pathogenesis of Multiple

Sclerosis. Autoimmune Dis. 2020;2020:5793817. doi:10.1155/2020/5793817
61. Do HT, Baars W, Borns K, Windhagen A, Schwinzer R. The 77C->G mutation in the human CD45 (PTPRC) gene leads to increased intensity of TCR signaling in T cell lines from healthy individuals and patients with multiple sclerosis. J Immunol. 2006;176(2):931-938. doi:10.4049/jimmunol.176.2.931
62. Göbel K, Ruck T, Meuth SG. Cytokine signaling in multiple sclerosis: Lost in translation. Mult Scler. 2018;24(4):432-439. doi:10.1177/1352458518763094
63. van Horssen J, Dijkstra CD, de Vries HE. The extracellular matrix in multiple sclerosis pathology. J Neurochem. 2007;103(4):1293-1301. doi:10.1111/j.1471-4159.2007.04897.x
64. Pineda-Torra I, Siddique S, Waddington KE, Farrell R, Jury EC. Disrupted Lipid Metabolism in Multiple Sclerosis: A Role for Liver X Receptors?. Front Endocrinol (Lausanne). 2021;12:639757. doi:10.3389/fendo.2021.639757
65. Park SJ, Choi JW. Brain energy metabolism and multiple sclerosis: progress and prospects. Arch Pharm Res. 2020;43(10):1017-1030. doi:10.1007/s12272-020-01278-3
66. Ziliotto N, Bernardi F, Jakimovski D, Baroni M, Bergsland N, Ramasamy DP, Weinstock-Guttman B, Zamboni P, Marchetti G, Zivadinov R, et al. Increased CCL18 plasma levels are associated with neurodegenerative MRI outcomes in multiple sclerosis patients. Mult Scler Relat Disord. 2018;25:37-42. doi:10.1016/j.msard.2018.07.009
67. Yuan M, Wei L, Zhou R, Bai Q, Wei Y, Zhang W, Huang Y. Four FCRL3 Gene Polymorphisms (FCRL3_3, _5, _6, _8) Confer Susceptibility to Multiple Sclerosis: Results from a Case-Control Study. Mol Neurobiol. 2016;53(3):2029-2035. doi:10.1007/s12035-015-9149-7
68. Morille J, Mandon M, Rodriguez S, Roulois D, Leonard S, Garcia A, Wiertlewski S, Le Page E, Berthelot L, Nicot A, et al. Multiple Sclerosis CSF Is Enriched With Follicular T Cells Displaying a Th1/Eomes Signature. Neurol Neuroimmunol Neuroinflamm. 2022;9(6):e200033. doi:10.1212/NXI.0000000000200033

69. Prins M, Dutta R, Baselmans B, Brevé JJ, Bol JG, Deckard SA, van der Valk P, Amor S, Trapp BD, de Vries HE, et al. Discrepancy in CCL2 and CCR2 expression in white versus grey matter hippocampal lesions of Multiple Sclerosis patients. Acta Neuropathol Commun. 2014;2:98. doi:10.1186/s40478-014-0098-6
70. Cavanillas ML, Alcina A, Núñez C, de las Heras V, Fernández-Arquero M, Bartolomé M, de la Concha EG, Fernández O, Arroyo R, Matesanz F, et al. Polymorphisms in the IL2, IL2RA and IL2RB genes in multiple sclerosis risk. Eur J Hum Genet. 2010;18(7):794-799. doi:10.1038/ejhg.2010.15
71. Jaime-Pérez JC, Turrubiates-Hernández GA, López-Silva LJ, Salazar-Riojas R, Gómez-Almaguer D. Early changes in IL-21, IL-22, CCL2, and CCL4 serum cytokines after outpatient autologous transplantation for multiple sclerosis: A proof of concept study. Clin Transplant. 2020;34(12):e14114. doi:10.1111/ctr.14114
72. Volpe E, Sambucci M, Battistini L, Borsellino G. Fas-Fas Ligand: Checkpoint of T Cell Functions in Multiple Sclerosis. Front Immunol. 2016;7:382. doi:10.3389/fimmu.2016.00382
73. Yang W, Zhou W, Zhang BK, Kong LS, Zhu XX, Wang RX, Yang Y, Chen YF, Chen LR. Association between CD24 Ala/Val polymorphism and multiple sclerosis risk: A meta analysis. Medicine (Baltimore). 2020;99(15):e19530. doi:10.1097/MD.0000000000019530
74. Stefanović M, Životić I, Stojković L, Dinčić E, Stanković A, Živković M. The association of genetic variants IL2RA rs2104286, IFI30 rs11554159 and IKZF3 rs12946510 with multiple sclerosis onset and severity in patients from Serbia. J Neuroimmunol. 2020;347:577346. doi:10.1016/j.jneuroim.2020.577346
75. Baecher-Allan CM, Costantino CM, Cvetanovich GL, Ashley CW, Beriou G, Dominguez-Villar M, Hafler DA. CD2 costimulation reveals defective activity by human CD4+CD25(hi) regulatory cells in patients with multiple sclerosis. J Immunol. 2011;186(6):3317-3326. doi:10.4049/jimmunol.1002502
76. Kunkl M, Sambucci M, Ruggieri S, Amormino C, Tortorella C, Gasperini C, Battistini L, Tuosto L. CD28 Autonomous Signaling Up-Regulates C-Myc Expression and Promotes Glycolysis Enabling Inflammatory T Cell

Responses in Multiple Sclerosis. Cells. 2019;8(6):575. doi:10.3390/cells8060575

77. Galarza-Muñoz G, Briggs FBS, Evsyukova I, Schott-Lerner G, Kennedy EM, Nyanhete T, Wang L, Bergamaschi L, Widen SG, Tomaras GD, et al. Human Epistatic Interaction Controls IL7R Splicing and Increases Multiple Sclerosis Risk. Cell. 2017;169(1):72-84.e13. doi:10.1016/j.cell.2017.03.007
78. Delfan N, Galehdari H, Ghanbari Mardasi F, Zabihi R, Latifi Pakdehi T, Seifi T, Majdinasab N. Association of HLA-DR2-Related Haplotype (HLA-DRB5*01-DRB1*1501-DQB1*0602) in Patients with Multiple Sclerosis in Khuzestan Province. Iran J Child Neurol. 2021;15(3):35-46. doi:10.22037/ijcn.v14i4.18795
79. Wiendl H, Neuhaus O, Mehling M, Wintterle S, Schreiner B, Mitsdoerffer M, Wienhold W, Weissert R, Wessels J, Hartung HP, et al. The CD28 related molecule ICOS: T cell modulation in the presence and absence of B7.1/2 and regulational expression in multiple sclerosis. J Neuroimmunol. 2003;140(1-2):177-187. doi:10.1016/s0165-5728(03)00172-3
80. Guerrero S, Sánchez-Tirado E, Agüí L, González-Cortés A, Yáñez-Sedeño P, Pingarrón JM. Development of an Electrochemical CCL5 Chemokine Immunoplatform for Rapid Diagnosis of Multiple Sclerosis. Biosensors (Basel). 2022;12(8):610. doi:10.3390/bios12080610
81. Derakhshani A, Asadzadeh Z, Safarpour H, Leone P, Shadbad MA, Heydari A, Baradaran B, Racanelli V. Regulation of CTLA-4 and PD-L1 Expression in Relapsing-Remitting Multiple Sclerosis Patients after Treatment with Fingolimod, IFNβ-1α, Glatiramer Acetate, and Dimethyl Fumarate Drugs. J Pers Med. 2021;11(8):721. doi:10.3390/jpm11080721
82. Sha Y, Markovic-Plese S. Activated IL-1RI Signaling Pathway Induces Th17 Cell Differentiation via Interferon Regulatory Factor 4 Signaling in Patients with Relapsing-Remitting Multiple Sclerosis. Front Immunol. 2016;7:543. doi:10.3389/fimmu.2016.00543
83. Schröder R, Zander H, Andreas A, Mauff G. Multiple sclerosis: immunogenetic analyses of sib-pair double case families. II. Studies on the association of multiple sclerosis with C2, C4, BF, C3, C6, and GLO polymorphisms. Immunobiology. 1983;164(2):160-170. doi:10.1016/S0171-2985(83)80007-2

84. Galuppo M, Giacoppo S, Sessa E, Bramanti P, Mazzon E. Are natural killer cells involved in multiple sclerosis etiology? Evidences from NKp46/NCR1 receptor modulation in an observational study. J Neurol Sci. 2014;345(1-2):248-251. doi:10.1016/j.jns.2014.07.045
85. Oldoni E, Smets I, Mallants K, Vandebergh M, Van Horebeek L, Poesen K, Dupont P, Dubois B, Goris A. CHIT1 at Diagnosis Reflects Long-Term Multiple Sclerosis Disease Activity. Ann Neurol. 2020;87(4):633-645. doi:10.1002/ana.25691
86. Zappulo E, Buonomo AR, Saccà F, Russo CV, Scotto R, Scalia G, Nozzolillo A, Lanzillo R, Tosone G, Gentile I. Incidence and Predictive Risk Factors of Infective Events in Patients With Multiple Sclerosis Treated With Agents Targeting CD20 and CD52 Surface Antigens. Open Forum Infect Dis. 2019;6(11):ofz445. doi:10.1093/ofid/ofz445
87. Stilund M, Gjelstrup MC, Petersen T, Møller HJ, Rasmussen PV, Christensen T. Biomarkers of inflammation and axonal degeneration/damage in patients with newly diagnosed multiple sclerosis: contributions of the soluble CD163 CSF/serum ratio to a biomarker panel. PLoS One. 2015;10(4):e0119681. doi:10.1371/journal.pone.0119681
88. Moghadam S, Erfanmanesh M, Esmaeilzadeh A. Interleukin 35 and Hepatocyte Growth Factor; as a novel combined immune gene therapy for Multiple Sclerosis disease. Med Hypotheses. 2017;109:102-105. doi:10.1016/j.mehy.2017.09.017
89. Baulina NM, Kabaeva AR, Boyko AN, Favorova OO. Analiz ekspressii mikroRNK iz lokusa DLK1-DIO3 v CD4+ i CD14+ kletkakh pri remittiruyushchem rasseyannom skleroze. Zh Nevrol Psikhiatr Im S S Korsakova. 2022;122(7. Vyp. 2):52-59. doi:10.17116/jnevro202212207252
90. Ostendorf L, Dittert P, Biesen R, Duchow A, Stiglbauer V, Ruprecht K, Bellmann-Strobl J, Seelow D, Stenzel W, Niesner RA, et al. SIGLEC1 (CD169): a marker of active neuroinflammation in the brain but not in the blood of multiple sclerosis patients. Sci Rep. 2021;11(1):10299. doi:10.1038/s41598-021-89786-0
91. Pieragostino D, Del Boccio P, Di Ioia M, Pieroni L, Greco V, De Luca G, D'Aguanno S, Rossi C, Franciotta D, Centonze D, et al. Oxidative modifications of cerebral transthyretin are associated with multiple sclerosis. Proteomics. 2013;13(6):1002-1009. doi:10.1002/pmic.201200395

92. Donninelli G, Saraf-Sinik I, Mazziotti V, Capone A, Grasso MG, Battistini L, Reynolds R, Magliozzi R, Volpe E. Interleukin-9 regulates macrophage activation in the progressive multiple sclerosis brain. J Neuroinflammation. 2020;17(1):149. doi:10.1186/s12974-020-01770-z
93. Azimi G, Ranjbaran F, Arsang-Jang S, Ghafouri-Fard S, Mazdeh M, Sayad A, Taheri M. Upregulation of VEGF-A and correlation between VEGF-A and FLT-1 expressions in Iranian multiple sclerosis patients. Neurol Sci. 2020;41(6):1459-1465. doi:10.1007/s10072-019-04234-2
94. Lindblom RP, Aeinehband S, Ström M, Al Nimer F, Sandholm K, Khademi M, Nilsson B, Piehl F, Ekdahl KN. Complement Receptor 2 is increased in cerebrospinal fluid of multiple sclerosis patients and regulates C3 function. Clin Immunol. 2016;166-167:89-95. doi:10.1016/j.clim.2016.04.003
95. Kamermans A, Rijnsburger M, Chakraborty A, van der Pol S, de Vries HE, van Horssen J. Reduced Angiopoietin-Like 4 Expression in Multiple Sclerosis Lesions Facilitates Lipid Uptake by Phagocytes via Modulation of Lipoprotein-Lipase Activity. Front Immunol. 2019;10:950. doi:10.3389/fimmu.2019.00950
96. Floro S, Carandini T, Pietroboni AM, De Riz MA, Scarpini E, Galimberti D. Role of Chitinase 3-like 1 as a Biomarker in Multiple Sclerosis: A Systematic Review and Meta-analysis. Neurol Neuroimmunol Neuroinflamm. 2022;9(4):e1164. doi:10.1212/NXI.0000000000001164
97. Zhang Y, Burger D, Saruhan G, Jeannet M, Steck AJ. The T-lymphocyte response against myelin-associated glycoprotein and myelin basic protein in patients with multiple sclerosis. Neurology. 1993;43(2):403-407. doi:10.1212/wnl.43.2.403
98. Muraro PA, Kalbus M, Afshar G, McFarland HF, Martin R. T cell response to 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) in multiple sclerosis patients. J Neuroimmunol. 2002;130(1-2):233-242. doi:10.1016/s0165-5728(02)00229-1
99. Zhan J, Gao Y, Heinig L, Beecken M, Huo Y, Zhang W, Wang P, Wei T, Tian R, Han W, Yu ACH, Kipp M, Kaddatz H. Loss of the Novel Myelin Protein CMTM5 in Multiple Sclerosis Lesions and Its Involvement in Oligodendroglial Stress Responses. Cells. 2023;12(16):2085. doi:10.3390/cells12162085

100. Kuklina EM, Baidina TV, Danchenko IY, Nekrasova IV. Semaforin Sema4D in the immune system in multiple sclerosis. Bull Exp Biol Med. 2014;157(2):234-237. doi:10.1007/s10517-014-2533-x
101. Valdo P, Stegagno C, Mazzucco S, Zuliani E, Zanusso G, Moretto G, Raine CS, Bonetti B. Enhanced expression of NGF receptors in multiple sclerosis lesions. J Neuropathol Exp Neurol. 2002;61(1):91-98. doi:10.1093/jnen/61.1.91
102. Stachowska L, Koziarska D, Karakiewicz B, Kotwas A, Knyszyńska A, Folwarski M, Dec K, Stachowska E, Hawryłkowicz V, Kulaszyńska M, et al. Hepcidin (rs10421768), Transferrin (rs3811647, rs1049296) and Transferrin Receptor 2 (rs7385804) Gene Polymorphism Might Be Associated with the Origin of Multiple Sclerosis. Int J Environ Res Public Health. 2022;19(11):6875. doi:10.3390/ijerph19116875
103. Duncan GJ, Plemel JR, Assinck P, Manesh SB, Muir FGW, Hirata R, Berson M, Liu J, Wegner M, Emery B, et al. Myelin regulatory factor drives remyelination in multiple sclerosis. Acta Neuropathol. 2017;134(3):403-422. doi:10.1007/s00401-017-1741-7
104. Androutsou ME, Tapeinou A, Vlamis-Gardikas A, Tselios T. Myelin Oligodendrocyte Glycoprotein and Multiple Sclerosis. Med Chem. 2018;14(2):120-128. doi:10.2174/1573406413666170906123204
105. Haddock G, Cross AK, Plumb J, Surr J, Buttle DJ, Bunning RA, Woodroofe MN. Expression of ADAMTS-1, -4, -5 and TIMP-3 in normal and multiple sclerosis CNS white matter. Mult Scler. 2006;12(4):386-396. doi:10.1191/135248506ms1300oa
106. Penn M, Mausner-Fainberg K, Golan M, Karni A. High serum levels of BMP-2 correlate with BMP-4 and BMP-5 levels and induce reduced neuronal phenotype in patients with relapsing-remitting multiple sclerosis. J Neuroimmunol. 2017;310:120-128. doi:10.1016/j.jneuroim.2017.07.008
107. Hjæresen S, Sejbaek T, Axelsson M, Vinsløv-Jensen H, Mortensen SK, Pihl-Jensen G, Novakova L, Christensen JDR, Pedersen CB, Halle B, et al. The levels of the serine protease HTRA1 in cerebrospinal fluid correlate with progression and disability in multiple sclerosis. J Neurol. 2021;268(9):3316-3324. doi:10.1007/s00415-021-10489-7
108. Capone F, De Vincentis A, Ferraro E, Rossi M, Motolese F, Picardi A, Giannetti B, Di Battista G, Vespasiani-Gentilucci U, Di Lazzaro V. The

PNPLA3 rs738409 variant can increase the risk of liver toxicity in multiple sclerosis patients treated with beta-interferon. Clin Neurol Neurosurg. 2020;197:106166. doi:10.1016/j.clineuro.2020.106166

109. Hochmeister S, Grundtner R, Bauer J, Engelhardt B, Lyck R, Gordon G, Korosec T, Kutzelnigg A, Berger JJ, Bradl M, et al. Dysferlin is a new marker for leaky brain blood vessels in multiple sclerosis. J Neuropathol Exp Neurol. 2006;65(9):855-865. doi:10.1097/01.jnen.0000235119.52311.16

110. Sorosina M, Peroni S, Mascia E, Santoro S, Osiceanu AM, Ferrè L, Clarelli F, Giordano A, Cannizzaro M, Martinelli Boneschi F, et al. nvolvement of NINJ2 Protein in Inflammation and Blood-Brain Barrier Transmigration of Monocytes in Multiple Sclerosis. Genes (Basel). 2022;13(11):1946. doi:10.3390/genes13111946

111. Chow HH, Talbot J, Marstrand L, Lundell H, Roman Siebner H, Bach Søndergaard H, Sellebjerg F. Smoking, cardiovascular risk factors and LRP2 gene variation: Associations with disease severity, cognitive function and brain structure in primary progressive multiple sclerosis. Mult Scler Relat Disord. 2021;56:103296. doi:10.1016/j.msard.2021.103296

112. Goertsches R, Comabella M, Navarro A, Perkal H, Montalban X. Genetic association between polymorphisms in the ADAMTS14 gene and multiple sclerosis. J Neuroimmunol. 2005;164(1-2):140-147. doi:10.1016/j.jneuroim.2005.04.005

113. Alloza I, Otaegui D, de Lapuente AL, Antigüedad A, Varadé J, Núñez C, Arroyo R, Urcelay E, Fernandez O, Leyva L, et al. ANKRD55 and DHCR7 are novel multiple sclerosis risk loci. Genes Immun. 2012;13(3):253-257. doi:10.1038/gene.2011.81

114. Subramanian N, Hofwimmer K, Tavira B, Massier L, Andersson DP, Arner P, Laurencikiene J. Adipose tissue specific CCL18 associates with cardiometabolic diseases in non-obese individuals implicating CD4+ T cells. Cardiovasc Diabetol. 2023;22(1):84. doi:10.1186/s12933-023-01803-w

115. Xia Z, Gu M, Jia X, Wang X, Wu C, Guo J, Zhang L, Du Y, Wang J. Integrated DNA methylation and gene expression analysis identifies SLAMF7 as a key regulator of atherosclerosis. Aging (Albany NY). 2018;10(6):1324-1337. doi:10.18632/aging.101470

116. Meng XW, Zhang M, Hu JK, Chen XY, Long YQ, Liu H, Feng XM, Ji FH, Peng K. Activation of CCL21-GPR174/CCR7 on cardiac fibroblasts underlies myocardial ischemia/reperfusion injury. Front Genet. 2022;13:946524. doi:10.3389/fgene.2022.946524
117. Noori F, Naeimi S, Zibaeenezhad MJ, Gharemirshamlu FR. CCL22 and CCR4 Gene Polymorphisms in Myocardial Infarction: Risk Assessment of rs4359426 and rs2228428 in Iranian Population. Clin Lab. 2018;64(6):907-913. doi:10.7754/Clin.Lab.2018.171106
118. Budhram-Mahadeo VS, Solomons MR, Mahadeo-Heads EAO. Linking metabolic dysfunction with cardiovascular diseases: Brn-3b/POU4F2 transcription factor in cardiometabolic tissues in health and disease. Cell Death Dis. 2021;12(3):267. doi:10.1038/s41419-021-03551-9
119. Zhang H, Yang K, Chen F, Liu Q, Ni J, Cao W, Hua Y, He F, Liu Z, Li L, et al. Role of the CCL2-CCR2 axis in cardiovascular disease: Pathogenesis and clinical implications. Front Immunol. 2022;13:975367. doi:10.3389/fimmu.2022.975367
120. Chen X, Wang X, Zhang Z, Chen Y, Wang C. Role of IL-9, IL-2RA, and IL-2RB genetic polymorphisms in coronary heart disease. Bedeutung der genetischen Polymorphismen IL-9, IL-2RA und IL-2RB bei koronarer Herzkrankheit. Herz. 2021;46(6):558-566. doi:10.1007/s00059-020-05004-z
121. Kazemian S, Ahmadi R, Ferns GA, Rafiei A, Azadegan-Dehkordi F, Khaledifar A, Mohammad-Rezaei M, Bagheri N. Correlation of miR-24-3p and miR-595 expression with CCL3, CCL4, IL1-beta, TNFalphaIP3, and NF-kappaBIalpha genes in PBMCs of patients with coronary artery disease. EXCLI J. 2022;21:1184-1195. doi:10.17179/excli2022-5266
122. Wang Z, Xu H, Chen M, Lu Y, Zheng L, Ma L. CCL24/CCR3 axis plays a central role in angiotensin II-induced heart failure by stimulating M2 macrophage polarization and fibroblast activation. Cell Biol Toxicol. 2023;39(4):1413-1431. doi:10.1007/s10565-022-09767-5
123. Szymanowski A, Li W, Lundberg A, Evaldsson C, Nilsson L, Backteman K, Ernerudh J, Jonasson L. Soluble Fas ligand is associated with natural killer cell dynamics in coronary artery disease. Atherosclerosis. 2014;233(2):616-622. doi:10.1016/j.atherosclerosis.2014.01.030
124. Liu Y, Duan WR, Liu S, Liu T, Chang YJ, Fan XM. Correlation of CD19+CD24hiCD38hi B cells in coronary artery disease with severity of

atherosclerosis. Chin Med J (Engl). 2020;133(10):1257-1258. doi:10.1097/CM9.0000000000000765

125. Wang B, Yan J, Peng Z, Wang J, Liu S, Xie X, Ma X. Teratocarcinoma-derived growth factor 1 (TDGF1) sequence variants in patients with congenital heart defect. Int J Cardiol. 2011;146(2):225-227. doi:10.1016/j.ijcard.2009.08.046

126. Alber HF, Duftner C, Wanitschek M, Dörler J, Schirmer M, Suessenbacher A, Frick M, Dichtl W, Pachinger O, Weidinger F.Neopterin, CD4+CD28- lymphocytes and the extent and severity of coronary artery disease. Int J Cardiol. 2009;135(1):27-35. doi:10.1016/j.ijcard.2008.03.010

127. Sun Y, Yan J, Zhang J, Wang A, Zou J, Gao C. Contribution of IL-7/7R genetic polymorphisms in coronary heart disease in Chinese Han population. Int Immunopharmacol. 2020;79:106084. doi:10.1016/j.intimp.2019.106084

128. Huang X, Cheng Y, Wang N. Genetic variants in CYP11B1 influence the susceptibility to coronary heart disease. BMC Med Genomics. 2022;15(1):158. doi:10.1186/s12920-022-01307-8

129. Mohtavinejad N, Nakhaee A, Harati H, Gholipour N, Mahmoodzade Y. Association of CCL5 rs2107538, and CCL2 rs3760396 Gene Polymorphisms with the Risk of Cardiovascular Disease. Iran J Public Health. 2021;50(7):1436-1444. doi:10.18502/ijph.v50i7.6634

130. Kazemian S, Ahmadi R, Ferns GA, Rafiei A, Azadegan-Dehkordi F, Khaledifar A, Mohammad-Rezaei M, Bagheri N. Correlation of miR-24-3p and miR-595 expression with CCL3, CCL4, IL1-beta, TNFalphaIP3, and NF-kappaBIalpha genes in PBMCs of patients with coronary artery disease. EXCLI J. 2022;21:1184-1195. doi:10.17179/excli2022-5266

131. Ye T, Yan Z, Chen C, Wang D, Wang A, Li T, Yang B, Ding X, Shen C. Lactoferrin attenuates cardiac fibrosis and cardiac remodeling after myocardial infarction via inhibiting mTORC1/S6K signaling pathway. Theranostics. 2023;13(10):3419-3433. doi:10.7150/thno.85361

132. Lin LY, Chun Chang S, O'Hearn J, Hui ST, Seldin M, Gupta P, Bondar G, Deng M, Jauhiainen R, et al. Systems Genetics Approach to Biomarker Discovery: GPNMB and Heart Failure in Mice and Humans. G3 (Bethesda). 2018;8(11):3499-3506. doi:10.1534/g3.118.200655

133. Xue Y, Li Q, Park CG, Klena JD, Anisimov AP, Sun Z, Wei X, Chen T. Proteus mirabilis Targets Atherosclerosis Plaques in Human Coronary Arteries via DC-SIGN (CD209). Front Immunol. 2021;11:579010. doi:10.3389/fimmu.2020.579010
134. Liu S, Liu F, Zhang Z, Zhuang Z, Yuan X, Chen Y. The SELP, CD93, IL2RG, and VAV1 Genes Associated with Atherosclerosis May Be Potential Diagnostic Biomarkers for Psoriasis. J Inflamm Res. 2023;16:827-843. doi:10.2147/JIR.S398862
135. Piras I, Falchi A, Melis A, Ghiani ME, Calò CM, Varesi L, Vona G. 24 bp duplication of CHIT1 gene is not correlated with coronary artery disease in Corsica Island (France). Exp Mol Pathol. 2007;83(3):490-492. doi:10.1016/j.yexmp.2007.08.001
136. Ye B, Chen X, Chen Y, Lin W, Xu D, Fang Z, Chattipakorn N, Huang W, Wang X, Wu G, et al. Inhibition of TAK1/TAB2 complex formation by costunolide attenuates obesity cardiomyopathy via the NF-κB signaling pathway. Phytomedicine. 2023;108:154523. doi:10.1016/j.phymed.2022.154523
137. Durda P, Raffield LM, Lange EM, Olson NC, Jenny NS, Cushman M, Deichgraeber P, Grarup N, Jonsson A, Hansen T, et al. Circulating Soluble CD163, Associations With Cardiovascular Outcomes and Mortality, and Identification of Genetic Variants in Older Individuals: The Cardiovascular Health Study. J Am Heart Assoc. 2022;11(21):e024374. doi:10.1161/JAHA.121.024374
138. Wuest SJ, Horn T, Marti-Jaun J, Kühn H, Hersberger M. Association of polymorphisms in the ALOX15B gene with coronary artery disease. Clin Biochem. 2014;47(6):349-355. doi:10.1016/j.clinbiochem.2013.12.013
139. Tannous C, Deloux R, Karoui A, Mougenot N, Burkin D, Blanc J, Coletti D, Lavery G, Li Z, Mericskay M. NMRK2 Gene Is Upregulated in Dilated Cardiomyopathy and Required for Cardiac Function and NAD Levels during Aging. Int J Mol Sci. 2021;22(7):3534. doi:10.3390/ijms22073534
140. Lönn J, Starkhammar Johansson C, Kälvegren H, Brudin L, Skoglund C, Garvin P, Särndahl E, Ravald N, Richter A, Bengtsson T, et al. Hepatocyte growth factor in patients with coronary artery disease and its

relation to periodontal condition. Results Immunol. 2011;2:7-12. doi:10.1016/j.rinim.2011.12.002

141. Alves QL, de Jesus RLC, Silva DF. Beneficial Effects Induced by TRPM8 Channels Activation to Treat Myocardial Infarction. Am J Hypertens. 2020;33(3):214-217. doi:10.1093/ajh/hpz195

142. Dill TL, Naya FJ. A Hearty Dose of Noncoding RNAs: The Imprinted DLK1-DIO3 Locus in Cardiac Development and Disease. J Cardiovasc Dev Dis. 2018;5(3):37. doi:10.3390/jcdd5030037

143. Clancy RM, Halushka M, Rasmussen SE, Lhakhang T, Chang M, Buyon JP. Siglec-1 Macrophages and the Contribution of IFN to the Development of Autoimmune Congenital Heart Block. J Immunol. 2019;202(1):48-55. doi:10.4049/jimmunol.1800357

144. Wieczorek E, Ożyhar A. Transthyretin: From Structural Stability to Osteoarticular and Cardiovascular Diseases. Cells. 2021;10(7):1768. doi:10.3390/cells10071768

145. Wang Z, Wang Y, Chen Y, Lv J. The IL-24 gene protects human umbilical vein endothelial cells against H□O□-induced injury and may be useful as a treatment for cardiovascular disease. Int J Mol Med. 2016;37(3):581-592. doi:10.3892/ijmm.2016.2466

146. Ansani L, Marchesini J, Pestelli G, Luisi GA, Scillitani G, Longo G, Milani D, Serino ML, Tisato V, Gemmati D. F13A1 Gene Variant (V34L) and Residual Circulating FXIIIA Levels Predict Short- and Long-Term Mortality in Acute Myocardial Infarction after Coronary Angioplasty. Int J Mol Sci. 2018;19(9):2766. doi:10.3390/ijms19092766

147. Zha L, Dong J, Chen Q, Liao Y, Zhang H, Xie T, Tang T, Xia N, Zhang M, Jiao J, et al. Genetic association analysis between IL9 and coronary artery disease in a Chinese Han population. Cytokine. 2022;150:155761. doi:10.1016/j.cyto.2021.155761

148. Palmer BR, Paterson MA, Frampton CM, Pilbrow AP, Skelton L, Pemberton CJ, Doughty RN, Ellis CJ, Troughton RW, Richards AM, et al. Vascular endothelial growth factor-A promoter polymorphisms, circulating VEGF-A and survival in acute coronary syndromes. PLoS One. 2021;16(7):e0254206. doi:10.1371/journal.pone.0254206

149. Xu X, Tan X, Tampe B, Nyamsuren G, Liu X, Maier LS, Sossalla S, Kalluri R, Zeisberg M, Hasenfuss G, et al. Epigenetic balance of aberrant

Rasal1 promoter methylation and hydroxymethylation regulates cardiac fibrosis. Cardiovasc Res. 2015;105(3):279-291. doi:10.1093/cvr/cvv015

150. Kita T, Kitamura K. Translational studies of adrenomedullin and related peptides regarding cardiovascular diseases. Hypertens Res. 2022;45(3):389-400. doi:10.1038/s41440-021-00806-y

151. Katanasaka Y, Saito A, Sunagawa Y, Sari N, Funamoto M, Shimizu S, Shimizu K, Akimoto T, Ueki C, Kitano M, et al. ANGPTL4 Expression Is Increased in Epicardial Adipose Tissue of Patients with Coronary Artery Disease. J Clin Med. 2022;11(9):2449. doi:10.3390/jcm11092449

152. Bakırcı EM, Ünver E, Değirmenci H, Kıvanç T, Günay M, Hamur H, Büyüklü M, Ceyhun G, Topal E, Çoban TA. Serum YKL-40/chitinase 3-like protein 1 level is an independent predictor of atherosclerosis development in patients with obstructive sleep apnea syndrome. Turk Kardiyol Dern Ars. 2015;43(4):333-339. doi:10.5543/tkda.2015.56805

153. Koopmann TT, Jamshidi Y, Naghibi-Sistani M, van der Klift HM, Birjandi H, Al-Hassnan Z, Alwadai A, Zifarelli G, Karimiani EG, Sedighzadeh S, et al. Biallelic loss of LDB3 leads to a lethal pediatric dilated cardiomyopathy. Eur J Hum Genet. 2023;31(1):97-104. doi:10.1038/s41431-022-01204-9

154. Tan KS, Wang D, Lu Z, Zhang Y, Li S, Lin Y, Tan W. CNPase, a 2',3'-Cyclic-nucleotide 3'-phosphodiesterase, as a Therapeutic Target to Attenuate Cardiac Hypertrophy by Enhancing Mitochondrial Energy Production. Int J Mol Sci. 2021;22(19):10806. doi:10.3390/ijms221910806

155. Bai Z, Luo Y, Tian L. ERCC5, HES6 and RORA are potential diagnostic markers of coronary artery disease. FEBS Open Bio. 2022;12(10):1814-1827. doi:10.1002/2211-5463.13469

156. Zhang JW, Liu TF, Chen XH, Liang WY, Feng XR, Wang L, Fu SW, McCaffrey TA, Liu ML. Validation of aspirin response-related transcripts in patients with coronary artery disease and preliminary investigation on CMTM5 function. Gene. 2017;624:56-65. doi:10.1016/j.gene.2017.04.041

157. Feng Z, Chen X, Li T, Gao H, Chen W, Gao Y, Yao Q, Zhuang Q, Ma X, Sheng W, et al. An X-linked PLXNB3 mutation identified in patients with congenital heart disease with neurodevelopmental disabilities. Transl Pediatr. 2022;11(11):1852-1863. doi:10.21037/tp-22-556

158. Song J, Du J, Tan X, Li Y, Yu Q, Liu W, Zhu X, Cong B. Tissue kallikrein-related peptidase8 accentuates cardiac fibrosis after myocardial ischemia-reperfusion injury via regulation of cardiac fibroblasts. Life Sci. 2023;329:121973. doi:10.1016/j.lfs.2023.121973
159. Lalem T, Zhang L, Scholz M, Burkhardt R, Saccheti V, Teren A, Thiery J, Devaux Y. Cyclin dependent kinase inhibitor 1 C is a female-specific marker of left ventricular function after acute myocardial infarction. Int J Cardiol. 2019;274:319-325. doi:10.1016/j.ijcard.2018.07.042
160. Liu X, Li Y, Wang L, Zhao Q, Lu X, Huang J, Fan Z, Gu D. The INSIG1 gene, not the INSIG2 gene, associated with coronary heart disease: tagSNPs and haplotype-based association study. The Beijing Atherosclerosis Study. Thromb Haemost. 2008;100(5):886-892.
161. Müller II, Müller KA, Karathanos A, Schönleber H, Rath D, Vogel S, Chatterjee M, Schmid M, Haas M, Seizer P, et al. Impact of counterbalance between macrophage migration inhibitory factor and its inhibitor Gremlin-1 in patients with coronary artery disease. Atherosclerosis. 2014;237(2):426-432. doi:10.1016/j.atherosclerosis.2014.09.010
162. Li HF, Liu HT, Chen PY, Lin H, Tseng TL. Role of PVAT in obesity-related cardiovascular disease through the buffering activity of ATF3. iScience. 2022;25(12):105631. doi:10.1016/j.isci.2022.105631
163. Wu R, Smeele KM, Wyatt E, Ichikawa Y, Eerbeek O, Sun L, Chawla K, Hollmann MW, Nagpal V, Heikkinen S, et al. Reduction in hexokinase II levels results in decreased cardiac function and altered remodeling after ischemia/reperfusion injury. Circ Res. 2011;108(1):60-69. doi:10.1161/CIRCRESAHA.110.223115
164. Banach J, Grochowska M, Gackowska L, Buszko K, Bujak R, Gilewski W, Kubiszewska I, Wołowiec Ł, Michałkiewicz J, Sinkiewicz W. Melanoma cell adhesion molecule as an emerging biomarker with prognostic significance in systolic heart failure. Biomark Med. 2016;10(7):733-742. doi:10.2217/bmm-2016-0053
165. Bai J, Chen L, Xu L, Zhang Q, Liu J, Zheng K. The value of serum Sema4D level in predicting the prognosis of patients with acute ST-segment elevation myocardial infarction and with high thrombus burden. BMC Cardiovasc Disord. 2023;23(1):230. doi:10.1186/s12872-023-03244-5

166. Look AHEAD Research Group. Prospective Association of GLUL rs10911021 With Cardiovascular Morbidity and Mortality Among Individuals With Type 2 Diabetes: The Look AHEAD Study. Diabetes. 2016;65(1):297-302. doi:10.2337/db15-0890
167. Xiong F, Mao R, Zhao R, Zhang L, Tan K, Liu C, Wang S, Xu M, Li Y, Zhang T. Plasma Exosomal S1PR5 and CARNS1 as Potential Non-invasive Screening Biomarkers of Coronary Heart Disease. Front Cardiovasc Med. 2022;9:845673. doi:10.3389/fcvm.2022.845673
168. Alderawi A, Caramori G, Baker EH, Hitchings AW, Rahman I, Rossios C, Adcock I, Cassolari P, Papi A, Ortega VE, et al. FN3K expression in COPD: a potential comorbidity factor for cardiovascular disease. BMJ Open Respir Res. 2020;7(1):e000714. doi:10.1136/bmjresp-2020-000714
169. Bouilloux F, Thireau J, Ventéo S, Farah C, Karam S, Dauvilliers Y, Valmier J, Copeland NG, Jenkins NA, Richard S, et al. Loss of the transcription factor Meis1 prevents sympathetic neurons target-field innervation and increases susceptibility to sudden cardiac death. Elife. 2016;5:e11627. doi:10.7554/eLife.11627
170. Khanam R, Sengupta A, Mukhopadhyay D, Chakraborty S. Identification of Adamts4 as a novel adult cardiac injury biomarker with therapeutic implications in patients with cardiac injuries. Sci Rep. 2022;12(1):9898. doi:10.1038/s41598-022-13918-3
171. Díaz-Vesga MC, Flores-Vergara R, Riquelme JA, Llancaqueo M, Sánchez G, Vergara C, Michea L, Donoso P, Quest AFG, Olmedo I, et al. Polycystin-1 Is a Crucial Regulator of BIN1 Expression and T-Tubule Remodeling Associated with the Development of Dilated Cardiomyopathy. Int J Mol Sci. 2022;24(1):667. doi:10.3390/ijms24010667
172. Bobos D, Soufla G, Angouras DC, Lekakis I, Georgopoulos S, Melissari E. Investigation of the Role of BMP2 and -4 in ASD, VSD and Complex Congenital Heart Disease. Diagnostics (Basel). 2023;13(16):2717. doi:10.3390/diagnostics13162717
173. Crasto S, My I, Di Pasquale E. The Broad Spectrum of LMNA Cardiac Diseases: From Molecular Mechanisms to Clinical Phenotype. Front Physiol. 2020;11:761. doi:10.3389/fphys.2020.00761

174. Maitusong B, Xie X, Ma YT, Fu ZY, Yang YN, Li XM, Liu F, Chen BD, Gai MT. Association between ErbB3 genetic polymorphisms and coronary artery disease in the Han and Uyghur populations of China. Int J Clin Exp Med. 2015;8(9):16520-16527.
175. Norum HM, Broch K, Michelsen AE, Lunde IG, Lekva T, Abraityte A, Dahl CP, Fiane AE, Andreassen AK, Christensen G, et al. he Notch Ligands DLL1 and Periostin Are Associated with Symptom Severity and Diastolic Function in Dilated Cardiomyopathy. J Cardiovasc Transl Res. 2017;10(4):401-410. doi:10.1007/s12265-017-9748-y
176. Hsu CH, Liu IF, Kuo HF, Li CY, Lian WS, Chang CY, Chen YH, Liu WL, Lu CY, Liu YR, et al. miR-29a-3p/THBS2 Axis Regulates PAH-Induced Cardiac Fibrosis. Int J Mol Sci. 2021;22(19):10574. doi:10.3390/ijms221910574
177. Wang J, Wang H, Chen J, Wang X, Sun K, Wang Y, Wang J, Yang X, Song X, Xin Y, et al. GADD45B inhibits MKK7-induced cardiac hypertrophy and the polymorphisms of GADD45B is associated with inter-ventricular septum hypertrophy. Biochem Biophys Res Commun. 2008;372(4):623-628. doi:10.1016/j.bbrc.2008.05.122
178. Anfinson M, Fitts RH, Lough JW, James JM, Simpson PM, Handler SS, Mitchell ME, Tomita-Mitchell A. Significance of α-Myosin Heavy Chain (MYH6) Variants in Hypoplastic Left Heart Syndrome and Related Cardiovascular Diseases. J Cardiovasc Dev Dis. 2022;9(5):144. doi:10.3390/jcdd9050144
179. Akuta N, Kawamura Y, Arase Y, Saitoh S, Fujiyama S, Sezaki H, Hosaka T, Kobayashi M, Kobayashi M, Suzuki Y, et al. NPLA3 genotype and fibrosis-4 index predict cardiovascular diseases of Japanese patients with histopathologically-confirmed NAFLD. BMC Gastroenterol. 2021;21(1):434. doi:10.1186/s12876-021-02020-z
180. Broadway-Stringer S, Jiang H, Wadmore K, Hooper C, Douglas G, Steeples V, Azad AJ, Singer E, Reyat JS, Galatik F, et al. Insights into the Role of a Cardiomyopathy-Causing Genetic Variant in ACTN2. Cells. 2023;12(5):721. doi:10.3390/cells12050721
181. Abdelrahman HA, Akawi N, Al-Shamsi AM, Ali A, Al-Jasmi F, John A, Hertecant J, Al-Gazali L, Ali BR. Bi-allelic null variant in matrix metalloproteinase-15, causes congenital cardiac defect, cholestasis jaundice,

and failure to thrive. Clin Genet. 2022;101(4):403-410. doi:10.1111/cge.14107
182. Jung IH, Elenbaas JS, Alisio A, Santana K, Young EP, Kang CJ, Kachroo P, Lavine KJ, Razani B, Mecham RP, et al. SVEP1 is a human coronary artery disease locus that promotes atherosclerosis. Sci Transl Med. 2021;13(586):eabe0357. doi:10.1126/scitranslmed.abe0357
183. Leenaerts D, Bosmans JM, van der Veken P, Sim Y, Lambeir AM, Hendriks D. Plasma levels of carboxypeptidase U (CPU, CPB2 or TAFIa) are elevated in patients with acute myocardial infarction. J Thromb Haemost. 2015;13(12):2227-2232. doi:10.1111/jth.13135
184. Zhang X, He D, Xiang Y, Wang C, Liang B, Li B, Qi D, Deng Q, Yu H, Lu Z, et al. DYSF promotes monocyte activation in atherosclerotic cardiovascular disease as a DNA methylation-driven gene. Transl Res. 2022;247:19-38. doi:10.1016/j.trsl.2022.04.001
185. Rypdal KB, Erusappan PM, Melleby AO, Seifert DE, Palmero S, Strand ME, Tønnessen T, Dahl CP, Almaas V, Hubmacher D, et al. The extracellular matrix glycoprotein ADAMTSL2 is increased in heart failure and inhibits TGFβ signalling in cardiac fibroblasts. Sci Rep. 2021;11(1):19757. doi:10.1038/s41598-021-99032-2
186. Wang P, Wang Y, Peng H, Wang J, Zheng Q, Wang P, Wang J, Zhang H, Huang Y, Xiong L, et al. Functional rare variant in a C/EBPbeta binding site in NINJ2 gene increases the risk of coronary artery disease. Aging (Albany NY). 2021;13(23):25393-25407. doi:10.18632/aging.203755
187. Meng X, Zhang L, Han B, Zhang Z. PHLDA3 inhibition protects against myocardial ischemia/reperfusion injury by alleviating oxidative stress and inflammatory response via the Akt/Nrf2 axis. Environ Toxicol. 2021;36(11):2266-2277. doi:10.1002/tox.23340
188. Posadas-Sánchez R, Ocampo-Arcos WA, López-Uribe ÁR, Posadas-Romero C, Villarreal-Molina T, León EÁ, Pérez-Hernández N, Rodríguez-Pérez JM, Cardoso-Saldaña G, et al. Hepatic lipase (LIPC) C-514T gene polymorphism is associated with cardiometabolic parameters and cardiovascular risk factors but not with fatty liver in Mexican population. Exp Mol Pathol. 2015;98(1):93-98. doi:10.1016/j.yexmp.2014.12.010
189. Xiong F, Mao R, Zhao R, Zhang L, Tan K, Liu C, Wang S, Xu M, Li Y, Zhang T. Plasma Exosomal S1PR5 and CARNS1 as Potential Non-

invasive Screening Biomarkers of Coronary Heart Disease. Front Cardiovasc Med. 2022;9:845673. doi:10.3389/fcvm.2022.845673

190. Moreira JBN, Wohlwend M, Fenk S, Åmellem I, Flatberg A, Kraljevic J, Marinovic J, Ljubkovic M, Bjørkøy G, Wisløff U. Exercise Reveals Proline Dehydrogenase as a Potential Target in Heart Failure. Prog Cardiovasc Dis. 2019;62(2):193-202. doi:10.1016/j.pcad.2019.03.002

191. Zhang H, Ding P, Zheng L. TRPV6 Is Associated with Prognosis of ST-Elevation Acute Myocardial Infarction. Ann Clin Lab Sci. 2020;50(6):775-780.

192. Alkhalaf A, Landman GW, van Hateren KJ, Groenier KH, Mooyaart AL, De Heer E, Gans RO, Navis GJ, Bakker SJ, Kleefstra N, et al. Sex specific association between carnosinase gene CNDP1 and cardiovascular mortality in patients with type 2 diabetes (ZODIAC-22). J Nephrol. 2015;28(2):201-207. doi:10.1007/s40620-014-0096-6

193. Abu El Maaty MA, Hassanein SI, Sleem HM, Gad MZ. Effect of polymorphisms in the NADSYN1/DHCR7 locus (rs12785878 and rs1790349) on plasma 25-hydroxyvitamin D levels and coronary artery disease incidence. J Nutrigenet Nutrigenomics. 2013;6(6):327-335. doi:10.1159/000360422

194. Abbott GW. KCNE4 and KCNE5: K(+) channel regulation and cardiac arrhythmogenesis. Gene. 2016;593(2):249-260. doi:10.1016/j.gene.2016.07.069

195. Wang MM, Gai MT, Wang BZ, Maituxun M, Yesitayi G, Chen BD, Ma X. The diagnostic and prognostic value of SAA1 as a novel biomarker for acute aortic dissection. J Proteomics. 2023;286:104958. doi:10.1016/j.jprot.2023.104958

196. Wen HY, Xia Y, Young ME, Taegtmeyer H, Kellems RE. The adenylosuccinate synthetase-1 gene is activated in the hypertrophied heart. J Cell Mol Med. 2002;6(2):235-243. doi:10.1111/j.1582-4934.2002.tb00190.x

197. Ma Z, Qin X, Zhong X, Liao Y, Su Y, Liu X, Liu P, Lu J, Zhou S. Flavine adenine dinucleotide inhibits pathological cardiac hypertrophy and fibrosis through activating short chain acyl-CoA dehydrogenase. Biochem Pharmacol. 2020;178:114100. doi:10.1016/j.bcp.2020.114100

198. Giguère H, Dumont AA, Berthiaume J, Oliveira V, Laberge G, Auger-Messier M. ADAP1 limits neonatal cardiomyocyte hypertrophy by

reducing integrin cell surface expression. Sci Rep. 2018;8(1):13605. doi:10.1038/s41598-018-31784-w

199. Williams D, Mahmoud M, Liu R, Andueza A, Kumar S, Kang DW, Zhang J, Tamargo I, Villa-Roel N, Baek KI, et al. Stable flow-induced expression of KLK10 inhibits endothelial inflammation and atherosclerosis. Elife. 2022;11:e72579. doi:10.7554/eLife.72579

200. Hadova K, Kralova E, Doka G, Bies Pivackova L, Kmecova Z, Krenek P, Klimas J.Isolated downregulation of HCN2 in ventricles of rats with streptozotocin-induced diabetic cardiomyopathy. BMC Cardiovasc Disord. 2021;21(1):118. doi:10.1186/s12872-021-01929-3

201. Stępień K, Siudut J, Konieczyńska M, Nowak K, Zalewski J, Undas A. Effect of high-dose statin therapy on coagulation factors: Lowering of factor XI as a modifier of fibrin clot properties in coronary artery disease. Vascul Pharmacol. 2023;149:107153. doi:10.1016/j.vph.2023.107153

202. Zechendorf E, O'Riordan CE, Stiehler L, Wischmeyer N, Chiazza F, Collotta D, Denecke B, Ernst S, Müller-Newen G, Coldewey SM, et al. Ribonuclease 1 attenuates septic cardiomyopathy and cardiac apoptosis in a murine model of polymicrobial sepsis. JCI Insight. 2020;5(8):e131571. doi:10.1172/jci.insight.131571

203. Persic V, Ruzic A, Miletic B, Samsa DT, Rakic M, Raljevic D, Pejcinovic VP, Eminovic S, Zaputovic L, Laskarin G. Granulysin Expression in Lymphocytes that Populate the Peripheral Blood and the Myocardium after an Acute Coronary Event. Scand J Immunol. 2012;75(2):231-242. doi:10.1111/j.1365-3083.2011.02646.x

204. Li J, Chen Y, Gao J, Chen Y, Zhou C, Lin X, Liu C, Zhao M, Xu Y, Ji L, et al. Eva1a ameliorates atherosclerosis by promoting re-endothelialization of injured arteries via Rac1/Cdc42/Arpc1b. Cardiovasc Res. 2021;117(2):450-461. doi:10.1093/cvr/cvaa011

205. Ren X, Xie H, Zhang J, Jin X, Cui L, Chen L, Chen L, Zuo G. Prognostic Value of Plasma Cold-Inducible RNA-Binding Protein in Patients with Acute Coronary Syndrome. Dis Markers. 2022;2022:6119601. doi:10.1155/2022/6119601

206. Wei X, Zou S, Xie Z, Wang Z, Huang N, Cen Z, Hao Y, Zhang C, Chen Z, Zhao F, et al. EDIL3 deficiency ameliorates adverse cardiac remodelling by neutrophil extracellular traps (NET)-mediated macrophage

polarization. Cardiovasc Res. 2022;118(9):2179-2195. doi:10.1093/cvr/cvab269
207. Orr AW, Woolard MD. Cardiovascular disease is obNOXious: New insights into NoxA1 in smooth muscle phenotype. Redox Biol. 2019;22:101081. doi:10.1016/j.redox.2018.101081
208. El-Lebedy D. Association of serum angiopoietin-like protein 2 with elevated risk of cardiovascular diseases in subjects with type 2 diabetes. J Diabetes Complications. 2019;33(11):107421. doi:10.1016/j.jdiacomp.2019.107421
209. Mappangara I, Yusuf I, Aspar Mappahya A, Qanitha A. CYP2A6 gene polymorphism and severity of coronary atherosclerosis in Indonesian male smokers: A pilot study. Medicine (Baltimore). 2022;101(37):e30308. doi:10.1097/MD.0000000000030308
210. Reitz CJ, Tavassoli M, Kim DH, Shah S, Lakin R, Teng ACT, Zhou YQ, Li W, Hadipour-Lakmehsari S, Backx PH, et al. Proteomics and phosphoproteomics of failing human left ventricle identifies dilated cardiomyopathy-associated phosphorylation of CTNNA3. Proc Natl Acad Sci U S A. 2023;120(19):e2212118120. doi:10.1073/pnas.2212118120
211. Martinez-Merino L, Iridoy M, Galbete A, Roldán M, Rivero A, Acha B, Irún P, Canosa C, Pocoví M, Mendioroz M, et al. Evaluation of Chitotriosidase and CC-Chemokine Ligand 18 as Biomarkers of Microglia Activation in Amyotrophic Lateral Sclerosis. Neurodegener Dis. 2018;18(4):208-215. doi:10.1159/000490920
212. Chen S, Huan X, Xu CZ, Luo SS, Zhao CB, Zhong HH, Zheng XY, Qiao K, Dong Y, Wang Y, et al. Eomesodermin expression in CD4+ T-cells associated with disease progression in amyotrophic lateral sclerosis. CNS Neurosci Ther. 2023;10.1111/cns.14503. doi:10.1111/cns.14503
213. Iłżecka J. Granzymes A and B levels in serum of patients with amyotrophic lateral sclerosis. Clin Biochem. 2011;44(8-9):650-653. doi:10.1016/j.clinbiochem.2011.02.006a
214. Yang X, Zheng J, Tian S, Chen Y, An R, Zhao Q, Xu Y. HLA-DRA/HLA-DRB5 polymorphism affects risk of sporadic ALS and survival in a southwest Chinese cohort. J Neurol Sci. 2017;373:124-128. doi:10.1016/j.jns.2016.12.055

215. Oeckl P, Weydt P, Thal DR, Weishaupt JH, Ludolph AC, Otto M. Proteomics in cerebrospinal fluid and spinal cord suggests UCHL1, MAP2 and GPNMB as biomarkers and underpins importance of transcriptional pathways in amyotrophic lateral sclerosis. Acta Neuropathol. 2020;139(1):119-134. doi:10.1007/s00401-019-02093-x
216. Muresan V, Villegas C, Ladescu Muresan Z. Functional interaction between amyloid-β precursor protein and peripherin neurofilaments: a shared pathway leading to Alzheimer's disease and amyotrophic lateral sclerosis?. Neurodegener Dis. 2014;13(2-3):122-125. doi:10.1159/000354238
217. Nomura M, Oketa Y, Yasui K, Ishikawa H, Ono S. Expression of hepatocyte growth factor in the skin of amyotrophic lateral sclerosis. Acta Neurol Scand. 2012;125(6):389-397. doi:10.1111/j.1600-0404.2011.01579.x
218. Lozeron P, Lacroix C, Theaudin M, Richer A, Gugenheim M, Adams D, Misrahi M. An amyotrophic lateral sclerosis-like syndrome revealing an amyloid polyneuropathy associated with a novel transthyretin mutation. Amyloid. 2013;20(3):188-192. doi:10.3109/13506129.2013.818535
219. da Costa CCP, de Lima NS, da Cruz Pereira Bento D, da Silva Santos R, da Silva Reis AA. A strong association between VEGF-A rs28357093 and amyotrophic lateral sclerosis: a brazilian genetic study. Mol Biol Rep. 2022;49(9):9129-9133. doi:10.1007/s11033-022-07647-z
220. Bombaci A, Manera U, De Marco G, Casale F, Salamone P, Fuda G, Marchese G, Iazzolino B, Peotta L, Moglia C, et al. Plasma CHI3L1 in Amyotrophic Lateral Sclerosis: A Potential Differential Diagnostic Biomarker. J Clin Med. 2023;12(6):2367. doi:10.3390/jcm12062367
221. Vrabec K, Boštjančič E, Koritnik B, Leonardis L, Dolenc Grošelj L, Zidar J, Rogelj B, Glavač D, Ravnik-Glavač M. Differential Expression of Several miRNAs and the Host Genes AATK and DNM2 in Leukocytes of Sporadic ALS Patients. Front Mol Neurosci. 2018;11:106. doi:10.3389/fnmol.2018.00106
222. Yuan X, Cao B, Wu Y, Chen Y, Wei Q, Ou R, Yang J, Chen X, Zhao B, Song W, et al. Association analysis of SNP rs11868035 in SREBF1 with sporadic Parkinson's disease, sporadic amyotrophic lateral sclerosis and multiple system atrophy in a Chinese population. Neurosci Lett. 2018;664:128-132. doi:10.1016/j.neulet.2017.11.015

223. Satoh J, Asahina N, Kitano S, Kino Y. A Comprehensive Profile of ChIP-Seq-Based Olig2 Target Genes in Motor Neuron Progenitor Cells Suggests the Possible Involvement of Olig2 in the Pathogenesis of Amyotrophic Lateral Sclerosis. J Cent Nerv Syst Dis. 2015;7:1-14. doi:10.4137/JCNSD.S23210
224. Yazar V, Kühlwein JK, Knehr A, Grozdanov V, Ekici AB, Ludolph AC, Danzer KM. Impaired ATF3 signaling involves SNAP25 in SOD1 mutant ALS patients. Sci Rep. 2023;13(1):12019. doi:10.1038/s41598-023-38684-8
225. Kerkhoff H, Jennekens FG, Troost D, Veldman H. Nerve growth factor receptor immunostaining in the spinal cord and peripheral nerves in amyotrophic lateral sclerosis. Acta Neuropathol. 1991;81(6):649-656. doi:10.1007/BF00296375
226. Lemarchant S, Pomeshchik Y, Kidin I, Kärkkäinen V, Valonen P, Lehtonen S, Goldsteins G, Malm T, Kanninen K, Koistinaho J. ADAMTS-4 promotes neurodegeneration in a mouse model of amyotrophic lateral sclerosis. Mol Neurodegener. 2016;11:10. doi:10.1186/s13024-016-0078-3
227. Volkening K, Farhan SMK, Kao J, Leystra-Lantz C, Ang LC, McIntyre A, Wang J, Hegele RA, Strong MJ. Evidence of synergism among three genetic variants in a patient with LMNA-related lipodystrophy and amyotrophic lateral sclerosis leading to a remarkable nuclear phenotype. Mol Cell Biochem. 2021;476(7):2633-2650. doi:10.1007/s11010-021-04103-7
228. Hashimoto K, Hayashi Y, Watabe K, Inuzuka T, Hozumi I. Metallothionein-III prevents neuronal death and prolongs life span in amyotrophic lateral sclerosis model mice. Neuroscience. 2011;189:293-298. doi:10.1016/j.neuroscience.2011.05.034
229. Dave U, Khan S, Gomes J. Characterization of E121K mutation of D-amino acid oxidase - Insights into mechanisms leading to amyotrophic lateral sclerosis. Biochim Biophys Acta Proteins Proteom. 2023;1871(6):140947. doi:10.1016/j.bbapap.2023.140947
230. Costa J, Pronto-Laborinho A, Pinto S, Gromicho M, Bonucci S, Tranfield E, Correia C, Alexandre BM, de Carvalho M. Investigating LGALS3BP/90□K glycoprotein in the cerebrospinal fluid of patients with

neurological diseases. Sci Rep. 2020;10(1):5649. doi:10.1038/s41598-020-62592-w

231. O'Connell P, Blake MK, Godbehere S, Amalfitano A, Aldhamen YA. SLAMF7 modulates B cells and adaptive immunity to regulate susceptibility to CNS autoimmunity. J Neuroinflammation. 2022;19(1):241. doi:10.1186/s12974-022-02594-9

232. Napier C, Mitchell AL, Gan E, Wilson I, Pearce SH. Role of the X-linked gene GPR174 in autoimmune Addison's disease. J Clin Endocrinol Metab. 2015;100(1):E187-E190. doi:10.1210/jc.2014-2694

233. Yang Y, Su X, Zhang K, Zhou R. The Fc receptor-like 3 gene polymorphisms and susceptibility to autoimmune diseases: an updated meta-analysis. Autoimmunity. 2013;46(8):547-558. doi:10.3109/08916934.2013.835804

234. Wang N, Keszei M, Halibozek P, Yigit B, Engel P, Terhorst C. Slamf6 negatively regulates autoimmunity. Clin Immunol. 2016;173:19-26. doi:10.1016/j.clim.2016.06.009

235. Chen S, Zhang J, Yu WB, Zhuang JC, Xiao W, Wu ZY, Xiao BG. Eomesodermin in CD4+T cells is essential for Ginkgolide K ameliorating disease progression in experimental autoimmune encephalomyelitis. Int J Biol Sci. 2021;17(1):50-61. doi:10.7150/ijbs.5004

236. Scheu S, Ali S, Ruland C, Arolt V, Alferink J. The C-C Chemokines CCL17 and CCL22 and Their Receptor CCR4 in CNS Autoimmunity. Int J Mol Sci. 2017;18(11):2306. doi:10.3390/ijms18112306

237. Rafei M, Galipeau J. A CCL2-based fusokine as a novel biopharmaceutical for the treatment of CCR2-driven autoimmune diseases. Crit Rev Immunol. 2010;30(5):449-461. doi:10.1615/critrevimmunol.v30.i5.40

238. Hu M, You Z, Li Y, Huang B, Cui N, Wang R, Wei Y, Li B, Liang J, Liu Q, et al. Serum Biomarkers for Autoimmune Hepatitis Type 1: the Case for CD48 and a Review of the Literature. Clin Rev Allergy Immunol. 2022;63(3):342-356. doi:10.1007/s12016-022-08935-z

239. Mansour H, Banaganapalli B, Nasser KK, Al-Aama JY, Shaik NA, Saadah OI, Elango R. Genome-Wide Association Study-Guided Exome Rare Variant Burden Analysis Identifies IL1R1 and CD3E as Potential

Autoimmunity Risk Genes for Celiac Disease. Front Pediatr. 2022;10:837957. doi:10.3389/fped.2022.837957

240. Shou J, Peng J, Zhao Z, Huang X, Li H, Li L, Gao X, Xing Y, Liu H. CCL26 and CCR3 are associated with the acute inflammatory response in the CNS in experimental autoimmune encephalomyelitis. J Neuroimmunol. 2019;333:576967. doi:10.1016/j.jneuroim.2019.576967

241. Wu B, Wang W, Zhan Y, Li F, Zou S, Sun L, Cheng Y. CXCL13, CCL4, and sTNFR as circulating inflammatory cytokine markers in primary and SLE-related autoimmune hemolytic anemia. J Transl Med. 2015;13:112. doi:10.1186/s12967-015-0474-4

242. Magnusson L, Espes D, Casas R, Carlsson PO. Increased Plasma Levels of the Co-stimulatory Proteins CDCP1 and SLAMF1 in Patients With Autoimmune Endocrine Diseases. Front Immunol. 2020;11:1916. doi:10.3389/fimmu.2020.01916

243. Tan Y, Zhao M, Xiang B, Chang C, Lu Q. CD24: from a Hematopoietic Differentiation Antigen to a Genetic Risk Factor for Multiple Autoimmune Diseases. Clin Rev Allergy Immunol. 2016;50(1):70-83. doi:10.1007/s12016-015-8470-2

244. Li L, Ding X, Wang X, Yao Q, Shao X, An X, Yan N, Jiang Y, Wang W, Shi L, et al. Polymorphisms of IKZF3 Gene and Autoimmune Thyroid Diseases: Associated with Graves' Disease but Not with Hashimoto's Thyroiditis. Cell Physiol Biochem. 2018;45(5):1787-1796. doi:10.1159/000487870

245. Fernandez Lahore G, Förster M, Johannesson M, Sabatier P, Lönnblom E, Aoun M, He Y, Nandakumar KS, Zubarev RA, Holmdahl R. Polymorphic estrogen receptor binding site causes Cd2-dependent sex bias in the susceptibility to autoimmune diseases. Nat Commun. 2021;12(1):5565. doi:10.1038/s41467-021-25828-5

246. Ceeraz S, Thompson CR, Beatson R, Choy EH. Harnessing CD8+CD28- Regulatory T Cells as a Tool to Treat Autoimmune Disease. Cells. 2021;10(11):2973. doi:10.3390/cells10112973

247. Meyer A, Parmar PJ, Shahrara S. Significance of IL-7 and IL-7R in RA and autoimmunity. Autoimmun Rev. 2022;21(7):103120. doi:10.1016/j.autrev.2022.103120

248. Li Q, Zhong J, Luo H, Urbonaviciute V, Xu Z, He C, Holmdahl R. Two major genes associated with autoimmune arthritis, Ncf1 and Fcgr2b, additively protect mice by strengthening T cell tolerance. Cell Mol Life Sci. 2022;79(9):482. doi:10.1007/s00018-022-04501-0

249. Howarth S, Sneddon G, Allinson KR, Razvi S, Mitchell AL, Pearce SHS. Replication of association at the LPP and UBASH3A loci in a UK autoimmune Addison's disease cohort. Eur J Endocrinol. 2023;188(1):lvac010. doi:10.1093/ejendo/lvac010

250. Chen P, Denniston A, Hannes S, Tucker W, Wei L, Liu B, Xiao T, Hirani S, Li Z, Jawad S, et al. Increased CD1c+ mDC1 with mature phenotype regulated by TNFα-p38 MAPK in autoimmune ocular inflammatory disease. Clin Immunol. 2015;158(1):35-46. doi:10.1016/j.clim.2015.03.002

251. Frey O, Meisel J, Hutloff A, Bonhagen K, Bruns L, Kroczek RA, Morawietz L, Kamradt T. Inducible costimulator (ICOS) blockade inhibits accumulation of polyfunctional T helper 1/T helper 17 cells and mitigates autoimmune arthritis. Ann Rheum Dis. 2010;69(8):1495-1501. doi:10.1136/ard.2009.119164

252. Lee WI, Fan WL, Lu CH, Chen SH, Kuo ML, Lin SJ, Tsai WS, Jaing TH, Chen LC, Yeh KW, et al. A Novel CD3G Mutation in a Taiwanese Patient With Normal T Regulatory Function Presenting With the CVID Phenotype Free of Autoimmunity-Analysis of all Genotypes and Phenotypes. Front Immunol. 2019;10:2833. doi:10.3389/fimmu.2019.02833

253. Manczak M, Jiang S, Orzechowska B, Adamus G. Crucial role of CCL3/MIP-1alpha in the recurrence of autoimmune anterior uveitis induced with myelin basic protein in Lewis rats. J Autoimmun. 2002;18(4):259-270. doi:10.1006/jaut.2002.0591

254. Esaguy N, Aguas AP, van Embden JD, Silva MT. Mycobacteria and human autoimmune disease: direct evidence of cross-reactivity between human lactoferrin and the 65-kilodalton protein of tubercle and leprosy bacilli. Infect Immun. 1991;59(3):1117-1125. doi:10.1128/iai.59.3.1117-1125.1991

255. Tsou PS, Sawalha AH. Glycoprotein nonmetastatic melanoma protein B: A key mediator and an emerging therapeutic target in autoimmune diseases. FASEB J. 2020;34(7):8810-8823. doi:10.1096/fj.202000651

256. Hosseini A, Gharibi T, Marofi F, Babaloo Z, Baradaran B. CTLA-4: From mechanism to autoimmune therapy. Int Immunopharmacol. 2020;80:106221. doi:10.1016/j.intimp.2020.106221
257. Kang M, Lee HS, Choi JK, Yu CR, Egwuagu CE. Deletion of Irf4 in T Cells Suppressed Autoimmune Uveitis and Dysregulated Transcriptional Programs Linked to CD4+ T Cell Differentiation and Metabolism. Int J Mol Sci. 2021;22(5):2775. doi:10.3390/ijms22052775
258. Forsberg MH, Foda B, Serreze DV, Chen YG. Combined congenic mapping and nuclease-based gene targeting for studying allele-specific effects of Tnfrsf9 within the Idd9.3 autoimmune diabetes locus. Sci Rep. 2019;9(1):4316. doi:10.1038/s41598-019-40898-8
259. Ono C, Tanaka S, Myouzen K, Iwasaki T, Ueda M, Oda Y, Yamamoto K, Kochi Y, Baba Y. Upregulated Fcrl5 disrupts B cell anergy causes autoimmune disease. Front Immunol. 2023;14:1276014. doi:10.3389/fimmu.2023.1276014
260. Simone R, Pesce G, Antola P, Merlo DF, Bagnasco M, Saverino D. Serum LAIR-2 is increased in autoimmune thyroid diseases. PLoS One. 2013;8(5):e63282. doi:10.1371/journal.pone.0063282
261. Zhu S, Pan W, Song X, Liu Y, Shao X, Tang Y, Liang D, He D, Wang H, Liu W, et al. The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-α. Nat Med. 2012;18(7):1077-1086. doi:10.1038/nm.2815
262. Hao W, Luo Q, Menger MD, Fassbender K, Liu Y. Treatment With CD52 Antibody Protects Neurons in Experimental Autoimmune Encephalomyelitis Mice During the Recovering Phase. Front Immunol. 2021;12:792465. doi:10.3389/fimmu.2021.792465
263. Zhou D, Wang Y, Chen LU, Zhang W, Luan J. Soluble CD163: A Novel Biomarker with Diagnostic and Therapeutic Implications in Autoimmune Diseases. J Rheumatol. 2016;43(4):830. doi:10.3899/jrheum.151317
264. Haasken S, Auger JL, Taylor JJ, Hobday PM, Goudy BD, Titcombe PJ, Mueller DL, Binstadt BA. Macrophage scavenger receptor 1 (Msr1, SR-A) influences B cell autoimmunity by regulating soluble autoantigen concentration. J Immunol. 2013;191(3):1055-1062. doi:10.4049/jimmunol.1201680

265. Molnarfi N, Benkhoucha M, Funakoshi H, Nakamura T, Lalive PH. Hepatocyte growth factor: A regulator of inflammation and autoimmunity. Autoimmun Rev. 2015;14(4):293-303. doi:10.1016/j.autrev.2014.11.013
266. Eakin AJ, Bustard MJ, McGeough CM, Ahmed T, Bjourson AJ, Gibson DS. Siglec-1 and -2 as potential biomarkers in autoimmune disease. Proteomics Clin Appl. 2016;10(6):635-644. doi:10.1002/prca.201500069
267. Clement CC, Moncrieffe H, Lele A, Janow G, Becerra A, Bauli F, Saad FA, Perino G, Montagna C, Cobelli N, et al. Autoimmune response to transthyretin in juvenile idiopathic arthritis. JCI Insight. 2016;1(2):e85633. doi:10.1172/jci.insight.85633
268. Leng RX, Pan HF, Tao JH, Ye DQ. IL-19, IL-20 and IL-24: potential therapeutic targets for autoimmune diseases. Expert Opin Ther Targets. 2011;15(2):119-126. doi:10.1517/14728222.2011.534461
269. Deng Y, Wang Z, Chang C, Lu L, Lau CS, Lu Q. Th9 cells and IL-9 in autoimmune disorders: Pathogenesis and therapeutic potentials. Hum Immunol. 2017;78(2):120-128. doi:10.1016/j.humimm.2016.12.010
270. Jiang W, Zhu F, Xu H, Xu L, Li H, Yang X, Khan Afridi S, Lai S, Qiu X, Liu C, et al. CHI3L1 signaling impairs hippocampal neurogenesis and cognitive function in autoimmune-mediated neuroinflammation. Sci Adv. 2023;9(39):eadg8148. doi:10.1126/sciadv.adg8148
271. Almasi-Nasrabadi M, Amoli MM, Robati RM, Rajabi F, Ghalamkarpour F, Gauthier Y. CDH1 and DDR1 common variants confer risk to vitiligo and autoimmune comorbidities. Gene. 2019;700:17-22. doi:10.1016/j.gene.2019.03.026
272. Cassiani-Ingoni R, Coksaygan T, Xue H, Reichert-Scrivner SA, Wiendl H, Rao MS, Magnus T. Cytoplasmic translocation of Olig2 in adult glial progenitors marks the generation of reactive astrocytes following autoimmune inflammation. Exp Neurol. 2006;201(2):349-358. doi:10.1016/j.expneurol.2006.04.030
273. Zhao PY, Wang YQ, Liu XH, Zhu YJ, Zhao H, Zhang QX, Qi F, Li JL, Zhang N, Fan YP, et al. Corrigendum to "Bu Shen Yi Sui capsule promotes remyelination correlating with Sema3A/ NRP-1, LIF/LIFR and Nkx6.2 in mice with experimental autoimmune encephalomyelitis". J Ethnopharmacol. 2024;318(Pt A):116853. doi:10.1016/j.jep.2023.116853

274. Zhuang W, Liu X, Liu G, Lv J, Qin H, Wang C, Xie L, Saimaier K, Han S, Shi C, et al. Purinergic receptor P2Y12 boosts autoimmune hepatitis through hexokinase 2-dependent glycolysis in T cells. Int J Biol Sci. 2023;19(11):3576-3594. doi:10.7150/ijbs.85133
275. Mederacke YS, Kirstein MM, Großhennig A, Marhenke S, Metzler F, Manns MP, Vogel A, Mederacke I. he PNPLA3 rs738409 GG genotype is associated with poorer prognosis in 239 patients with autoimmune hepatitis. Aliment Pharmacol Ther. 2020;51(11):1160-1168. doi:10.1111/apt.15722
276. Ray K. CPB2 dampens inflammation in autoimmune arthritis. Nat Rev Rheumatol. 2011;7(10):558. doi:10.1038/nrrheum.2011.135
277. Rajabinejad M, Asadi G, Ranjbar S, Afshar Hezarkhani L, Salari F, Gorgin Karaji A, Rezaiemanesh A. Semaphorin 4A, 4C, and 4D: Function comparison in the autoimmunity, allergy, and cancer. Gene. 2020;746:144637. doi:10.1016/j.gene.2020.144637
278. Perez-Gomez MV, Sanchez-Niño MD, Ortiz A. Megalin/lipoprotein receptor-related protein 2 autoimmunity and kidney disease. Clin Kidney J. 2020;13(3):281-286. doi:10.1093/ckj/sfz171
279. Tsai LJ, Hsiao SH, Tsai LM, Lin CY, Tsai JJ, Liou DM, Lan JL. The sodium-dependent glucose cotransporter SLC5A11 as an autoimmune modifier gene in SLE. Tissue Antigens. 2008;71(2):114-126. doi:10.1111/j.1399-0039.2007.00975.x
280. Kohs TCL, Fallon ME, Oseas EC, Healy LD, Tucker EI, Gailani D, McCarty OJT, Vandenbark AA, Offner H, Verbout NG. Pharmacological targeting of coagulation factor XI attenuates experimental autoimmune encephalomyelitis in mice. Metab Brain Dis. 2023;38(7):2383-2391. doi:10.1007/s11011-023-01251-1
281. Horiguchi H, Kadomatsu T, Yamashita T, Yumoto S, Terada K, Sato M, Morinaga J, Miyata K, Oike Y. ANGPTL2 promotes immune checkpoint inhibitor-related murine autoimmune myocarditis. Commun Biol. 2023;6(1):965. doi:10.1038/s42003-023-05338-4
282. Bogdanos DP, McFarlane IG. Cytochrome P450 2A6 meets P450 2D6: an enigma of viral infections and autoimmunity. J Hepatol. 2003;39(5):860-863. doi:10.1016/s0168-8278(03)00417-3
283. Su Y, Guan P, Li D, Hang Y, Ye X, Han L, Lu Y, Bai X, Zhang P, Hu W. Intermedin attenuates macrophage phagocytosis via regulation of the

long noncoding RNA Dnm3os/miR-27b-3p/SLAMF7 axis in a mouse model of atherosclerosis in diabetes. Biochem Biophys Res Commun. 2021;583:35-42. doi:10.1016/j.bbrc.2021.10.038

284. Pawłowicz M, Filipów R, Krzykowski G, Stanisławska-Sachadyn A, Morzuch L, Kulczycka J, Balcerska A, Limon J. Coincidence of PTPN22 c.1858CC and FCRL3 -169CC genotypes as a biomarker of preserved residual β-cell function in children with type 1 diabetes. Pediatr Diabetes. 2017;18(8):696-705. doi:10.1111/pedi.12429

285. Kim SH, Cleary MM, Fox HS, Chantry D, Sarvetnick N. CCR4-bearing T cells participate in autoimmune diabetes. J Clin Invest. 2002;110(11):1675-1686. doi:10.1172/JCI15547

286. Mollah ZUA, Quah HS, Graham KL, Jhala G, Krishnamurthy B, Dharma JFM, Chee J, Trivedi PM, Pappas EG, Mackin L, et al. Granzyme A Deficiency Breaks Immune Tolerance and Promotes Autoimmune Diabetes Through a Type I Interferon-Dependent Pathway. Diabetes. 2017;66(12):3041-3050. doi:10.2337/db17-0517

287. Di Prospero NA, Artis E, Andrade-Gordon P, Johnson DL, Vaccaro N, Xi L, Rothenberg P. CCR2 antagonism in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Diabetes Obes Metab. 2014;16(11):1055-1064. doi:10.1111/dom.12309

288. Ramos-Lopez E, Ghebru S, Van Autreve J, Aminkeng F, Herwig J, Seifried E, Seidl C, Van der Auwera B, Badenhoop K. Neither an intronic CA repeat within the CD48 gene nor the HERV-K18 polymorphisms are associated with type 1 diabetes. Tissue Antigens. 2006;68(2):147-152. doi:10.1111/j.1399-0039.2006.00637.x

289. Wong S, Moore S, Orisio S, Millward A, Demaine AG. Susceptibility to type I diabetes in women is associated with the CD3 epsilon locus on chromosome 11. Clin Exp Immunol. 1991;83(1):69-73. doi:10.1111/j.1365-2249.1991.tb05590.x

290. Chang TT, Chen C, Lin LY, Chen JW. CCL4 Deletion Accelerates Wound Healing by Improving Endothelial Cell Functions in Diabetes Mellitus. Biomedicines. 2022;10(8):1963. doi:10.3390/biomedicines10081963

291. Blüher M, Klöting N, Wueest S, Schoenle EJ, Schön MR, Dietrich A, Fasshauer M, Stumvoll M, Konrad D. Fas and FasL expression in human

adipose tissue is related to obesity, insulin resistance, and type 2 diabetes. J Clin Endocrinol Metab. 2014;99(1):E36-E44. doi:10.1210/jc.2013-2488

292. Tabassum R, Mahajan A, Dwivedi OP, Chauhan G, Spurgeon CJ, Kumar MV, Ghosh S, Madhu SV, Mathur SK, Chandak GR, et al. Common variants of SLAMF1 and ITLN1 on 1q21 are associated with type 2 diabetes in Indian population. J Hum Genet. 2012;57(3):184-190. doi:10.1038/jhg.2011.150

293. Bailin SS, Kundu S, Wellons M, Freiberg MS, Doyle MF, Tracy RP, Justice AC, Wanjalla CN, Landay AL, So-Armah K, et al. Circulating CD4+ TEMRA and CD4+ CD28- T cells and incident diabetes among persons with and without HIV. AIDS. 2022;36(4):501-511. doi:10.1097/QAD.0000000000003137

294. Santiago JL, Alizadeh BZ, Martínez A, Espino L, de la Calle H, Fernández-Arquero M, Figueredo MA, de la Concha EG, Roep BO, Koeleman BP, et al. Study of the association between the CAPSL-IL7R locus and type 1 diabetes. Diabetologia. 2008;51(9):1653-1658. doi:10.1007/s00125-008-1070-4

295. Newman JRB, Concannon P, Ge Y. UBASH3A Interacts with PTPN22 to Regulate IL2 Expression and Risk for Type 1 Diabetes. Int J Mol Sci. 2023;24(10):8671. doi:10.3390/ijms24108671

296. Aparicio JM, Wakisaka A, Takada A, Matsuura N, Yoshiki T. Non-HLA genetic factors and insulin dependent diabetes mellitus in the Japanese: TCRA, TCRB and TCRG, INS, THY1, CD3D and ETS1. Dis Markers. 1990;8(5):283-294.

297. Zhang HY, Ruan LB, Li Y, Yang TR, Liu WJ, Jiang YX, Li TR, Quan J, Xuan W. ICOS/ICOSL upregulation mediates inflammatory response and endothelial dysfunction in type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci. 2018;22(24):8898-8908. doi:10.26355/eurrev_201812_16659

298. Alshammary AF, Alshammari AM, Alsobaie SF, Alageel AA, Ali Khan I. Evidence from genetic studies among rs2107538 variant in the CCL5 gene and Saudi patients diagnosed with type 2 diabetes mellitus. Saudi J Biol Sci. 2023;30(6):103658. doi:10.1016/j.sjbs.2023.103658

299. Zhong Y, Du G, Liu J, Li S, Lin J, Deng G, Wei J, Huang J.RUNX1 and CCL3 in Diabetes Mellitus-Related Coronary Artery Disease: A

Bioinformatics Analysis. Int J Gen Med. 2022;15:955-963. doi:10.2147/IJGM.S350732

300. Mohamed WA, Schaalan MF. Antidiabetic efficacy of lactoferrin in type 2 diabetic pediatrics; controlling impact on PPAR-γ, SIRT-1, and TLR4 downstream signaling pathway. Diabetol Metab Syndr. 2018;10:89. doi:10.1186/s13098-018-0390-x

301. Short AD, Saleh NM, Catchpole B, Kennedy LJ, Barnes A, Jones CA, Fretwell N, Ollier WE. CTLA4 promoter polymorphisms are associated with canine diabetes mellitus. Tissue Antigens. 2010;75(3):242-252. doi:10.1111/j.1399-0039.2009.01434.x

302. Kirk RL, Ranford PR, Court J, Zimmet P. Distribution of complement C'2 and C'6 types in Australian cases of diabetes mellitus. Med J Aust. 1980;2(11):614-615. doi:10.5694/j.1326-5377.1980.tb77064.x

303. Luk AO, Wang Y, Ma RC, Tam CH, Ng MC, Lam V, Yang X, Baum L, Tong PC, Chan JC, et al. Predictive role of polymorphisms in interleukin-5 receptor alpha-subunit, lipoprotein lipase, integrin A2 and nitric oxide synthase genes on ischemic stroke in type 2 diabetes--an 8-year prospective cohort analysis of 1327 Chinese patients. Atherosclerosis. 2011;215(1):130-135. doi:10.1016/j.atherosclerosis.2010.11.042

304. Unger WW, Pearson T, Abreu JR, Laban S, van der Slik AR, der Kracht SM, Kester MG, Serreze DV, Shultz LD, Griffioen M, et al. Islet-specific CTL cloned from a type 1 diabetes patient cause beta-cell destruction after engraftment into HLA-A2 transgenic NOD/scid/IL2RG null mice. PLoS One. 2012;7(11):e49213. doi:10.1371/journal.pone.0049213

305. Campbell CD, Lyon HN, Nemesh J, Drake JA, Tuomi T, Gaudet D, Zhu X, Cooper RS, Ardlie KG, Groop LC, et al. Association studies of BMI and type 2 diabetes in the neuropeptide Y pathway: a possible role for NPY2R as a candidate gene for type 2 diabetes in men. Diabetes. 2007;56(5):1460-1467. doi:10.2337/db06-1051

306. Xiu L, Lin M, Liu W, Kong D, Liu Z, Zhang Y, Ouyang P, Liang Y, Zhong S, Chen C, et al. Association of DRD3, COMT, and SLC6A4 Gene Polymorphisms with Type 2 Diabetes in Southern Chinese: A Hospital-Based Case-Control Study. Diabetes Technol Ther. 2015;17(8):580-586. doi:10.1089/dia.2014.0344

307. Mao R, Yang F, Zhang Y, Liu H, Guo P, Liu Y, Zhang T. High expression of CD52 in adipocytes: a potential therapeutic target for obesity with type 2 diabetes. Aging (Albany NY). 2021;13(8):11043-11060. doi:10.18632/aging.202714
308. Semnani-Azad Z, Blanco Mejia S, Connelly PW, Bazinet RP, Retnakaran R, Jenkins DJA, Harris SB, Hanley AJ. The association of soluble CD163, a novel biomarker of macrophage activation, with type 2 diabetes mellitus and its underlying physiological disorders: A systematic review. Obes Rev. 2021;22(9):e13257. doi:10.1111/obr.13257
309. Vaitheesvaran B, Hartil K, Navare A, Zheng, OBroin P, Golden A, Guha, Lee W, Kurland IJ, Bruce JE. Role of the tumor suppressor IQGAP2 in metabolic homeostasis: Possible link between diabetes and cancer. Metabolomics. 2014;10(5):920-937. doi:10.1007/s11306-014-0639-9
310. Doran TM, Morimoto J, Simanski S, Koesema EJ, Clark LF, Pels K, Stoops SL, Pugliese A, Skyler JS, Kodadek T. Discovery of Phosphorylated Peripherin as a Major Humoral Autoantigen in Type 1 Diabetes Mellitus. Cell Chem Biol. 2016;23(5):618-628. doi:10.1016/j.chembiol.2016.04.006
311. Nance SA, Muir L, Delproprosto J, Lumeng CN. MSR1 is not required for obesity-associated inflammation and insulin resistance in mice. Sci Rep. 2023;13(1):2651. doi:10.1038/s41598-023-29736-0
312. Oliveira AG, Araújo TG, Carvalho BM, Rocha GZ, Santos A, Saad MJA. The Role of Hepatocyte Growth Factor (HGF) in Insulin Resistance and Diabetes. Front Endocrinol (Lausanne). 2018;9:503. doi:10.3389/fendo.2018.00503
313. Westermark GT, Westermark P. Transthyretin and amyloid in the islets of Langerhans in type-2 diabetes. Exp Diabetes Res. 2008;2008:429274. doi:10.1155/2008/429274
314. Semenchuk J, Sullivan K, Moineddin R, Mahmud F, Dart A, Wicklow B, Xiao F, Medeiros T, Scholey J, Burger D. Urinary interleukin-9 in youth with type 1 diabetes mellitus. Acta Diabetol. 2022;59(7):939-947. doi:10.1007/s00592-022-01873-4
315. Wong HK, Tang F, Cheung TT, Cheung BM. Adrenomedullin and diabetes. World J Diabetes. 2014;5(3):364-371. doi:10.4239/wjd.v5.i3.364
316. Gusarova V, O'Dushlaine C, Teslovich TM, Benotti PN, Mirshahi T, Gottesman O, Van Hout CV, Murray MF, Mahajan A, et al. Genetic

inactivation of ANGPTL4 improves glucose homeostasis and is associated with reduced risk of diabetes. Nat Commun. 2018;9(1):2252.doi:10.1038/s41467-018-04611-z

317. Di Rosa M, Malaguarnera L. Chitinase 3 Like-1: An Emerging Molecule Involved in Diabetes and Diabetic Complications. Pathobiology. 2016;83(5):228-242. doi:10.1159/000444855

318. Saito T, Mizukami H, Umetsu S, Uchida C, Inaba W, Abe M, Takahashi K, Kudo K, Itabashi C, Yagihashi S, et al. Worsened outcome in patients with pancreatic ductal carcinoma on long-term diabetes: association with E-cadherin1 (CDH1) promoter methylation. Sci Rep. 2017;7(1):18056. doi:10.1038/s41598-017-18438-z

319. Krause C, Sievert H, Geißler C, Grohs M, El Gammal AT, Wolter S, Ohlei O, Kilpert F, Krämer UM, Kasten M, et al. Critical evaluation of the DNA-methylation markers ABCG1 and SREBF1 for Type 2 diabetes stratification. Epigenomics. 2019;11(8):885-897. doi:10.2217/epi-2018-0159

320. Hiramoto M, Udagawa H, Ishibashi N, Takahashi E, Kaburagi Y, Miyazawa K, Funahashi N, Nammo T, Yasuda K. A type 2 diabetes-associated SNP in KCNQ1 (rs163184) modulates the binding activity of the locus for Sp3 and Lsd1/Kdm1a, potentially affecting CDKN1C expression. Int J Mol Med. 2018;41(2):717-728. doi:10.3892/ijmm.2017.3273

321. Ekim Üstünel B, Friedrich K, Maida A, Wang X, Krones-Herzig A, Seibert O, Sommerfeld A, Jones A, Sijmonsma TP, Sticht C, et al. Control of diabetic hyperglycaemia and insulin resistance through TSC22D4. Nat Commun. 2016;7:13267. doi:10.1038/ncomms13267

322. Hasan S, Khan MS, Lansang MC. The effect of cystic fibrosis transmembrane conductance regulator modulators on impaired glucose tolerance and cystic fibrosis related diabetes. J Clin Transl Endocrinol. 2022;29:100301. doi:10.1016/j.jcte.2022.100301

323. Szopa M, Meirhaeghe A, Luan J, Moreno LA, Gonzalez-Gross M, Vidal-Puig A, Cooper C, Hagen R, Amouyel P, Wareham NJ, et al. No association between polymorphisms in the INSIG1 gene and the risk of type 2 diabetes and related traits. Am J Clin Nutr. 2010;92(1):252-257. doi:10.3945/ajcn.2010.2942

324. Rotroff DM, Pijut SS, Marvel SW, Jack JR, Havener TM, Pujol A, Schluter A, Graf GA, Ginsberg HN, Shah HS, et al. Genetic Variants in

HSD17B3, SMAD3, and IPO11 Impact Circulating Lipids in Response to Fenofibrate in Individuals With Type 2 Diabetes. Clin Pharmacol Ther. 2018;103(4):712-721. doi:10.1002/cpt.798

325. Mitroi AF, Leopa N, Dumitru E, Brînzan C, Tocia C, Dumitru A, Popescu RC. Association of TCF7L2, CASC8 and GREM1 Polymorphisms in Patients with Colorectal Cancer and Type II Diabetes Mellitus. Genes (Basel). 2022;13(8):1297. doi:10.3390/genes13081297

326. Kim JY, Park KJ, Kim GH, Jeong EA, Lee DY, Lee SS, Kim DJ, Roh GS, Song J, Ki SH, et al. In vivo activating transcription factor 3 silencing ameliorates the AMPK compensatory effects for ER stress-mediated β-cell dysfunction during the progression of type-2 diabetes. Cell Signal. 2013;25(12):2348-2361. doi:10.1016/j.cellsig.2013.07.028

327. Rabbani N, Xue M, Thornalley PJ. Hexokinase-2-Linked Glycolytic Overload and Unscheduled Glycolysis-Driver of Insulin Resistance and Development of Vascular Complications of Diabetes. Int J Mol Sci. 2022;23(4):2165. doi:10.3390/ijms23042165

328. Ma Y, Cai J, Wang Y, Liu J, Fu S. Non-Enzymatic Glycation of Transferrin and Diabetes Mellitus. Diabetes Metab Syndr Obes. 2021;14:2539-2548. doi:10.2147/DMSO.S304796

329. Griffin JWD, Liu Y, Bradshaw PC, Wang K. In Silico Preliminary Association of Ammonia Metabolism Genes GLS, CPS1, and GLUL with Risk of Alzheimer's Disease, Major Depressive Disorder, and Type 2 Diabetes. J Mol Neurosci. 2018;64(3):385-396. doi:10.1007/s12031-018-1035-0

330. Tao J, Yu XL, Yuan YJ, Shen X, Liu J, Gu PP, Wang Z, Ma YT, Li GQ. DMRT2 Interacts With FXR and Improves Insulin Resistance in Adipocytes and a Mouse Model. Front Endocrinol (Lausanne). 2022;12:723623. doi:10.3389/fendo.2021.723623

331. Dunmore SJ, Al-Derawi AS, Nayak AU, Narshi A, Nevill AM, Hellwig A, Majebi A, Kirkham P, Brown JE, Singh BM. Evidence That Differences in Fructosamine-3-Kinase Activity May Be Associated With the Glycation Gap in Human Diabetes. Diabetes. 2018;67(1):131-136. doi:10.2337/db17-0441

332. Muller YL, Hanson RL, Knowler WC, Fleming J, Goswami J, Huang K, Traurig M, Sutherland J, Wiedrich C, Wiedrich K, et al. Identification of

genetic variation that determines human trehalase activity and its association with type 2 diabetes. Hum Genet. 2013;132(6):697-707. doi:10.1007/s00439-013-1278-3

333. Uluçay S, Çam FS, Batır MB, Sütçü R, Bayturan Ö, Demircan K. A novel association between TGFb1 and ADAMTS4 in coronary artery disease: A new potential mechanism in the progression of atherosclerosis and diabetes. Anatol J Cardiol. 2015;15(10):823-829. doi:10.5152/akd.2014.5762

334. Zhang JM, Yu RQ, Wu FZ, Qiao L, Wu XR, Fu YJ, Liang YF, Pang Y, Xie CY. BMP-2 alleviates heart failure with type 2 diabetes mellitus and doxorubicin-induced AC16 cell injury by inhibiting NLRP3 inflammasome-mediated pyroptosis. Exp Ther Med. 2021;22(2):897. doi:10.3892/etm.2021.10329

335. Miranda M, Chacón MR, Gutiérrez C, Vilarrasa N, Gómez JM, Caubet E, Megía A, Vendrell J. LMNA mRNA expression is altered in human obesity and type 2 diabetes. Obesity (Silver Spring). 2008;16(8):1742-1748. doi:10.1038/oby.2008.276

336. Massignam ET, Dieter C, Assmann TS, Duarte GCK, Bauer AC, Canani LH, Crispim D. The rs705708 A allele of the ERBB3 gene is associated with lower prevalence of diabetic retinopathy and arterial hypertension and with improved renal function in type 1 diabetic patients. Microvasc Res. 2022;143:104378. doi:10.1016/j.mvr.2022.104378

337. Szweda-Gandor N, Śnit M, Grzeszczak W. Association between Selected Polymorphisms rs12086634, rs846910, rs4844880, rs3753519 of 11β-Hydroxysteroid Dehydrogenase Type 1 (HSD11B1) and the Presence of Insulin Resistance in the Polish Population of People Living in Upper Silesia. Int J Environ Res Public Health. 2021;18(19):10168. doi:10.3390/ijerph181910168

338. Qu J, Qu HQ, Bradfield JP, Glessner JT, Chang X, Tian L, March ME, Roizen JD, Sleiman PM, Hakonarson H. Association of DLL1 with type 1 diabetes in patients characterized by low polygenic risk score. Metabolism. 2021;114:154418. doi:10.1016/j.metabol.2020.154418

339. Kavitha B, Srikanth K, Singh D, Gopi S, Mohan V, Chandra N, Radha V. A novel stop-loss mutation in NKX2-2 gene as a cause of neonatal diabetes mellitus: molecular characterization and structural analysis. Acta

Diabetol. 2023;10.1007/s00592-023-02192-y. doi:10.1007/s00592-023-02192-y
340. Cheng S, Cui Y, Fan L, Mu X, Hua Y. T2DM inhibition of endothelial miR-342-3p facilitates angiogenic dysfunction via repression of FGF11 signaling. Biochem Biophys Res Commun. 2018;503(1):71-78. doi:10.1016/j.bbrc.2018.05.179
341. Surendran S, Matalon R, Tyring SK. Upregulation of aspartoacylase activity in the duodenum of obesity induced diabetes mouse: implications on diabetic neuropathy. Biochem Biophys Res Commun. 2006;345(3):973-975. doi:10.1016/j.bbrc.2006.04.179
342. Menendez JA, Vazquez-Martin A, Ortega FJ, Fernandez-Real JM. Fatty acid synthase: association with insulin resistance, type 2 diabetes, and cancer. Clin Chem. 2009;55(3):425-438. doi:10.1373/clinchem.2008.115352
343. Moon S, Chung GE, Joo SK, Park JH, Chang MS, Yoon JW, Koo BK, Kim W. A PNPLA3 Polymorphism Confers Lower Susceptibility to Incident Diabetes Mellitus in Subjects With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol. 2022;20(3):682-691.e8. doi:10.1016/j.cgh.2021.04.038
344. Yip L, Taylor C, Whiting CC, Fathman CG. Diminished adenosine A1 receptor expression in pancreatic α-cells may contribute to the pathology of type 1 diabetes. Diabetes. 2013;62(12):4208-4219. doi:10.2337/db13-0614
345. Wang W, Yan X, Lin Y, Ge H, Tan Q. Wnt7a promotes wound healing by regulation of angiogenesis and inflammation: Issues on diabetes and obesity. J Dermatol Sci. 2018. doi:10.1016/j.jdermsci.2018.02.007
346. Berk-Planken II, Hoogerbrugge N, Stolk RP, Bootsma AH, Jansen H; DALI Study Group. Atorvastatin dose-dependently decreases hepatic lipase activity in type 2 diabetes: effect of sex and the LIPC promoter variant. Diabetes Care. 2003;26(2):427-432. doi:10.2337/diacare.26.2.427
347. Kaushik AC, Kumar S, Wei DQ, Sahi S. Structure Based Virtual Screening Studies to Identify Novel Potential Compounds for GPR142 and Their Relative Dynamic Analysis for Study of Type 2 Diabetes. Front Chem. 2018;6:23. doi:10.3389/fchem.2018.00023
348. Li N, Chang G, Xu Y, Ding Y, Li G, Yu T, Yao R, Li J, Shen Y, Wang X, et al. Biallelic mutations in GPD1 gene in a Chinese boy mainly

presented with obesity, insulin resistance, fatty liver, and short stature. Am J Med Genet A. 2017;173(12):3189-3194. doi:10.1002/ajmg.a.38473

349. Muller YL, Sutherland J, Nair AK, Koroglu C, Kobes S, Knowler WC, Van Hout CV; Regeneron Genetics Center; Shuldiner AR, Hanson RL, Bogardus C, et al. A missense variant Arg611Cys in LIPE which encodes hormone sensitive lipase decreases lipolysis and increases risk of type 2 diabetes in American Indians. Diabetes Metab Res Rev. 2022;38(3):e3504. doi:10.1002/dmrr.3504

350. Sun L, Lu J, Yao D, Li X, Cao Y, Gao J, Liu J, Zheng T, Wang H, Zhan X. Effect of DHCR7 for the co-occurrence of hypercholesterolemia and vitamin D deficiency in type 2 diabetes: Perspective of health prevention. Prev Med. 2023;173:107576. doi:10.1016/j.ypmed.2023.107576

351. Wang Q, Li H, Lu H, Wang S, Li Y, Zhang Z, Han J, Yang Z, Yang Y, Hong Y. SAA1 exacerbates pancreatic β-cell dysfunction through activation of NF-κB signaling in high-fat diet-induced type 2 diabetes mice. Mol Cell Endocrinol. 2023;576:112043. doi:10.1016/j.mce.2023.112043

352. Coy JF, Dressler D, Wilde J, Schubert P. Mutations in the transketolase-like gene TKTL1: clinical implications for neurodegenerative diseases, diabetes and cancer. Clin Lab. 2005;51(5-6):257-273.

353. Chen Y, Chen J, Zhang C, Yang S, Zhang X, Liu Y, Su Z. Deficiency in the short-chain acyl-CoA dehydrogenase protects mice against diet-induced obesity and insulin resistance. FASEB J. 2019;33(12):13722-13733. doi:10.1096/fj.201901474RR

354. Oballa RM, Belair L, Black WC, Bleasby K, Chan CC, Desroches C, Du X, Gordon R, Guay J, Guiral S, et al. Development of a liver-targeted stearoyl-CoA desaturase (SCD) inhibitor (MK-8245) to establish a therapeutic window for the treatment of diabetes and dyslipidemia. J Med Chem. 2011;54(14):5082-5096. doi:10.1021/jm200319u

355. Rani L, Grewal AS, Sharma N, Singh S. Recent Updates on Free Fatty Acid Receptor 1 (GPR-40) Agonists for the Treatment of Type 2 Diabetes Mellitus. Mini Rev Med Chem. 2021;21(4):426-470. doi:10.2174/1389557520666201023141326

356. Paszek E, Polak M, Bryk-Wiązania AH, Konieczyńska M, Undas A. Elevated plasma factor XI predicts cardiovascular events in patients with

type 2 diabetes: a long-term observational study. Cardiovasc Diabetol. 2023;22(1):182. doi:10.1186/s12933-023-01905-5

357. Kurooka N, Eguchi J, Murakami K, Kamei S, Kikutsuji T, Sasaki S, Seki A, Yamaguchi S, Nojima I, Watanabe M, et al. irculating GPIHBP1 levels and microvascular complications in patients with type 2 diabetes: A cross-sectional study. J Clin Lipidol. 2022;16(2):237-245. doi:10.1016/j.jacl.2022.01.006

358. Waeber G, Delplanque J, Bonny C, Mooser V, Steinmann M, Widmann C, Maillard A, Miklossy J, Dina C, Hani EH, et al. The gene MAPK8IP1, encoding islet-brain-1, is a candidate for type 2 diabetes. Nat Genet. 2000;24(3):291-295. doi:10.1038/73523

359. Liu T, Chen WQ, David SP, Tyndale RF, Wang H, Chen YM, Yu XQ, Chen W, Zhou Q, Ling WH. Interaction between heavy smoking and CYP2A6 genotypes on type 2 diabetes and its possible pathways. Eur J Endocrinol. 2011;165(6):961-967. doi:10.1530/EJE-11-0596

360. Zhang Y, Zhou X, Dai W, Sun J, Lin M, Zhang Y, Ding Y.CTNNA3 genetic polymorphism may be a new genetic signal of type 2 diabetes in the Chinese Han population: a case control study. BMC Med Genomics. 2021;14(1):257. doi:10.1186/s12920-021-01105-8

361. Carter C. Alzheimer's Disease: APP, Gamma Secretase, APOE, CLU, CR1, PICALM, ABCA7, BIN1, CD2AP, CD33, EPHA1, and MS4A2, and Their Relationships with Herpes Simplex, C. Pneumoniae, Other Suspect Pathogens, and the Immune System. Int J Alzheimers Dis. 2011;2011:501862. doi:10.4061/2011/501862

362. Kim SH, Lim KH, Yang S, Joo JY. Boosting of tau protein aggregation by CD40 and CD48 gene expression in Alzheimer's disease. FASEB J. 2023;37(1):e22702. doi:10.1096/fj.202201197R

363. Yu L, Chibnik LB, Srivastava GP, Pochet N, Yang J, Xu J, Kozubek J, Obholzer N, Leurgans SE, Schneider JA, et al. Association of Brain DNA methylation in SORL1, ABCA7, HLA-DRB5, SLC24A4, and BIN1 with pathological diagnosis of Alzheimer disease. JAMA Neurol. 2015;72(1):15-24. doi:10.1001/jamaneurol.2014.3049

364. Costa AS, Agostini S, Guerini FR, Mancuso R, Clerici M, Pandey JP. Relation between FCGRIIB rs1050501 and HSV-1 specific IgG antibodies

in Alzheimer's disease. J Transl Med. 2020;18(1):325. doi:10.1186/s12967-020-02495-6

365. Ma W, Liu A, Wu X, Gao L, Chen J, Wu H, Liu M, Fan Y, Peng L, Yang J, et al. The intricate role of CCL5/CCR5 axis in Alzheimer disease. J Neuropathol Exp Neurol. 2023;82(11):894-900. doi:10.1093/jnen/nlad071

366. Geppert AM, Losy J, Przedpelska-Ober E, Kozubski W. CCL3 correlates with the number of mood disturbances and personality changes in patients with Alzheimer's disease. Psychiatry Res. 2010;176(2-3):261-264. doi:10.1016/j.psychres.2009.02.007

367. Tsatsanis A, McCorkindale AN, Wong BX, Patrick E, Ryan TM, Evans RW, Bush AI, Sutherland GT, Sivaprasadarao A, Guennewig B, et al. The acute phase protein lactoferrin is a key feature of Alzheimer's disease and predictor of Aβ burden through induction of APP amyloidogenic processing. Mol Psychiatry. 2021;26(10):5516-5531. doi:10.1038/s41380-021-01248-1

368. Doroszkiewicz J, Kulczyńska-Przybik A, Dulewicz M, Borawska R, Zajkowska M, Słowik A, Mroczko B. Potential Utility of Cerebrospinal Fluid Glycoprotein Nonmetastatic Melanoma Protein B as a Neuroinflammatory Diagnostic Biomarker in Mild Cognitive Impairment and Alzheimer's Disease. J Clin Med. 2023;12(14):4689. doi:10.3390/jcm12144689

369. Santos RR, Torres KC, Lima GS, Fiamoncini CM, Mapa FC, Pereira PA, Rezende VB, Martins LC, Bicalho MA, Moraes EN, et al. Reduced frequency of T lymphocytes expressing CTLA-4 in frontotemporal dementia compared to Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:1-5. doi:10.1016/j.pnpbp.2013.06.019

370. Kang WS, Park JK, Kim YJ, Cho AR, Park HJ, Kim SK, Paik JW, Lee KJ, Na HR, Kim YY, et al. Association of tripartite motif family-like 2 (TRIML2) polymorphisms with late-onset Alzheimer's disease risk in a Korean population. Neurosci Lett. 2016;630:127-131. doi:10.1016/j.neulet.2016.07.046

371. Wallace CH, Oliveros G, Serrano PA, Rockwell P, Xie L, Figueiredo-Pereira M. Timapiprant, a prostaglandin D2 receptor antagonist, ameliorates pathology in a rat Alzheimer's model. Life Sci Alliance. 2022;5(12):e202201555. doi:10.26508/lsa.202201555

372. Sato N, Ueki A, Ueno H, Shinjo H, Morita Y. Dopamine D3 receptor gene polymorphism influences on behavioral and psychological symptoms of dementia (BPSD) in mild dementia of Alzheimer's type. J Alzheimers Dis. 2009;17(2):441-448. doi:10.3233/JAD-2009-1054
373. Haasl RJ, Ahmadi MR, Meethal SV, Gleason CE, Johnson SC, Asthana S, Bowen RL, Atwood CS. A luteinizing hormone receptor intronic variant is significantly associated with decreased risk of Alzheimer's disease in males carrying an apolipoprotein E epsilon4 allele. BMC Med Genet. 2008;9:37. doi:10.1186/1471-2350-9-37
374. Pey P, Pearce RK, Kalaitzakis ME, Griffin WS, Gentleman SM. Phenotypic profile of alternative activation marker CD163 is different in Alzheimer's and Parkinson's disease. Acta Neuropathol Commun. 2014;2:21. doi:10.1186/2051-5960-2-21
375. Miron J, Picard C, Labonté A, Auld D, Poirier J; PREVENT-AD research group. MSR1 and NEP Are Correlated with Alzheimer's Disease Amyloid Pathology and Apolipoprotein Alterations. J Alzheimers Dis. 2022;86(1):283-296. doi:10.3233/JAD-215410
376. Zhao LJ, Wang ZT, Ma YH, Zhang W, Dong Q, Yu JT, Tan L; Associations of the cerebrospinal fluid hepatocyte growth factor with Alzheimer's disease pathology and cognitive function. BMC Neurol. 2021;21(1):387. doi:10.1186/s12883-021-02356-9
377. Cotrina EY, Santos LM, Rivas J, Blasi D, Leite JP, Liz MA, Busquets MA, Planas A, Prohens R, Gimeno A, et al. Targeting transthyretin in Alzheimer's disease: Drug discovery of small-molecule chaperones as disease-modifying drug candidates for Alzheimer's disease. Eur J Med Chem. 2021;226:113847. doi:10.1016/j.ejmech.2021.113847
378. Wharton W, Kollhoff AL, Gangishetti U, Verble DD, Upadhya S, Zetterberg H, Kumar V, Watts KD, Kippels AJ, Gearing M, et al. Interleukin 9 alterations linked to alzheimer disease in african americans. Ann Neurol. 2019;86(3):407-418. doi:10.1002/ana.25543
379. Ferrero H, Larrayoz IM, Martisova E, Solas M, Howlett DR, Francis PT, Gil-Bea FJ, Martínez A, Ramírez MJ. Increased Levels of Brain Adrenomedullin in the Neuropathology of Alzheimer's Disease. Mol Neurobiol. 2018;55(6):5177-5183. doi:10.1007/s12035-017-0700-6

380. Connolly K, Lehoux M, O'Rourke R, Assetta B, Erdemir GA, Elias JA, Lee CG, Huang YA. Potential role of chitinase-3-like protein 1 (CHI3L1/YKL-40) in neurodegeneration and Alzheimer's disease. Alzheimers Dement. 2023;19(1):9-24. doi:10.1002/alz.12612
381. Vlkolinský R, Cairns N, Fountoulakis M, Lubec G. Decreased brain levels of 2',3'-cyclic nucleotide-3'-phosphodiesterase in Down syndrome and Alzheimer's disease. Neurobiol Aging. 2001;22(4):547-553. doi:10.1016/s0197-4580(01)00218-4
382. Lapresa R, Agulla J, Bolaños JP, Almeida A. APC/C-Cdh1-targeted substrates as potential therapies for Alzheimer's disease. Front Pharmacol. 2022;13:1086540. doi:10.3389/fphar.2022.1086540
383. Sims R, Hollingworth P, Moskvina V, Dowzell K, O'Donovan MC, Powell J, Lovestone S, Brayne C, Rubinsztein D, Owen MJ, et al. Evidence that variation in the oligodendrocyte lineage transcription factor 2 (OLIG2) gene is associated with psychosis in Alzheimer's disease. Neurosci Lett. 2009;461(1):54-59. doi:10.1016/j.neulet.2009.05.051
384. Teuber-Hanselmann S, Rekowski J, Vogelgsang J, von Arnim C, Reetz K, Stang A, Jöckel KH, Wiltfang J, Esselmann H, Otto M, et al. CSF and blood Kallikrein-8: a promising early biomarker for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2020;91(1):40-48. doi:10.1136/jnnp-2019-321073
385. Lahousse SA, Stopa EG, Mulberg AE, de la Monte SM. Reduced expression of the cystic fibrosis transmembrane conductance regulator gene in the hypothalamus of patients with Alzheimer's disease. J Alzheimers Dis. 2003;5(6):455-462. doi:10.3233/jad-2003-5605
386. Hu W, Lin X, Zhang H, Zhao N. ATP Binding Cassette Subfamily A Member 2 (ABCA2) Expression and Methylation are Associated with Alzheimer's Disease. Med Sci Monit. 2017;23:5851-5861. doi:10.12659/msm.905524
387. Fairley LH, Lai KO, Wong JH, Chong WJ, Vincent AS, D'Agostino G, Wu X, Naik RR, Jayaraman A, Langley SR, et al. Mitochondrial control of microglial phagocytosis by the translocator protein and hexokinase 2 in Alzheimer's disease. Proc Natl Acad Sci U S A. 2023;120(8):e2209177120. doi:10.1073/pnas.2209177120

388. Bruno F, Abondio P, Montesanto A, Luiselli D, Bruni AC, Maletta R. The Nerve Growth Factor Receptor (NGFR/p75NTR): A Major Player in Alzheimer's Disease. Int J Mol Sci. 2023;24(4):3200. doi:10.3390/ijms24043200
389. Hoshi K, Ito H, Abe E, Fuwa TJ, Kanno M, Murakami Y, Abe M, Murakami T, Yoshihara A, Ugawa Y, et al. Transferrin Biosynthesized in the Brain Is a Novel Biomarker for Alzheimer's Disease. Metabolites. 2021;11(9):616. doi:10.3390/metabo11090616
390. Matsuzaki M, Yokoyama M, Yoshizawa Y, Kaneko N, Naito H, Kobayashi H, Korenaga A, Sekiya S, Ikemura K, Opoku G, et al. ADAMTS4 is involved in the production of the Alzheimer disease amyloid biomarker APP669-711. Mol Psychiatry. 2023;28(4):1802-1812. doi:10.1038/s41380-023-01946-y
391. Gao P, Ye L, Cheng H, Li H. The Mechanistic Role of Bridging Integrator 1 (BIN1) in Alzheimer's Disease. Cell Mol Neurobiol. 2021;41(7):1431-1440. doi:10.1007/s10571-020-00926-y
392. Dong Y, Li T, Ma Z, Zhou C, Wang X, Li J. HSPA1A, HSPA2, and HSPA8 Are Potential Molecular Biomarkers for Prognosis among HSP70 Family in Alzheimer's Disease. Dis Markers. 2022;2022:9480398. doi:10.1155/2022/9480398
393. Méndez-López I, Blanco-Luquin I, Sánchez-Ruiz de Gordoa J, Urdánoz-Casado A, Roldán M, Acha B, Echavarri C, Zelaya V, Jericó I, Mendioroz M. Hippocampal LMNA Gene Expression is Increased in Late-Stage Alzheimer's Disease. Int J Mol Sci. 2019;20(4):878. doi:10.3390/ijms20040878
394. Sooy K, Noble J, McBride A, Binnie M, Yau JL, Seckl JR, Walker BR, Webster SP. Cognitive and Disease-Modifying Effects of 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibition in Male Tg2576 Mice, a Model of Alzheimer's Disease. Endocrinology. 2015;156(12):4592-4603. doi:10.1210/en.2015-139
395. Liu G, Zhang H, Liu B, Ji X. Rs2293871 regulates HTRA1 expression and affects cerebral small vessel stroke and Alzheimer's disease. Brain. 2019;142(11):e61. doi:10.1093/brain/awz305
396. Guilarte TR. APLP1, Alzheimer's-like pathology and neurodegeneration in the frontal cortex of manganese-exposed non-human

primates. Neurotoxicology. 2010;31(5):572-574. doi:10.1016/j.neuro.2010.02.004

397. Yu WH, Lukiw WJ, Bergeron C, Niznik HB, Fraser PE. Metallothionein III is reduced in Alzheimer's disease. Brain Res. 2001;894(1):37-45. doi:10.1016/s0006-8993(00)03196-6

398. Saggu S, Chen Y, Chen L, Pizarro D, Pati S, Law WJ, McMahon L, Jiao K, Wang Q. A peptide blocking the ADORA1-neurabin interaction is anticonvulsant and inhibits epilepsy in an Alzheimer's model. JCI Insight. 2022;7(11):e155002. doi:10.1172/jci.insight.155002

399. Galvin JE, Palamand D, Strider J, Milone M, Pestronk A. The muscle protein dysferlin accumulates in the Alzheimer brain. Acta Neuropathol. 2006;112(6):665-671. doi:10.1007/s00401-006-0147-8

400. Yu L, Chibnik LB, Srivastava GP, Pochet N, Yang J, Xu J, Kozubek J, Obholzer N, Leurgans SE, Schneider JA, et al. Association of Brain DNA methylation in SORL1, ABCA7, HLA-DRB5, SLC24A4, and BIN1 with pathological diagnosis of Alzheimer disease. JAMA Neurol. 2015;72(1):15-24. doi:10.1001/jamaneurol.2014.3049

401. Kamasani U, Prendergast GC. Genetic response to DNA damage: proapoptotic targets of RhoB include modules for p53 response and susceptibility to Alzheimer's disease. Cancer Biol Ther. 2005;4(3):282-288. doi:10.4161/cbt.4.3.1498

402. Lin KP, Chen SY, Lai LC, Huang YL, Chen JH, Chen TF, Sun Y, Wen LL, Yip PK, Chu YM, et al. Genetic polymorphisms of a novel vascular susceptibility gene, Ninjurin2 (NINJ2), are associated with a decreased risk of Alzheimer's disease. PLoS One. 2011;6(6):e20573. doi:10.1371/journal.pone.0020573

403. Zhang B, Wang LL, Ren RJ, Dammer EB, Zhang YF, Huang Y, Chen SD, Wang G. MicroRNA-146a represses LRP2 translation and leads to cell apoptosis in Alzheimer's disease. FEBS Lett. 2016;590(14):2190-2200. doi:10.1002/1873-3468.12229

404. Xiao Z, Wang J, Chen W, Wang P, Zeng H, Chen W. Association studies of several cholesterol-related genes (ABCA1, CETP and LIPC) with serum lipids and risk of Alzheimer's disease. Lipids Health Dis. 2012;11:163. doi:10.1186/1476-511X-11-163

405. Liu X, Wu P, Shen L, Jiao B, Liao X, Wang H, Peng J, Lin Z. DHCR7 rs12785878 T>C Polymorphism Is Associated With an Increased Risk of Early Onset of Alzheimer's Disease in Chinese Population. Front Genet. 2021;12:583695. doi:10.3389/fgene.2021.583695
406. Hamilton LK, Moquin-Beaudry G, Mangahas CL, Pratesi F, Aubin M, Aumont A, Joppé SE, Légiot A, Vachon A, Plourde M, et al. Stearoyl-CoA Desaturase inhibition reverses immune, synaptic and cognitive impairments in an Alzheimer's disease mouse model. Nat Commun. 2022;13(1):2061. doi:10.1038/s41467-022-29506-y
407. Begic E, Hadzidedic S, Obradovic S, Begic Z, Causevic M. Increased Levels of Coagulation Factor XI in Plasma Are Related to Alzheimer's Disease Diagnosis. J Alzheimers Dis. 2020;77(1):375-386. doi:10.3233/JAD-200358
408. Bigl M, Bleyl AD, Zedlick D, Arendt T, Bigl V, Eschrich K. Changes of activity and isozyme pattern of phosphofructokinase in the brains of patients with Alzheimer's disease. J Neurochem. 1996;67(3):1164-1171. doi:10.1046/j.1471-4159.1996.67031164.x
409. Nikhil K, Viccaro K, Shah K. Multifaceted Regulation of ALDH1A1 by Cdk5 in Alzheimer's Disease Pathogenesis. Mol Neurobiol. 2019;56(2):1366-1390. doi:10.1007/s12035-018-1114-9
410. Park SY, Kang JY, Lee T, Nam D, Jeon CJ, Kim JB. SPON1 Can Reduce Amyloid Beta and Reverse Cognitive Impairment and Memory Dysfunction in Alzheimer's Disease Mouse Model. Cells. 2020;9(5):1275. doi:10.3390/cells9051275
411. Blomqvist ME, Andreasen N, Bogdanovic N, Blennow K, Brookes AJ, Prince JA. Genetic variation in CTNNA3 encoding alpha-3 catenin and Alzheimer's disease. Neurosci Lett. 2004;358(3):220-222. doi:10.1016/j.neulet.2004.01.032
412. Freff J, Beins EC, Bröker L, Schwarte K, Leite Dantas R, Maj C, Arolt V, Dannlowski U, Nöthen MM, Baune BT, et al. Chemokine receptor 4 expression on blood T lymphocytes predicts severity of major depressive disorder. J Affect Disord. 2022;310:343-353. doi:10.1016/j.jad.2022.05.003
413. Curzytek K, Leśkiewicz M. Targeting the CCL2-CCR2 axis in depressive disorders. Pharmacol Rep. 2021;73(4):1052-1062. doi:10.1007/s43440-021-00280-w

414. Nyegaard M, Demontis D, Thestrup BB, Hedemand A, Sørensen KM, Hansen T, Werge T, Hougaard DM, Yolken RH, Mortensen PB, et al. No association of polymorphisms in human endogenous retrovirus K18 and CD48 with schizophrenia. Psychiatr Genet. 2012;22(3):146-148. doi:10.1097/YPG.0b013e328353953c
415. Frydecka D, Beszłej JA, Pawlak-Adamska E, Misiak B, Karabon L, Tomkiewicz A, Partyka A, Jonkisz A, Szewczuk-Bogusławska M, Zawadzki M, et al. CTLA4 and CD28 Gene Polymorphisms with Respect to Affective Symptom Domain in Schizophrenia. Neuropsychobiology. 2015;71(3):158-167. doi:10.1159/000379751
416. Ghoryani M, Faridhosseini F, Talaei A, Faridhosseini R, Tavakkol-Afshari J, Dadgar Moghaddam M, Azim P, Salimi Z, Marzouni HZ, Mohammadi M. Gene expression pattern of CCL2, CCL3, and CXCL8 in patients with bipolar disorder. J Res Med Sci. 2019;24:45. doi:10.4103/jrms.JRMS_763_18
417. Miyamoto K, Funahashi Y, Yoshino Y, Kawabe K, Yamazaki K, Ozaki Y, Mori Y, Ochi S, Iga JI, Ueno SI. CTLA4 mRNA expression in blood is lower in schizophrenia, but not in affective disorders. Asian J Psychiatr. 2020;52:102112. doi:10.1016/j.ajp.2020.102112
418. Fañanás L, Moral P, Panadero MA, Bertranpetit J. Complement genetic markers in schizophrenia: C3, BF and C6 polymorphisms. Hum Hered. 1992;42(3):162-167. doi:10.1159/000154060
419. Shirts BH, Kim JJ, Reich S, Dickerson FB, Yolken RH, Devlin B, Nimgaonkar VL. Polymorphisms in MICB are associated with human herpes virus seropositivity and schizophrenia risk. Schizophr Res. 2007;94(1-3):342-353. doi:10.1016/j.schres.2007.04.021
420. Del Casale A, Paolini M, Gentile G, Borro M, Zocchi C, Fiaschè F, Padovano A, Zoppi T, Modesti MN, De Luca O, et al. Dopamine DRD2 and DRD3 Polymorphisms Involvement in Nicotine Dependence in Patients with Treatment-Resistant Mental Disorders. J Pers Med. 2022;12(4):565. doi:10.3390/jpm12040565
421. Russo AJ. Decreased Serum Hepatocyte Growth Factor (HGF) in Individuals with Depression Correlates with Severity of Disease. Biomark Insights. 2010;5:63-67. doi:10.4137/bmi.s5183

422. Małujło-Balcerska E, Pietras T. Deiodinase Types 1 and 3 and Proinflammatory Cytokine Values May Discriminate Depressive Disorder Patients from Healthy Controls. J Clin Med. 2023;12(19):6163. doi:10.3390/jcm12196163
423. Li J, Gao JJ, Zhang FC, Xing QH, Dang FL, Gao XC, Duan SW, Zheng ZJ, Qian XQ, Qin W, et al. An association study between the transthyretin (TTR) gene and mental retardation. Eur Arch Psychiatry Clin Neurosci. 2006;256(4):230-235. doi:10.1007/s00406-005-0630-6
424. Sargazi S, Heidari Nia M, Sheervalilou R, Mirinejad S, Harati-Sadegh M, Moudi M, Saravani R, Shakiba M. Relationship between Single Nucleotide Polymorphisms of GRHL3 and Schizophrenia Susceptibility: A Preliminary Case-Control Study and Bioinformatics Analysis. Int J Mol Cell Med. 2020;9(2):154-164. doi:10.22088/IJMCM.BUMS.9.2.154
425. Gałecki P, Gałecka E, Maes M, Orzechowska A, Berent D, Talarowska M, Bobińska K, Lewiński A, Bieńkiewicz M, Szemraj J. Vascular endothelial growth factor gene (VEGFA) polymorphisms may serve as prognostic factors for recurrent depressive disorder development. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:117-124. doi:10.1016/j.pnpbp.2013.04.011
426. Akpinar A, Yaman GB, Demirdas A, Onal S. Possible role of adrenomedullin and nitric oxide in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2013;46:120-125. doi:10.1016/j.pnpbp.2013.07.003
427. Ohi K, Hashimoto R, Yasuda Y, Yoshida T, Takahashi H, Iike N, Iwase M, Kamino K, Ishii R, Kazui H, et al. The chitinase 3-like 1 gene and schizophrenia: evidence from a multi-center case-control study and meta-analysis. Schizophr Res. 2010;116(2-3):126-132. doi:10.1016/j.schres.2009.12.002
428. Tahira AC, Barbosa AR, Feltrin AS, Gastaldi VD, de Toledo VHC, de Carvalho Pereira JG, Lisboa BCG, de Souza Reis VN, Dos Santos ACF, Maschietto M, Brentani H. Putative contributions of the sex chromosome proteins SOX3 and SRY to neurodevelopmental disorders. Am J Med Genet B Neuropsychiatr Genet. 2019;180(6):390-414. doi:10.1002/ajmg.b.32704
429. Felsky D, Voineskos AN, Lerch JP, Nazeri A, Shaikh SA, Rajji TK, Mulsant BH, Kennedy JL. Myelin-associated glycoprotein gene and brain

morphometry in schizophrenia. Front Psychiatry. 2012;3:40. doi:10.3389/fpsyt.2012.00040

430. Peirce TR, Bray NJ, Williams NM, Norton N, Moskvina V, Preece A, Haroutunian V, Buxbaum JD, Owen MJ, O'Donovan MC. Convergent evidence for 2',3'-cyclic nucleotide 3'-phosphodiesterase as a possible susceptibility gene for schizophrenia. Arch Gen Psychiatry. 2006;63(1):18-24. doi:10.1001/archpsyc.63.1.18

431. Yang L, Chen J, Li Y, Wang Y, Liang S, Shi Y, Shi S, Xu Y. Association between SCAP and SREBF1 gene polymorphisms and metabolic syndrome in schizophrenia patients treated with atypical antipsychotics. World J Biol Psychiatry. 2016;17(6):467-474. doi:10.3109/15622975.2016.1165865

432. Furuta S, Aleksic B, Nawa Y, Kimura H, Kushima I, Ishizuka K, Kato H, Toyama M, Arioka Y, Mori D, et al. Investigation of OLIG2 as a candidate gene for schizophrenia and autism spectrum disorder. Nagoya J Med Sci. 2022;84(2):260-268. doi:10.18999/nagjms.84.2.260

433. Weigelt K, Carvalho LA, Drexhage RC, Wijkhuijs A, de Wit H, van Beveren NJ, Birkenhäger TK, Bergink V, Drexhage HA. TREM-1 and DAP12 expression in monocytes of patients with severe psychiatric disorders. EGR3, ATF3 and PU.1 as important transcription factors. Brain Behav Immun. 2011;25(6):1162-1169. doi:10.1016/j.bbi.2011.03.006

434. Zhao L, Hou B, Ji L, Ren D, Yuan F, Liu L, Bi Y, Yang F, Yu S, Yi Z, et al. NGFR Gene and Single Nucleotide Polymorphisms, rs2072446 and rs11466162, Playing Roles in Psychiatric Disorders. Brain Sci. 2022;12(10):1372. doi:10.3390/brainsci12101372

435. Chen P, Wang D, Xiu M, Chen D, Lackey B, Wu HE, Wang L, Zhang X. Association of Transferrin Gene Polymorphism with Cognitive Deficits and Psychiatric Symptoms in Patients with Chronic Schizophrenia. J Clin Med. 2022;11(21):6414. doi:10.3390/jcm11216414

436. Zai G, King N, Wigg K, Couto J, Wong GW, Honer WG, Barr CL, Kennedy JL. Genetic study of the myelin oligodendrocyte glycoprotein (MOG) gene in schizophrenia. Genes Brain Behav. 2005;4(1):2-9. doi:10.1111/j.1601-183X.2004.00089.x

437. Milanesi E, Minelli A, Cattane N, Cattaneo A, Mora C, Barbon A, Mallei A, Popoli M, Florio V, Conca A, et al. ErbB3 mRNA leukocyte

levels as a biomarker for major depressive disorder. BMC Psychiatry. 2012;12:145. doi:10.1186/1471-244X-12-145

438. Carraro RS, Nogueira GA, Sidarta-Oliveira D, Gaspar RS, Dragano NR, Morari J, Bobbo VCD, Araujo EP, Mendes NF, Zanesco AM, et al. Arcuate Nucleus Overexpression of NHLH2 Reduces Body Mass and Attenuates Obesity-Associated Anxiety/Depression-like Behavior. J Neurosci. 2021;41(48):10004-10022. doi:10.1523/JNEUROSCI.0222-21.2021

439. Shen XY, Shi SH, Li H, Wang CC, Zhang Y, Yu H, Li YB, Liu B. The role of Gadd45b in neurologic and neuropsychiatric disorders: An overview. Front Mol Neurosci. 2022;15:1021207. doi:10.3389/fnmol.2022.1021207

440. Watanabe Y, Nunokawa A, Kaneko N, Arinami T, Ujike H, Inada T, Iwata N, Kunugi H, Itokawa M, Otowa T, et al. A two-stage case-control association study of PADI2 with schizophrenia. J Hum Genet. 2009;54(7):430-432. doi:10.1038/jhg.2009.52

441. Gotoh L, Mitsuyasu H, Kobayashi Y, Oribe N, Takata A, Ninomiya H, Stanton VP Jr, Springett GM, Kawasaki H, Kanba S. Association analysis of adenosine A1 receptor gene (ADORA1) polymorphisms with schizophrenia in a Japanese population. Psychiatr Genet. 2009;19(6):328-335. doi:10.1097/YPG.0b013e3283328e26

442. Sayad A, Ghafouri-Fard S, Omrani MD, Taheri M. Associations Between Two Single-Nucleotide Polymorphisms in NINJ2 Gene and Risk of Psychiatric Disorders. J Mol Neurosci. 2020;70(2):236-245. doi:10.1007/s12031-019-01462-1

443. Hu TM, Ping LY, Hsu SH, Tsai HY, Cheng MC. Mutation analysis of the WNT7A gene in patients with schizophrenia. Psychiatry Res. 2018;265:246-248. doi:10.1016/j.psychres.2018.04.057

444. Harrison PJ. D-Amino Acid Oxidase Inhibition: A New Glutamate Twist for Clozapine Augmentation in Schizophrenia?. Biol Psychiatry. 2018;84(6):396-398. doi:10.1016/j.biopsych.2018.06.001

445. Guo X, Tang P, Yang C, Li R. Proline dehydrogenase gene (PRODH) polymorphisms and schizophrenia susceptibility: a meta-analysis. Metab Brain Dis. 2018;33(1):89-97. doi:10.1007/s11011-017-0128-8

446. Fukunaka Y, Shinkai T, Hwang R, Hori H, Utsunomiya K, Sakata S, Naoe Y, Shimizu K, Matsumoto C, Ohmori O, et al. The orexin 1 receptor (HCRTR1) gene as a susceptibility gene contributing to polydipsia-hyponatremia in schizophrenia. Neuromolecular Med. 2007;9(4):292-297. doi:10.1007/s12017-007-8001-2
447. Bose S, Cho J. Role of chemokine CCL2 and its receptor CCR2 in neurodegenerative diseases. Arch Pharm Res. 2013;36(9):1039-1050. doi:10.1007/s12272-013-0161-z
448. Ethell DW, Buhler LA. Fas ligand-mediated apoptosis in degenerative disorders of the brain. J Clin Immunol. 2003;23(6):439-446. doi:10.1023/b:joci.0000010420.96419.a8
449. Budge KM, Neal ML, Richardson JR, Safadi FF. Glycoprotein NMB: an Emerging Role in Neurodegenerative Disease. Mol Neurobiol. 2018;55(6):5167-5176. doi:10.1007/s12035-017-0707-z
450. Kloster E, Saft C, Akkad DA, Epplen JT, Arning L. Association of age at onset in Huntington disease with functional promoter variations in NPY and NPY2R. J Mol Med (Berl). 2014;92(2):177-184. doi:10.1007/s00109-013-1092-3
451. Öz A, Çelik Ö. Downregulation of TRPM7, TRPM8, and TRPV1 channels modulate apoptotic parameters and neurodegenerative markers: Focus on neuronal differentiation and Parkinson's disease model. Cell Biol Int. 2023;47(9):1502-1518. doi:10.1002/cbin.12048
452. Hou X, Aguilar MI, Small DH. Transthyretin and familial amyloidotic polyneuropathy. Recent progress in understanding the molecular mechanism of neurodegeneration. FEBS J. 2007;274(7):1637-1650. doi:10.1111/j.1742-4658.2007.05712.x
453. Ferrero H, Larrayoz IM, Gil-Bea FJ, Martínez A, Ramírez MJ. Adrenomedullin, a Novel Target for Neurodegenerative Diseases. Mol Neurobiol. 2018;55(12):8799-8814. doi:10.1007/s12035-018-1031-y
454. Qu Z, D'Mello SR. Proteomic analysis identifies NPTX1 and HIP1R as potential targets of histone deacetylase-3-mediated neurodegeneration. Exp Biol Med (Maywood). 2018;243(7):627-638. doi:10.1177/1535370218761149
455. Smith ES, Jonason A, Reilly C, Veeraraghavan J, Fisher T, Doherty M, Klimatcheva E, Mallow C, Cornelius C, Leonard JE, et al. SEMA4D

compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease. Neurobiol Dis. 2015;73:254-268. doi:10.1016/j.nbd.2014.10.008

456. Wang Q, Zhou Q, Zhang S, Shao W, Yin Y, Li Y, Hou J, Zhang X, Guo Y, Wang X, et al. Elevated Hapln2 Expression Contributes to Protein Aggregation and Neurodegeneration in an Animal Model of Parkinson's Disease. Front Aging Neurosci. 2016;8:197. doi:10.3389/fnagi.2016.00197

457. Yin P, Liu Q, Pan Y, Yang W, Yang S, Wei W, Chen X, Hong Y, Bai D, Li XJ, et al. Phosphorylation of myelin regulatory factor by PRKG2 mediates demyelination in Huntington's disease. EMBO Rep. 2020;21(6):e49783. doi:10.15252/embr.201949783

458. Sudwarts A, Ramesha S, Gao T, Ponnusamy M, Wang S, Hansen M, Kozlova A, Bitarafan S, Kumar P, Beaulieu-Abdelahad D, et al. BIN1 is a key regulator of proinflammatory and neurodegeneration-related activation in microglia. Mol Neurodegener. 2022;17(1):33. doi:10.1186/s13024-022-00535-x

459. Saglam A, Kim S, Ahn K, Oh I, Lee KH. BMP2 shows neurotrophic effects including neuroprotection against neurodegeneration. Neuroreport. 2014;25(8):549-555. doi:10.1097/WNR.0000000000000130

460. Sitz JH, Baumgärtel K, Hämmerle B, Papadopoulos C, Hekerman P, Tejedor FJ, Becker W, Lutz B. The Down syndrome candidate dual-specificity tyrosine phosphorylation-regulated kinase 1A phosphorylates the neurodegeneration-related septin 4. Neuroscience. 2008;157(3):596-605. doi:10.1016/j.neuroscience.2008.09.034

461. Kim SH, Shishido Y, Sogabe H, Rachadech W, Yorita K, Kato Y, Fukui K. Age- and gender-dependent D-amino acid oxidase activity in mouse brain and peripheral tissues: implication for aging and neurodegeneration. J Biochem. 2019;166(2):187-196. doi:10.1093/jb/mvz025

462. Stricker R, Reiser G. Functions of the neuron-specific protein ADAP1 (centaurin-α1) in neuronal differentiation and neurodegenerative diseases, with an overview of structural and biochemical properties of ADAP1. Biol Chem. 2014;395(11):1321-1340. doi:10.1515/hsz-2014-0107

463. Ghosh SG, Lee S, Fabunan R, Chai G, Zaki MS, Abdel-Salam G, Sultan T, Ben-Omran T, Alvi JR, McEvoy-Venneri J, et al. Biallelic variants

in HPDL, encoding 4-hydroxyphenylpyruvate dioxygenase-like protein, lead to an infantile neurodegenerative condition. Genet Med. 2021;23(3):524-533. doi:10.1038/s41436-020-01010-y

464. Chen CW, Wang HL, Huang CW, Huang CY, Lim WK, Tu IC, Koorapati A, Hsieh ST, Kan HW, Tzeng SR, et al. Two separate functions of NME3 critical for cell survival underlie a neurodegenerative disorder. Proc Natl Acad Sci U S A. 2019;116(2):566-574. doi:10.1073/pnas.1818629116

465. Jahanshad N, Rajagopalan P, Hua X, Hibar DP, Nir TM, Toga AW, Jack CR Jr, Saykin AJ, Green RC, Weiner MW, et al. Genome-wide scan of healthy human connectome discovers SPON1 gene variant influencing dementia severity. Proc Natl Acad Sci U S A. 2013;110(12):4768-4773. doi:10.1073/pnas.1216206110

466. Gu C, Geng X, Wu Y, Dai Y, Zeng J, Wang Z, Fang H, Sun Y, Chen X. Engineered Macrophage Membrane-Coated Nanoparticles with Enhanced CCR2 Expression Promote Spinal Cord Injury Repair by Suppressing Neuroinflammation and Neuronal death. Small. 2023;e2305659. doi:10.1002/smll.202305659

467. Yu WR, Fehlings MG. Fas/FasL-mediated apoptosis and inflammation are key features of acute human spinal cord injury: implications for translational, clinical application. Acta Neuropathol. 2011;122(6):747-761. doi:10.1007/s00401-011-0882-3

468. Wu Y, Lin YH, Shi LL, Yao ZF, Xie XM, Jiang ZS, Tang J, Hu JG, Lü HZ. Temporal kinetics of CD8+ CD28+ and CD8+ CD28- T lymphocytes in the injured rat spinal cord. J Neurosci Res. 2017;95(8):1666-1676. doi:10.1002/jnr.23993

469. Yadav S, Surolia A. Lysozyme elicits pain during nerve injury by neuronal Toll-like receptor 4 activation and has therapeutic potential in neuropathic pain. Sci Transl Med. 2019;11(504):eaav4176. doi:10.1126/scitranslmed.aav4176

470. Yagura K, Ohtaki H, Tsumuraya T, Sato A, Miyamoto K, Kawada N, Suzuki K, Nakamura M, Kanzaki K, Dohi K, et al. The enhancement of CCL2 and CCL5 by human bone marrow-derived mesenchymal stem/stromal cells might contribute to inflammatory suppression and axonal

extension after spinal cord injury. PLoS One. 2020;15(3):e0230080. doi:10.1371/journal.pone.0230080

471. Pelisch N, Rosas Almanza J, Stehlik KE, Aperi BV, Kroner A. CCL3 contributes to secondary damage after spinal cord injury. J Neuroinflammation. 2020;17(1):362. doi:10.1186/s12974-020-02037-3

472. Su D, Hooshmand MJ, Galvan MD, Nishi RA, Cummings BJ, Anderson AJ. Complement C6 deficiency exacerbates pathophysiology after spinal cord injury. Sci Rep. 2020;10(1):19500. doi:10.1038/s41598-020-76441-3

473. Cao J, Pan C, Zhang J, Chen Q, Li T, He D, Cheng X. Analysis and verification of the circRNA regulatory network RNO_CIRCpedia_4214/RNO-miR-667-5p/Msr1 axis as a potential ceRNA promoting macrophage M2-like polarization in spinal cord injury. BMC Genomics. 2023;24(1):181. doi:10.1186/s12864-023-09273-w

474. Nagoshi N, Tsuji O, Kitamura K, Suda K, Maeda T, Yato Y, Abe T, Hayata D, Matsumoto M, Okano H, et al. Phase I/II Study of Intrathecal Administration of Recombinant Human Hepatocyte Growth Factor in Patients with Acute Spinal Cord Injury: A Double-Blind, Randomized Clinical Trial of Safety and Efficacy. J Neurotrauma. 2020;37(15):1752-1758. doi:10.1089/neu.2019.6854

475. Liu Y, Figley S, Spratt SK, Lee G, Ando D, Surosky R, Fehlings MG. An engineered transcription factor which activates VEGF-A enhances recovery after spinal cord injury. Neurobiol Dis. 2010;37(2):384-393. doi:10.1016/j.nbd.2009.10.018

476. Cheng L, Wang C, Yao F, Li Z, Liu W, Jing J. MicroRNA-26b inhibits oligodendrocyte precursor cell differentiation by targeting adrenomedullin in spinal cord injury. J Cell Physiol. 2020;235(3):2429-2440. doi:10.1002/jcp.29147

477. Lindblom RP, Berg A, Ström M, Aeinehband S, Dominguez CA, Al Nimer F, Abdelmagid N, Heinig M, Zelano J, Harnesk K, et al. Complement receptor 2 is up regulated in the spinal cord following nerve root injury and modulates the spinal cord response. J Neuroinflammation. 2015;12:192. doi:10.1186/s12974-015-0413-6

478. Ji B, Case LC, Liu K, Shao Z, Lee X, Yang Z, Wang J, Tian T, Shulga-Morskaya S, Scott M, et al. Assessment of functional recovery and

axonal sprouting in oligodendrocyte-myelin glycoprotein (OMgp) null mice after spinal cord injury. Mol Cell Neurosci. 2008;39(2):258-267. doi:10.1016/j.mcn.2008.07.004

479. Hu R, Li L, Li D, Tan W, Wan L, Zhu C, Zhang Y, Zhang C, Yao W. Downregulation of Cdh1 signalling in spinal dorsal horn contributes to the maintenance of mechanical allodynia after nerve injury in rats. Mol Pain. 2016;12:1744806916647376. doi:10.1177/1744806916647376

480. Ueno M, Nakamura Y, Nakagawa H, Niehaus JK, Maezawa M, Gu Z, Kumanogoh A, Takebayashi H, Lu QR, Takada M, et al. Olig2-Induced Semaphorin Expression Drives Corticospinal Axon Retraction After Spinal Cord Injury. Cereb Cortex. 2020;30(11):5702-5716. doi:10.1093/cercor/bhaa142

481. Peng SX, Yao L, Cui C, Zhao HD, Liu CJ, Li YH, Wang LF, Huang SB, Shen YQ. Semaphorin4D promotes axon regrowth and swimming ability during recovery following zebrafish spinal cord injury. Neuroscience. 2017;351:36-46. doi:10.1016/j.neuroscience.2017.03.030

482. Delarue Q, Mayeur A, Chalfouh C, Honoré A, Duclos C, Di Giovanni M, Li X, Salaun M, Dampierre J, Vaudry D, et al. Inhibition of ADAMTS-4 Expression in Olfactory Ensheathing Cells Enhances Recovery after Transplantation within Spinal Cord Injury. J Neurotrauma. 2020;37(3):507-516. doi:10.1089/neu.2019.6481

483. Cui ZS, Zhao P, Jia CX, Liu HJ, Qi R, Cui JW, Cui JH, Peng Q, Lin B, Rao YJ. Local expression and role of BMP-2/4 in injured spinal cord. Genet Mol Res. 2015;14(3):9109-9117. doi:10.4238/2015.August.7.20

484. Lindholm T, Cullheim S, Deckner M, Carlstedt T, Risling M. Expression of neuregulin and ErbB3 and ErbB4 after a traumatic lesion in the ventral funiculus of the spinal cord and in the intact primary olfactory system. Exp Brain Res. 2002;142(1):81-90. doi:10.1007/s00221-001-0922-7

485. Suyama K, Watanabe M, Sakai D, Osada T, Imai M, Mochida J. Nkx2.2 expression in differentiation of oligodendrocyte precursor cells and inhibitory factors for differentiation of oligodendrocytes after traumatic spinal cord injury. J Neurotrauma. 2007;24(6):1013-1025. doi:10.1089/neu.2006.0151

486. Lee SJ, Kang JS, Kim HM, Lee ES, Lee JH, Chung CH, Lee EY. CCR2 knockout ameliorates obesity-induced kidney injury through

inhibiting oxidative stress and ER stress. PLoS One. 2019;14(9):e0222352. doi:10.1371/journal.pone.0222352

487. Shapira S, Kazanov D, Dankner R, Fishman S, Stern N, Arber N. High Expression Level of PPARγ in CD24 Knockout Mice and Gender-Specific Metabolic Changes: A Model of Insulin-Sensitive Obesity. J Pers Med. 2021;11(1):50. doi:10.3390/jpm11010050

488. Zunino SJ, Storms DH, Freytag TL, Mackey BE, Zhao L, Gouffon JS, Hwang DH. Dietary strawberries increase the proliferative response of CD3/CD28-activated CD8 T cells and the production of TNF-α in lipopolysaccharide-stimulated monocytes from obese human subjects. Br J Nutr. 2013;110(11):2011-2019. doi:10.1017/S0007114513000937

489. Moreno-Navarrete JM, Latorre J, Lluch A, Ortega FJ, Comas F, Arnoriaga-Rodríguez M, Ricart W, Fernández-Real JM. Lysozyme is a component of the innate immune system linked to obesity associated-chronic low-grade inflammation and altered glucose tolerance. Clin Nutr. 2021;40(3):1420-1429. doi:10.1016/j.clnu.2020.08.03

490. Lee M, Song SJ, Choi MS, Yu R, Park T. IL-7 receptor deletion ameliorates diet-induced obesity and insulin resistance in mice. Diabetologia. 2015;58(10):2361-2370. doi:10.1007/s00125-015-3684-7

491. Chan PC, Hung LM, Huang JP, Day YJ, Yu CL, Kuo FC, Lu CH, Tian YF, Hsieh PS. Augmented CCL5/CCR5 signaling in brown adipose tissue inhibits adaptive thermogenesis and worsens insulin resistance in obesity. Clin Sci (Lond). 2022;136(1):121-137. doi:10.1042/CS20210959

492. Jamka M, Kaczmarek N, Mądry E, Krzyżanowska-Jankowska P, Bajerska J, Kręgielska-Narożna M, Bogdański P, Walkowiak J.Metabolic Health in Obese Subjects-Is There a Link to Lactoferrin and Lactoferrin Receptor-Related Gene Polymorphisms?. Nutrients. 2020;12(9):2843. doi:10.3390/nu12092843

493. Prabata A, Ikeda K, Rahardini EP, Hirata KI, Emoto N. GPNMB plays a protective role against obesity-related metabolic disorders by reducing macrophage inflammatory capacity. J Biol Chem. 2021;297(5):101232. doi:10.1016/j.jbc.2021.101232

494. Santos LOD, Bispo AVS, Barros JV, Laranjeira RSM, Pinto RDN, Silva JA, Duarte AR, Araújo J, Sandrin-Garcia P, Crovella S, et al. CTLA-4

gene polymorphisms are associated with obesity in Turner Syndrome. Genet Mol Biol. 2018;41(4):727-734. doi:10.1590/1678-4685-GMB-2017-0312

495. Duggan BM, Singh AM, Chan DY, Schertzer JD. Postbiotics engage IRF4 in adipocytes to promote sex-dependent changes in blood glucose during obesity. Physiol Rep. 2022;10(16):e15439. doi:10.14814/phy2.15439

496. aranu I, Răcătăianu N, Drugan C, Cătană CS, Mirea AM, Miclea D, Bolboacă SD. Exploratory Longitudinal Analysis of the Circulating CHIT1 Activity in Pediatric Patients with Obesity. Children (Basel). 2023;10(1):124. doi:10.3390/children10010124

497. Aerts E, Geets E, Sorber L, Beckers S, Verrijken A, Massa G, Van Hoorenbeeck K, Verhulst SL, Van Gaal LF, Van Hul W. Evaluation of a Role for NPY and NPY2R in the Pathogenesis of Obesity by Mutation and Copy Number Variation Analysis in Obese Children and Adolescents. Ann Hum Genet. 2018;82(1):1-10. doi:10.1111/ahg.12211

498. Cinkajzlová A, Lacinová Z, Kloučková J, Kaválková P, Trachta P, Kosák M, Krátký J, Kasalický M, DoleŽalová K, Mráz M, et al. An alternatively activated macrophage marker CD163 in severely obese patients: the influence of very low-calorie diet and bariatric surgery. Physiol Res. 2017;66(4):641-652. doi:10.33549/physiolres.933522

499. Vistoropsky Y, Trofimov S, Malkin I, Kobyliansky E, Livshits G. Genetic and environmental determinants of hepatocyte growth factor levels and their association with obesity and blood pressure. Ann Hum Biol. 2008;35(1):93-103. doi:10.1080/03014460701822003

500. Sanders OD, Rajagopal JA, Rajagopal L. Menthol to Induce Non-shivering Thermogenesis via TRPM8/PKA Signaling for Treatment of Obesity. J Obes Metab Syndr. 2021;30(1):4-11. doi:10.7570/jomes20038

501. Pandey GK, Balasubramanyam J, Balakumar M, Deepa M, Anjana RM, Abhijit S, Kaviya A, Velmurugan K, Miranda P, Balasubramanyam M, et al. Altered circulating levels of retinol binding protein 4 and transthyretin in relation to insulin resistance, obesity, and glucose intolerance in asian indians. Endocr Pract. 2015;21(8):861-869. doi:10.4158/EP14558.OR

502. Kaartinen MT, Arora M, Heinonen S, Rissanen A, Kaprio J, Pietiläinen KH. Transglutaminases and Obesity in Humans: Association of F13A1 to Adipocyte Hypertrophy and Adipose Tissue Immune Response. Int J Mol Sci. 2020;21(21):8289. doi:10.3390/ijms21218289

503. Del Ry S, Cabiati M, Bianchi V, Caponi L, Di Cecco P, Marchi B, Randazzo E, Caselli C, Prescimone T, Clerico A, et al. Mid-regional-pro-adrenomedullin plasma levels are increased in obese adolescents. Eur J Nutr. 2016;55(3):1255-1260. doi:10.1007/s00394-015-0938-6
504. Solovieva S, Lohiniva J, Leino-Arjas P, Raininko R, Luoma K, Ala-Kokko L, Riihimäki H. COL9A3 gene polymorphism and obesity in intervertebral disc degeneration of the lumbar spine: evidence of gene-environment interaction. Spine (Phila Pa 1976). 2002;27(23):2691-2696. doi:10.1097/00007632-200212010-00008
505. Schinzari F, Vizioli G, Campia U, Tesauro M, Cardillo C. Variable Changes of Circulating ANGPTL3 and ANGPTL4 in Different Obese Phenotypes: Relationship with Vasodilator Dysfunction. Biomedicines. 2021;9(8):1037. doi:10.3390/biomedicines9081037
506. Teitsdottir UD, Arnardottir ES, Bjornsdottir E, Gislason T, Petersen PH. Obesity modulates the association between sleep apnea treatment and CHI3L1 levels but not CHIT1 activity in moderate to severe OSA: an observational study. Sleep Breath. 2018;22(4):1101-1109. doi:10.1007/s11325-018-1731-6
507. Zhong S, Chen L, Li X, Wang X, Ji G, Sun C, Liu Z. Bmp8a deletion leads to obesity through regulation of lipid metabolism and adipocyte differentiation. Commun Biol. 2023;6(1):824. doi:10.1038/s42003-023-05194-2
508. Huang XY, Chen JX, Ren Y, Fan LC, Xiang W, He XJ. Exosomal miR-122 promotes adipogenesis and aggravates obesity through the VDR/SREBF1 axis. Obesity (Silver Spring). 2022;30(3):666-679. doi:10.1002/oby.23365
509. Van de Pette M, Tunster SJ, John RM. Loss of Imprinting of Cdkn1c Protects against Age and Diet-Induced Obesity. Int J Mol Sci. 2018;19(9):2734. doi:10.3390/ijms19092734
510. Carobbio S, Hagen RM, Lelliott CJ, Slawik M, Medina-Gomez G, Tan CY, Sicard A, Atherton HJ, Barbarroja N, Bjursell M, et al. Adaptive changes of the Insig1/SREBP1/SCD1 set point help adipose tissue to cope with increased storage demands of obesity. Diabetes. 2013;62(11):3697-3708. doi:10.2337/db12-1748

511. Ku HC, Chan TY, Chung JF, Kao YH, Cheng CF. The ATF3 inducer protects against diet-induced obesity via suppressing adipocyte adipogenesis and promoting lipolysis and browning. Biomed Pharmacother. 2022;145:112440. doi:10.1016/j.biopha.2021.112440
512. Cusi KJ, Pratipanawatr T, Koval J, Printz R, Ardehali H, Granner DK, Defronzo RA, Mandarino LJ. Exercise increases hexokinase II mRNA, but not activity in obesity and type 2 diabetes. Metabolism. 2001;50(5):602-606. doi:10.1053/meta.2001.22568
513. Ming X, Li Z, Yang X, Cai W, Wang G, Yang M, Pan D, Yuan Y, Chen X. Serum Transferrin Level Is Associated with the Severity of Obstructive Sleep Apnea Independently of Obesity: A Propensity Score-Match Observational Study. Obes Facts. 2022;15(4):487-497. doi:10.1159/000524542
514. Stiebel-Kalish H, Rubarth K, Shouchane-Blum K, Tiosano A, Lotan I, Hellmann MA, Wilf-Yarkoni A, Bialer O, Flanagan EP, Pittock SJ, et al. Obesity is associated with myelin oligodendrocyte glycoprotein antibody-associated disease in acute optic neuritis [published correction appears in Sci Rep. 2023 Feb 20;13(1):2944]. Sci Rep. 2022;12(1):21312. doi:10.1038/s41598-022-21592-8
515. Tseng C, Han Y, Lv Z, Song Q, Wang K, Shen H, Chen Z. Glucose-stimulated PGC-1α couples with CBP and Runx2 to mediate intervertebral disc degeneration through transactivation of ADAMTS4/5 in diet-induced obesity mice. Bone. 2023;167:116617. doi:10.1016/j.bone.2022.116617
516. Yarsilikal Guleroglu F, Selvi E, Turan Bakirci I, Bafalı O, Argun Atalmis H, Yasti Dayan M, Balkan Ozmen A, Yurtcu N, Seker Atas B, Ozdemir Anayurt E, et al. Clinical Value of Serum BMP-4, BMP-2, GDF-15, MMP-9, GP39 Levels in Pregnant Women with Obesity and the Related Comorbidities Diabetes Mellitus and Gestational Hypertension. Z Geburtshilfe Neonatol. 2023;227(1):42-50. doi:10.1055/a-1937-1155
517. Zhang W, Shi B, Li S, Liu Z, Li S, Dong S, Cheng Y, Zhu J, Zhang G, Zhong M. leeve gastrectomy improves lipid dysmetabolism by downregulating the USP20-HSPA2 axis in diet-induced obese mice. Front Endocrinol (Lausanne). 2022;13:1041027. doi:10.3389/fendo.2022.1041027
518. Chedid MF, do Nascimento FV, de Oliveira FS, de Souza BM, Kruel CRP, Gurski RR, Canani LH, Crispim D, Gerchman F. Interaction of

HSD11B1 and H6PD polymorphisms in subjects with type 2 diabetes are protective factors against obesity: a cross-sectional study. Diabetol Metab Syndr. 2019;11:78. doi:10.1186/s13098-019-0474-2

519. Auerbach A, Cohen A, Ofek Shlomai N, Weinberg-Shukron A, Gulsuner S, King MC, Hemi R, Levy-Lahad E, Abulibdeh A, Zangen D. NKX2-2 Mutation Causes Congenital Diabetes and Infantile Obesity With Paradoxical Glucose-Induced Ghrelin Secretion. J Clin Endocrinol Metab. 2020;105(11):dgaa563. doi:10.1210/clinem/dgaa563

520. Cho JH, Kim K, Cho HC, Lee J, Kim EK. Silencing of hypothalamic FGF11 prevents diet-induced obesity. Mol Brain. 2022;15(1):75. doi:10.1186/s13041-022-00962-3

521. Sun D, Zhao T, Zhang Q, Wu M, Zhang Z. Fat mass and obesity-associated protein regulates lipogenesis via m6 A modification in fatty acid synthase mRNA. Cell Biol Int. 2021;45(2):334-344. doi:10.1002/cbin.11490

522. Karamfilova V, Gateva A, Assyov Y, Alexiev A, Savov A, Yaneva N, Ivanova I, Ivanova-Boyanova R, Ivanova R, Vlahova Z, et al. PNPLA3 I148M Polymorphism in Patients with Nonalcoholic Fatty Liver Disease, Obesity and Prediabetes. J Gastrointestin Liver Dis. 2019;28(4):433-438.doi:10.15403/jgld-506

523. Majali-Martinez A, Hoch D, Tam-Amersdorfer C, Pollheimer J, Glasner A, Ghaffari-Tabrizi-Wizsy N, Beristain AG, Hiden U, Dieber-Rotheneder M, Desoye G. Matrix metalloproteinase 15 plays a pivotal role in human first trimester cytotrophoblast invasion and is not altered by maternal obesity. FASEB J. 2020;34(8):10720-10730. doi:10.1096/fj.202000773R

524. Morgan RA, Beck KR, Nixon M, Homer NZM, Crawford AA, Melchers D, Houtman R, Meijer OC, Stomby A, Anderson AJ, et al. arbonyl reductase 1 catalyzes 20β-reduction of glucocorticoids, modulating receptor activation and metabolic complications of obesity. Sci Rep. 2017;7(1):10633.doi:10.1038/s41598-017-104

525. Sandin ES, Folberth J, Müller-Fielitz H, Pietrzik CU, Herold E, Willnow TE, Pfluger PT, Nogueiras R, Prevot V, Krey T, et al. LRP2 Involved in Leptin Transport over the Blood-Brain Barrier and Development of Obesity?. Int J Mol Sci. 2021;22(9):4998. doi:10.3390/ijms22094998

526. Ueda Y, Iwakura H, Bando M, Doi A, Ariyasu H, Inaba H, Morita S, Akamizu T. Differential role of GPR142 in tryptophan-mediated enhancement of insulin secretion in obese and lean mice. PLoS One. 2018;13(6):e0198762. doi:10.1371/journal.pone.0198762
527. Hsiao PJ, Chen ZC, Hung WW, Yang YH, Lee MY, Huang JF, Kuo KK. Risk interaction of obesity, insulin resistance and hormone-sensitive lipase promoter polymorphisms (LIPE-60 C > G) in the development of fatty liver. BMC Med Genet. 2013;14:54. doi:10.1186/1471-2350-14-54
528. Yamakawa-Kobayashi K, Otagi E, Ohhara Y, Goda T, Kasezawa N, Kayashima Y. The Combined Effects of Genetic Variation in the CNDP1 and CNDP2 Genes and Dietary Carbohydrate and Carotene Intake on Obesity Risk. J Nutrigenet Nutrigenomics. 2017;10(5-6):146-154. doi:10.1159/000485798
529. Alharbi KK, Alshammary AF, Aljabri OS, Ali Khan I. Relationship Between Serum Amyloid A1 (SAA1) Gene Polymorphisms Studies with Obesity in the Saudi Population. Diabetes Metab Syndr Obes. 2021;14:895-900. doi:10.2147/DMSO.S294948
530. Sampath H, Ntambi JM. The role of stearoyl-CoA desaturase in obesity, insulin resistance, and inflammation. Ann N Y Acad Sci. 2011;1243:47-53. doi:10.1111/j.1749-6632.2011.06303.x
531. Aruga M, Tokita Y, Nakajima K, Kamachi K, Tanaka A. The effect of combined diet and exercise intervention on body weight and the serum GPIHBP1 concentration in overweight/obese middle-aged women. Clin Chim Acta. 2017;475:109-115. doi:10.1016/j.cca.2017.10.017
532. Chen WW, Yang Q, Li XY, Shi XL, Pu N, Lu GT, Tong ZH, Chen JM, Li WQ. Identification of a novel and heterozygous LMF1 nonsense mutation in an acute pancreatitis patient with severe hypertriglyceridemia, severe obesity and heavy smoking. Lipids Health Dis. 2019;18(1):68. doi:10.1186/s12944-019-1012-9
533. Ghanny S, Zidell A, Pedro H, Joustra SD, Losekoot M, Wit JM, Aisenberg J. The IGSF1 Deficiency Syndrome May Present with Normal Free T4 Levels, Severe Obesity, or Premature Testicular Growth. J Clin Res Pediatr Endocrinol. 2021;13(4):461-467. doi:10.4274/jcrpe.galenos.2020.2020.0125

534. Umano GR, Cirillo G, Rondinelli G, Sanchez G, Marzuillo P, Guarino S, Di Sessa A, Papparella A, Miraglia Del Giudice E. et al. LSS rs2254524 Increases the Risk of Hypertension in Children and Adolescents with Obesity. Genes (Basel). 2023;14(8):1618. doi:10.3390/genes14081618
535. Haenisch M, Nguyen T, Fihn CA, Goldstein AS, Amory JK, Treuting P, Brabb T, Paik J. Investigation of an ALDH1A1-specific inhibitor for suppression of weight gain in a diet-induced mouse model of obesity. Int J Obes (Lond). 2021;45(7):1542-1552. doi:10.1038/s41366-021-00818-1
536. Wu Z, Liu J, Chen G, Du J, Cai H, Chen X, Ye G, Luo Y, Luo Y, Zhang L, et al. CD146 is a Novel ANGPTL2 Receptor that Promotes Obesity by Manipulating Lipid Metabolism and Energy Expenditure. Adv Sci (Weinh). 2021;8(6):2004032. doi:10.1002/advs.202004032
537. Çelikkol A, Binay Ç, Ayçiçek Ö, Güzel S. Serum Neudesin Levels in Obese Adolescents. J Clin Res Pediatr Endocrinol. 2022;14(1):69-75. doi:10.4274/jcrpe.galenos.2021.2021.0208
538. Liu T, David SP, Tyndale RF, Wang H, Yu XQ, Chen W, Zhou Q, Chen WQ. Relationship between amounts of daily cigarette consumption and abdominal obesity moderated by CYP2A6 genotypes in Chinese male current smokers. Ann Behav Med. 2012;43(2):253-261. doi:10.1007/s12160-011-9318-5
539. Kashyap S, Warner GM, Hartono SP, Boyilla R, Knudsen BE, Zubair AS, Lien K, Nath KA, Textor SC, Lerman LO, et al. Blockade of CCR2 reduces macrophage influx and development of chronic renal damage in murine renovascular hypertension. Am J Physiol Renal Physiol. 2016;310(5):F372-F384. doi:10.1152/ajprenal.00131.2015
540. Zhao Z, Zhang C, Lin J, Zheng L, Li H, Qi X, Huo H, Lou X, Hammock BD, Hwang SH, et al. COX-2/sEH Dual Inhibitor PTUPB Alleviates CCl 4 -Induced Liver Fibrosis and Portal Hypertension. Front Med (Lausanne). 2021;8:761517. doi:10.3389/fmed.2021.761517
541. Shinya Y, Hiraide T, Momoi M, Goto S, Suzuki H, Katsumata Y, Kurebayashi Y, Endo J, Sano M, Fukuda K, et al. TNFRSF13B c.226G>A (p.Gly76Ser) as a Novel Causative Mutation for Pulmonary Arterial Hypertension. J Am Heart Assoc. 2021;10(5):e019245. doi:10.1161/JAHA.120.019245

542. Akagi S, Nakamura K, Matsubara H, Kusano KF, Kataoka N, Oto T, Miyaji K, Miura A, Ogawa A, Yoshida M, et al. Prostaglandin I2 induces apoptosis via upregulation of Fas ligand in pulmonary artery smooth muscle cells from patients with idiopathic pulmonary arterial hypertension. Int J Cardiol. 2013;165(3):499-505. doi:10.1016/j.ijcard.2011.09.004

543. Vinh A, Chen W, Blinder Y, Weiss D, Taylor WR, Goronzy JJ, Weyand CM, Harrison DG, Guzik TJ. Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. Circulation. 2010;122(24):2529-2537. doi:10.1161/CIRCULATIONAHA.109.930446

544. Alvarez-Madrazo S, Mackenzie SM, Davies E, Fraser R, Lee WK, Brown M, Caulfield MJ, Dominiczak AF, Farrall M, Lathrop M, et al. Common polymorphisms in the CYP11B1 and CYP11B2 genes: evidence for a digenic influence on hypertension. Hypertension. 2013;61(1):232-239. doi:10.1161/HYPERTENSIONAHA.112.2007410

545. Nie X, Tan J, Dai Y, Liu Y, Zou J, Sun J, Ye S, Shen C, Fan L, Chen J, et al. CCL5 deficiency rescues pulmonary vascular dysfunction, and reverses pulmonary hypertension via caveolin-1-dependent BMPR2 activation. J Mol Cell Cardiol. 2018;116:41-56. doi:10.1016/j.yjmcc.2018.01.016

546. Alexander MR, Norlander AE, Elijovich F, Atreya RV, Gaye A, Gnecco JS, Laffer CL, Galindo CL, Madhur MS. Human monocyte transcriptional profiling identifies IL-18 receptor accessory protein and lactoferrin as novel immune targets in hypertension. Br J Pharmacol. 2019;176(12):2015-2027. doi:10.1111/bph.14364

547. Tomaszewski M, Małkowska P, Sierawska O, Hrynkiewicz R, Mroczek E, Darocha S, Hymos A, Błaszczak P, Grywalska E, Niedźwiedzka-Rystwej P. CTLA-4 Expression Is a Promising Biomarker of Idiopathic Pulmonary Arterial Hypertension and Allows Differentiation of the Type of Pulmonary Hypertension. Int J Mol Sci. 2022;23(24):15910. doi:10.3390/ijms232415910

548. Yang H, Zhong L, Bai S, Dong Y, Wang Y, Li Q, Yang Q, Jiang D, Bi H, Xiao C, et al. Association of Dopamine D1 and D3 Receptor Gene Polymorphisms with Essential Hypertension in 3 Ethnic Groups in China. Med Sci Monit Basic Res. 2017;23:234-239. doi:10.12659/MSMBR.900432

549. Huang F, Ni M, Zhang JM, Li DJ, Shen FM. TRPM8 downregulation by angiotensin II in vascular smooth muscle cells is involved in hypertension. Mol Med Rep. 2017;15(4):1900-1908. doi:10.3892/mmr.2017.6158
550. Yang Y, Tang S, Zhai C, Zeng X, Liu Q, Xu C, Chen H. Interleukin-9 Deletion Relieves Vascular Dysfunction and Decreases Blood Pressure via the STAT3 Pathway in Angiotensin II-Treated Mice. Mediators Inflamm. 2020;2020:5741047. doi:10.1155/2020/5741047
551. Nakao K, Kuwahara K, Nishikimi T, Nakagawa Y, Kinoshita H, Minami T, Kuwabara Y, Yamada C, Yamada Y, Tokudome T, et al. Endothelium-Derived C-Type Natriuretic Peptide Contributes to Blood Pressure Regulation by Maintaining Endothelial Integrity. Hypertension. 2017;69(2):286-296. doi:10.1161/HYPERTENSIONAHA.116.08219
552. Abu-Farha M, Cherian P, Qaddoumi MG, AlKhairi I, Sriraman D, Alanbaei M, Abubaker J. Increased plasma and adipose tissue levels of ANGPTL8/Betatrophin and ANGPTL4 in people with hypertension. Lipids Health Dis. 2018;17(1):35. doi:10.1186/s12944-018-0681-0
553. Sun X, Nakajima E, Norbrun C, Sorkhdini P, Yang AX, Yang D, Ventetuolo CE, Braza J, Vang A, Aliotta J, et al. Chitinase 3 like 1 contributes to the development of pulmonary vascular remodeling in pulmonary hypertension. JCI Insight. 2022;7(18):e159578. doi:10.1172/jci.insight.159578
554. Pravenec M, Kazdova L, Landa V, Zidek V, Mlejnek P, Simakova M, Jansa P, Forejt J, Kren V, Krenova D, et al. Identification of mutated Srebf1 as a QTL influencing risk for hepatic steatosis in the spontaneously hypertensive rat. Hypertension. 2008;51(1):148-153. doi:10.1161/HYPERTENSIONAHA.107.100743
555. Chomette L, Hupkens E, Romitti M, Dewachter L, Vachiéry JL, Bailly S, Costagliola S, Smits G, Tillet E, Bondue A. Pediatric pulmonary arterial hypertension due to a novel homozygous GDF2 missense variant affecting BMP9 processing and activity. Am J Med Genet A. 2023;191(8):2064-2073. doi:10.1002/ajmg.a.63236
556. Zhang YP, Ye LL, Yuan H, Duan DD. CFTR plays an important role in the regulation of vascular resistance and high-fructose/salt-diet induced

hypertension in mice. J Cyst Fibros. 2021;20(3):516-524. doi:10.1016/j.jcf.2020.11.014
557. Davis J. Putting the Brakes on Hypertensive Remodeling: An ATF3 Mechanism of Myofibroblast Restraint. Circulation. 2017;135(21):2058-2061. doi:10.1161/CIRCULATIONAHA.117.028020
558. Luo L, Xiao L, Lian G, Wang H, Xie L. miR-125a-5p inhibits glycolysis by targeting hexokinase-II to improve pulmonary arterial hypertension. Aging (Albany NY). 2020;12(10):9014-9030. doi:10.18632/aging.103163
559. Goten C, Usui S, Takashima SI, Inoue O, Okada H, Shimojima M, Sakata K, Kawashiri M, Kaneko S, Takamura M. Circulating nerve growth factor receptor positive cells are associated with severity and prognosis of pulmonary arterial hypertension. Pulm Circ. 2021;11(1):2045894021990525. doi:10.1177/2045894021990525
560. Yao MZ, Ge XY, Liu T, Huang N, Liu H, Chen Y, Zhang Z, Hu CP. MEIS1 regulated proliferation and migration of pulmonary artery smooth muscle cells in hypoxia-induced pulmonary hypertension. Life Sci. 2020;255:117822. doi:10.1016/j.lfs.2020.117822
561. Chaudhuri JR, Bagul JJ, Swathi A, Singhal BS, Reddy NC, Vallam KK. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease Presenting as Intracranial Hypertension: A Case Report. Neurol Neuroimmunol Neuroinflamm. 2022;9(6):e200020. doi:10.1212/NXI.0000000000200020
562. Xing Y, Zhao S, Wei Q, Gong S, Zhao X, Zhou F, Ai-Lamki R, Ortmann D, Du M, Pedersen R, et al. A novel piperidine identified by stem cell-based screening attenuates pulmonary arterial hypertension by regulating BMP2 and PTGS2 levels. Eur Respir J. 2018;51(4):1702229. doi:10.1183/13993003.02229-2017
563. Hegele RA, Anderson CM, Wang J, Jones DC, Cao H. Association between nuclear lamin A/C R482Q mutation and partial lipodystrophy with hyperinsulinemia, dyslipidemia, hypertension, and diabetes. Genome Res. 2000;10(5):652-658. doi:10.1101/gr.10.5.652
564. Rahman TJ, Mayosi BM, Hall D, Avery PJ, Stewart PM, Connell JM, Watkins H, Keavney B. Common variation at the 11-β hydroxysteroid dehydrogenase type 1 gene is associated with left ventricular mass. Circ

Cardiovasc Genet. 2011;4(2):156-162. doi:10.1161/CIRCGENETICS.110.958496

565. Oguri M, Kato K, Yokoi K, Watanabe S, Metoki N, Yoshida H, Satoh K, Aoyagi Y, Nishigaki Y, Yoshida H, et al. Association of polymorphisms of THBS2 and HSPA8 with hypertension in Japanese individuals with chronic kidney disease. Mol Med Rep. 2009;2(2):205-211. doi:10.3892/mmr_00000085

566. Mayas MD, Ortega FJ, Gómez-Huelgas R, Roca N, Fernández-Real JM, Tinahones FJ. Decrease in FASN expression in adipose tissue of hypertensive individuals. Am J Hypertens. 2009;22(12):1258-1262. doi:10.1038/ajh.2009.178

567. Scheiner B, Mandorfer M, Schwabl P, Payer BA, Bucsics T, Bota S, Aichelburg MC, Grabmeier-Pfistershammer K, Stättermayer A, Ferenci P, et al. he Impact of PNPLA3 rs738409 SNP on Liver Fibrosis Progression, Portal Hypertension and Hepatic Steatosis in HIV/HCV Coinfection. PLoS One. 2015;10(11):e0143429.doi:10.1371/journal.pone.0143429

568. Le Ribeuz H, Courboulin A, Ghigna MR, Lambert M, Hautefort A, Humbert M, Montani D, Cohen-Kaminsky S, Perros F, Antigny F. In vivo miR-138-5p inhibition alleviates monocrotaline-induced pulmonary hypertension and normalizes pulmonary KCNK3 and SLC45A3 expression. Respir Res. 2020;21(1):186. doi:10.1186/s12931-020-01444-7

569. Chakraborty A, Nathan A, Orcholski M, Agarwal S, Shamskhou EA, Auer N, Mitra A, Guardado ES, Swaminathan G, Condon DF, et al. Wnt7a deficit is associated with dysfunctional angiogenesis in pulmonary arterial hypertension. Eur Respir J. 2023;61(6):2201625. doi:10.1183/13993003.01625-2022

570. Fan P, Pan XC, Zhang D, Yang KQ, Zhang Y, Tian T, Luo F, Ma WJ, Liu YX, Wang LP, et al. Pediatric Liddle Syndrome Caused by a Novel SCNN1G Variant in a Chinese Family and Characterized by Early-Onset Hypertension. Am J Hypertens. 2020;33(7):670-675. doi:10.1093/ajh/hpaa037

571. Jiang Y, Ferguson WB, Peng JB. WNK4 enhances TRPV5-mediated calcium transport: potential role in hypercalciuria of familial hyperkalemic hypertension caused by gene mutation of WNK4. Am J Physiol Renal Physiol. 2007;292(2):F545-F554. doi:10.1152/ajprenal.00187.2006

572. Zhong X, Ma Z, Su Y, Li Z, Liao Y, Pan X, Zang L, Zhou S. Flavin adenine dinucleotide ameliorates hypertensive vascular remodeling via activating short chain acyl-CoA dehydrogenase. Life Sci. 2020;258:118156. doi:10.1016/j.lfs.2020.118156
573. Perros F, Cohen-Kaminsky S, Gambaryan N, Girerd B, Raymond N, Klingelschmitt I, Huertas A, Mercier O, Fadel E, Simonneau G, et al. Cytotoxic cells and granulysin in pulmonary arterial hypertension and pulmonary veno-occlusive disease. Am J Respir Crit Care Med. 2013;187(2):189-196. doi:10.1164/rccm.201208-1364OC
574. Vendrov AE, Stevenson MD, Lozhkin A, Hayami T, Holland NA, Yang X, Moss N, Pan H, Wickline SA, Stockand JD, et al. Renal NOXA1/NOX1 Signaling Regulates Epithelial Sodium Channel and Sodium Retention in Angiotensin II-induced Hypertension. Antioxid Redox Signal. 2022;36(7-9):550-566. doi:10.1089/ars.2021.0047
575. Arab Sadeghabadi Z, Nourbakhsh M, Alaee M, Nourbakhsh M, Ghorbanhosseini SS, Sharifi R, Razzaghy-Azar M. Angiopoietin-Like Proteins 2 and 3 in Children and Adolescents with Obesity and Their Relationship with Hypertension and Metabolic Syndrome. Int J Hypertens. 2021;2021:6748515. doi:10.1155/2021/6748515
576. Heximer S, Husain M. A candidate hypertension gene: will SPON1 hold salt and water?. Circ Res. 2007;100(7):940-942. doi:10.1161/01.RES.0000265134.57140.da
577. Liu T, Tyndale RF, David SP, Wang H, Yu XQ, Chen W, Wen XZ, Chen WQ. Association between daily cigarette consumption and hypertension moderated by CYP2A6 genotypes in Chinese male current smokers. J Hum Hypertens. 2013;27(1):24-30. doi:10.1038/jhh.2011.111
578. Prohaska CC, Zhang X, Schwantes-An TL, Stearman RS, Hooker S, Kittles RA, Aldred MA, Lutz KA, Pauciulo MW, Nichols WC, et al. RASA3 is a candidate gene in sickle cell disease-associated pulmonary hypertension and pulmonary arterial hypertension. Pulm Circ. 2023;13(2):e12227. doi:10.1002/pul2.12227
579. Saito M, Nakamura N, Nagai M, Shirakawa K, Sato H, Kawahigashi N, Furukawa Y, Usuku K, Nakagawa M, Izumo S, et al. Increased levels of soluble Fas ligand in CSF of rapidly progressive HTLV-1-associated

myelopathy/tropical spastic paraparesis patients. J Neuroimmunol. 1999;98(2):221-226. doi:10.1016/s0165-5728(99)00095-8

580. Orthmann-Murphy JL, Salsano E, Abrams CK, Bizzi A, Uziel G, Freidin MM, Lamantea E, Zeviani M, Scherer SS, Pareyson D. Hereditary spastic paraplegia is a novel phenotype for GJA12/GJC2 mutations. Brain. 2009;132(Pt 2):426-438. doi:10.1093/brain/awn328

581. Zaman Q, Khan MA, Sahar K, Rehman G, Khan H, Rehman M, Najumuddin, Ahmad I, Tariq M, Muthaffar OY, et al. Novel Variants in MPV17, PRX, GJB1, and SACS Cause Charcot-Marie-Tooth and Spastic Ataxia of Charlevoix-Saguenay Type Diseases. Genes (Basel). 2023;14(2):328. doi:10.3390/genes14020328

582. Stott SR, Hayat S, Carnwath T, Garas S, Sleeman JP, Barker RA. CD24 expression does not affect dopamine neuronal survival in a mouse model of Parkinson's disease. PLoS One. 2017;12(2):e0171748. doi:10.1371/journal.pone.0171748

583. Badr M, McFleder RL, Wu J, Knorr S, Koprich JB, Hünig T, Brotchie JM, Volkmann J, Lutz MB, Ip CW. Expansion of regulatory T cells by CD28 superagonistic antibodies attenuates neurodegeneration in A53T-α-synuclein Parkinson's disease mice. J Neuroinflammation. 2022;19(1):319. doi:10.1186/s12974-022-02685-7

584. Su WM, Gu XJ, Hou YB, Zhang LY, Cao B, Ou RW, Wu Y, Chen XP, Song W, Zhao B, et al. Association Analysis of WNT3, HLA-DRB5 and IL1R2 Polymorphisms in Chinese Patients With Parkinson's Disease and Multiple System Atrophy. Front Genet. 2021;12:765833. doi:10.3389/fgene.2021.765833

585. Tang S, Wang A, Yan X, Chu L, Yang X, Song Y, Sun K, Yu X, Liu R, Wu Z, et al. Brain-targeted intranasal delivery of dopamine with borneol and lactoferrin co-modified nanoparticles for treating Parkinson's disease. Drug Deliv. 2019;26(1):700-707. doi:10.1080/10717544.2019.1636420

586. Diaz-Ortiz ME, Seo Y, Posavi M, Carceles Cordon M, Clark E, Jain N, Charan R, Gallagher MD, Unger TL, Amari N, et al. GPNMB confers risk for Parkinson's disease through interaction with α-synuclein. Science. 2022;377(6608):eabk0637. doi:10.1126/science.abk0637

587. Güler S, Gül T, Güler Ş, Haerle MC, Başak AN. Early-Onset Parkinson's Disease: A Novel Deletion Comprising the DJ-1 and TNFRSF9 Genes. Mov Disord. 2021;36(12):2973-2976. doi:10.1002/mds.28812
588. Bowles KR, Pugh DA, Liu Y, Patel T, Renton AE, Bandres-Ciga S, Gan-Or Z, Heutink P, Siitonen A, Bertelsen S, et al. 17q21.31 sub-haplotypes underlying H1-associated risk for Parkinson's disease are associated with LRRC37A/2 expression in astrocytes. Mol Neurodegener. 2022;17(1):48. doi:10.1186/s13024-022-00551-x
589. Dong AQ, Yang YP, Jiang SM, Yao XY, Qi D, Mao CJ, Cheng XY, Wang F, Hu LF, Liu CF. Pramipexole inhibits astrocytic NLRP3 inflammasome activation via Drd3-dependent autophagy in a mouse model of Parkinson's disease. Acta Pharmacol Sin. 2023;44(1):32-43. doi:10.1038/s41401-022-00951-1
590. Salehi Z, Rajaei F. Expression of hepatocyte growth factor in the serum and cerebrospinal fluid of patients with Parkinson's disease. J Clin Neurosci. 2010;17(12):1553-1556. doi:10.1016/j.jocn.2010.04.034
591. Argüelles S, Venero JL, García-Rodriguez S, Tomas-Camardiel M, Ayala A, Cano J, Machado A. Use of haptoglobin and transthyretin as potential biomarkers for the preclinical diagnosis of Parkinson's disease. Neurochem Int. 2010;57(3):227-234. doi:10.1016/j.neuint.2010.05.014
592. Lan G, Wang P, Chan RB, Liu Z, Yu Z, Liu X, Yang Y, Zhang J. Astrocytic VEGFA: An essential mediator in blood-brain-barrier disruption in Parkinson's disease. Glia. 2022;70(2):337-353. doi:10.1002/glia.24109
593. Haji S, Sako W, Murakami N, Osaki Y, Izumi Y. Serum NfL and CHI3L1 for ALS and parkinsonian disorders in the process of diagnosis. J Neural Transm (Vienna). 2022;129(3):301-309. doi:10.1007/s00702-022-02470-z
594. Papuć E, Wilczyńska B, Rejdak K. Humoral response against myelin associated glycoprotein reflects oligodendroglial degeneration in Parkinson's disease. Ann Agric Environ Med. 2016;23(2):390-393. doi:10.5604/12321966.1203998
595. Li NN, Tan EK, Chang XL, Mao XY, Zhang JH, Zhao DM, Liao Q, Yu WJ, Peng R. Genetic association study between STK39 and CCDC62/HIP1R and Parkinson's disease. PLoS One. 2013;8(11):e79211. doi:10.1371/journal.pone.0079211

596. Li J, Chen L, Qin Q, Wang D, Zhao J, Gao H, Yuan X, Zhang J, Zou Y, Mao Z, et al. Upregulated hexokinase 2 expression induces the apoptosis of dopaminergic neurons by promoting lactate production in Parkinson's disease. Neurobiol Dis. 2022;163:105605. doi:10.1016/j.nbd.2021.105605
597. Morató X, Garcia-Esparcia P, Argerich J, Llorens F, Zerr I, Paslawski W, Borràs E, Sabidó E, Petäjä-Repo UE, Fernández-Dueñas V, et al. Ecto-GPR37: a potential biomarker for Parkinson's disease. Transl Neurodegener. 2021;10(1):8. doi:10.1186/s40035-021-00232-7
598. Strada O, Hirsch EC, Javoy-Agid F, Duyckaerts C, Hauw JJ, Agid Y. Low affinity nerve growth factor receptor, adrenal transplant and Parkinson's disease. J Neurol Sci. 1993;120(1):33-37. doi:10.1016/0022-510x(93)90021-p
599. Ayton S, Lei P, Mclean C, Bush AI, Finkelstein DI. Transferrin protects against Parkinsonian neurotoxicity and is deficient in Parkinson's substantia nigra. Signal Transduct Target Ther. 2016;1:16015. doi:10.1038/sigtrans.2016.15
600. Kurkowska-Jastrzebska I, Bałkowiec-Iskra E, Ciesielska A, Joniec I, Cudna A, Zaremba MM, Członkowski A, Członkowska A. Decreased inflammation and augmented expression of trophic factors correlate with MOG-induced neuroprotection of the injured nigrostriatal system in the murine MPTP model of Parkinson's disease. Int Immunopharmacol. 2009;9(6):781-791. doi:10.1016/j.intimp.2009.03.003
601. Li CY, Ou RW, Chen YP, Gu XJ, Wei QQ, Hou YB, Cao B, Zhang LY, Lin JY, Liu KC, et al. Enrichment of rare variants of BIN1 but not APOE genes in Chinese patients with Parkinson's disease. J Intern Med. 2022;291(5):698-701. doi:10.1111/joim.13444
602. Goulding SR, Sullivan AM, O'Keeffe GW, Collins LM. The potential of bone morphogenetic protein 2 as a neurotrophic factor for Parkinson's disease. Neural Regen Res. 2020;15(8):1432-1436. doi:10.4103/1673-5374.274327
603. Yang TC, Wu PC, Chung IF, Jiang JH, Fann MJ, Kao LS. Cell death caused by the synergistic effects of zinc and dopamine is mediated by a stress sensor gene Gadd45b - implication in the pathogenesis of Parkinson's disease. J Neurochem. 2016;139(1):120-133. doi:10.1111/jnc.13728

604. Ahn EH, Kang SS, Qi Q, Liu X, Ye K. Netrin1 deficiency activates MST1 via UNC5B receptor, promoting dopaminergic apoptosis in Parkinson's disease. Proc Natl Acad Sci U S A. 2020;117(39):24503-24513. doi:10.1073/pnas.2004087117
605. Sarasola LI, Del Torrent CL, Pérez-Arévalo A, Argerich J, Casajuana-Martín N, Chevigné A, Fernández-Dueñas V, Ferré S, Pardo L, Ciruela F. The ADORA1 mutation linked to early-onset Parkinson's disease alters adenosine A1-A2A receptor heteromer formation and function. Biomed Pharmacother. 2022;156:113896. doi:10.1016/j.biopha.2022.113896
606. Shehadeh L, Mitsi G, Adi N, Bishopric N, Papapetropoulos S. Expression of Lewy body protein septin 4 in postmortem brain of Parkinson's disease and control subjects. Mov Disord. 2009;24(2):204-210. doi:10.1002/mds.22306
607. Alaylıoğlu M, Dursun E, Genç G, Şengül B, Bilgiç B, Gündüz A, Apaydın H, Kızıltan G, Gürvit H, Hanağası H, et al. Genetic variants of vitamin D metabolism-related DHCR7/NADSYN1 locus and CYP2R1 gene are associated with clinical features of Parkinson's disease. Int J Neurosci. 2022;132(5):439-449. doi:10.1080/00207454.2020.1820502
608. Tardiff DF, Lucas M, Wrona I, Chang B, Chung CY, Le Bourdonnec B, Rhodes KJ, Scannevin RH. Non-clinical Pharmacology of YTX-7739: a Clinical Stage Stearoyl-CoA Desaturase Inhibitor Being Developed for Parkinson's Disease. Mol Neurobiol. 2022;59(4):2171-2189. doi:10.1007/s12035-021-02695-1
609. Pan Y, Xue J, Chen J, Zhang X, Tu T, Xiao Q, Huang W, Liu Q, Zhu L, Li J, et al. Assessment of GGC Repeat Expansion in GIPC1 in Patients with Parkinson's Disease. Mov Disord. 2022;37(7):1557-1559. doi:10.1002/mds.29041
610. Fan HH, Zheng J, Huang XY, Wu KY, Cui L, Dong HJ, Wang Z, Zhang X, et al . An antisense Alu transposon insertion/deletion polymorphism of ALDH1A1 may functionally associate with Parkinson's disease. BMC Geriatr. 2022;22(1):427. doi:10.1186/s12877-022-03132-1
611. Shi CH, Cheng Y, Tang MB, Liu YT, Yang ZH, Li F, Fan Y, Yang J, Xu YM. Analysis of Single Nucleotide Polymorphisms of STK32B, PPARGC1A and CTNNA3 Gene With Sporadic Parkinson's Disease

Susceptibility in Chinese Han Population. Front Neurol. 2018;9:387. doi:10.3389/fneur.2018.00387

612. Hecker M, Fitzner B, Putscher E, Schwartz M, Winkelmann A, Meister S, Dudesek A, Koczan D, Lorenz P, Boxberger N, et al. Implication of genetic variants in primary microRNA processing sites in the risk of multiple sclerosis. EBioMedicine. 2022;80:104052. doi:10.1016/j.ebiom.2022.104052

613. Holzmann C, Bauer I, Meyer P. Co-occurrence of multiple sclerosis and cancer in a BRCA1 positive family. Eur J Med Genet. 2013;56(10):577-579. doi:10.1016/j.ejmg.2013.07.006

614. Fazia T, Nova A, Gentilini D, Beecham A, Piras M, Saddi V, Ticca A, Bitti P, McCauley JL, Berzuini C, et al. Investigating the Causal Effect of Brain Expression of CCL2, NFKB1, MAPK14, TNFRSF1A, CXCL10 Genes on Multiple Sclerosis: A Two-Sample Mendelian Randomization Approach. Front Bioeng Biotechnol. 2020;8:397. doi:10.3389/fbioe.2020.00397

615. Zhu Q, Han SX, Zhou CY, Cai MJ, Dai LP, Zhang JY. Autoimmune response to PARP and BRCA1/BRCA2 in cancer. Oncotarget. 2015;6(13):11575-11584. doi:10.18632/oncotarget.3428

616. Bergbreiter A, Jaeger T, Karle A, Bitzinger D, Ettl T, Spanier G, Jägle H, Neu R, Söder Y, Evert M, et al. Recurrent necrotizing cellulitis, multi-organ autoimmune disease and humoral immunodeficiency due to a novel NFKB1 frameshift mutation. Eur J Med Genet. 2021;64(3):104144. doi:10.1016/j.ejmg.2021.104144

617. Li G, Ding H, Yu X, Meng Y, Li J, Guo Q, Zhou H, Shen N. Spermidine Suppresses Inflammatory DC Function by Activating the FOXO3 Pathway and Counteracts Autoimmunity. iScience. 2020;23(1):100807. doi:10.1016/j.isci.2019.100807

618. Scărlătescu AI, Barbălată T, Sima AV, Stancu C, Niculescu L□, Micheu MM. miR-146a-5p, miR-223-3p and miR-142-3p as Potential Predictors of Major Adverse Cardiac Events in Young Patients with Acute ST Elevation Myocardial Infarction-Added Value over Left Ventricular Myocardial Work Indices. Diagnostics (Basel). 2022;12(8):1946. doi:10.3390/diagnostics12081946

619. Wang G, Zheng X, Zheng Y, Cao R, Zhang M, Sun Y, Wu J. Construction and analysis of the lncRNA□miRNA□mRNA network based on competitive endogenous RNA reveals functional genes in heart failure. Mol Med Rep. 2019;19(2):994-1003. doi:10.3892/mmr.2018.9734
620. Istas G, Declerck K, Pudenz M, Szic KSV, Lendinez-Tortajada V, Leon-Latre M, Heyninck K, Haegeman G, Casasnovas JA, Tellez-Plaza M, et al. Identification of differentially methylated BRCA1 and CRISP2 DNA regions as blood surrogate markers for cardiovascular disease. Sci Rep. 2017;7(1):5120. doi:10.1038/s41598-017-03434-0
621. Luo JY, Liu F, Zhang T, Tian T, Luo F, Li XM, Yang YN. Association of NFKB1 gene rs28362491 mutation with the occurrence of major adverse cardiovascular events. BMC Cardiovasc Disord. 2022;22(1):313. doi:10.1186/s12872-022-02755-x
622. Liu R, Lee J, Kim BS, Wang Q, Buxton SK, Balasubramanyam N, Kim JJ, Dong J, Zhang A, Li S, et al. Tead1 is required for maintaining adult cardiomyocyte function, and its loss results in lethal dilated cardiomyopathy. JCI Insight. 2017;2(17):e93343. doi:10.1172/jci.insight.93343
623. Zeng M, Wei X, He YL, Chen JX, Lin WT. TFAP2C inhibits cell autophagy to alleviate myocardial ischemia/reperfusion injury by regulating miR-23a-5p/SFRP5/Wnt5a axis. FASEB J. 2023;37(6):e22959. doi:10.1096/fj.202201962R
624. Lei J, Wang S, Kang W, Chu Q, Liu Z, Sun L, Ji Y, Esteban CR, Yao Y, Belmonte JCI, et al. FOXO3-engineered human mesenchymal progenitor cells efficiently promote cardiac repair after myocardial infarction. Protein Cell. 2021;12(2):145-151. doi:10.1007/s13238-020-00779-7
625. Chong H, Wei Z, Na M, Sun G, Zheng S, Zhu X, Xue Y, Zhou Q, Guo S, Xu J, et al. The PGC-1α/NRF1/miR-378a axis protects vascular smooth muscle cells from FFA-induced proliferation, migration and inflammation in atherosclerosis. Atherosclerosis. 2020;297:136-145. doi:10.1016/j.atherosclerosis.2020.02.001
626. Bhardwaj P, Iyengar NM, Zahid H, Carter KM, Byun DJ, Choi MH, Sun Q, Savenkov O, Louka C, Liu C, et al. Obesity promotes breast epithelium DNA damage in women carrying a germline mutation in BRCA1 or BRCA2. Sci Transl Med. 2023;15(684):eade1857. doi:10.1126/scitranslmed.ade1857

627. Yenmis G, Soydas T, Arkan H, Tasan E, Kanigur Sultuybek G. Genetic Variation in NFKB1 Gene Influences Liver Enzyme Levels in Morbidly Obese Women. Arch Iran Med. 2018;21(1):13-18.
628. Lv Y, Xia F, Yu J, Sheng Y, Jin Y, Li Y, Ding G. Distinct response of adipocyte progenitors to glucocorticoids determines visceral obesity via the TEAD1-miR-27b-PRDM16 axis. Obesity (Silver Spring). 2023;31(9):2335-2348. doi:10.1002/oby.23839
629. Boal F, Roumegoux J, Alfarano C, Timotin A, Calise D, Anesia R, Drougard A, Knauf C, Lagente C, Roncalli J, et al. Apelin regulates FoxO3 translocation to mediate cardioprotective responses to myocardial injury and obesity. Sci Rep. 2015;5:16104. doi:10.1038/srep16104
630. Patel P, Selvaraju V, Babu JR, Wang X, Geetha T. Racial Disparities in Methylation of NRF1, FTO, and LEPR Gene in Childhood Obesity. Genes (Basel). 2022;13(11):2030. doi:10.3390/genes13112030
631. Greco M, Mirabelli M, Salatino A, Accattato F, Aiello V, Brunetti FS, Chiefari E, Pullano SA, Fiorillo AS, Foti DP, et al. From Euglycemia to Recent Onset of Type 2 Diabetes Mellitus: A Proof-of-Concept Study on Circulating microRNA Profiling Reveals Distinct, and Early microRNA Signatures. Diagnostics (Basel). 2023;13(14):2443. doi:10.3390/diagnostics13142443
632. Hu Y, Li Q, Zhang L, Zhong L, Gu M, He B, Qu Q, Lao Y, Gu K, Zheng B, et al. Serum miR-195-5p Exhibits Clinical Significance in the Diagnosis of Essential Hypertension with Type 2 Diabetes Mellitus by Targeting DRD1. Clinics (Sao Paulo). 2021;76:e2502. doi:10.6061/clinics/2021/e250
633. Li JY, Cheng B, Wang XF, Wang ZJ, Zhang HM, Liu SF, Chen LS, Huang WJ, Liu J, Deng AP. Circulating MicroRNA-4739 May Be a Potential Biomarker of Critical Limb Ischemia in Patients with Diabetes. Biomed Res Int. 2018;2018:4232794. doi:10.1155/2018/4232794
634. Azizi SM, Sarhangi N, Afshari M, Abbasi D, Aghaei Meybodi HR, Hasanzad M. Association Analysis of the HNF4A Common Genetic Variants with Type 2 Diabetes Mellitus Risk. Int J Mol Cell Med. 2019;8(Suppl1):56-62. doi:10.22088/IJMCM.BUMS.8.2.56
635. Raza W, Guo J, Qadir MI, Bai B, Muhammad SA. qPCR Analysis Reveals Association of Differential Expression of SRR, NFKB1, and

PDE4B Genes With Type 2 Diabetes Mellitus. Front Endocrinol (Lausanne). 2022;12:774696. doi:10.3389/fendo.2021.774696

636. Ji X, Sun J, Wang Z. High level of lncRNA NR2F1-AS1 predict the onset and progression of diabetic retinopathy in type 2 diabetes. Exp Eye Res. 2022;219:109069. doi:10.1016/j.exer.2022.109069

637. Hussain S, Dwivedi KL, Yadav SS, Usman K, Nath R, Khattri S. No Association Between a Genetic Variant of FOXO3 and Risk of Type 2 Diabetes Mellitus in the Elderly Population of North India. Indian J Clin Biochem. 2021;36(3):330-336. doi:10.1007/s12291-020-00917-2

638. Qu L, He B, Pan Y, Xu Y, Zhu C, Tang Z, Bao Q, Tian F, Wang S. Association between polymorphisms in RAPGEF1, TP53, NRF1 and type 2 diabetes in Chinese Han population. Diabetes Res Clin Pract. 2011;91(2):171-176. doi:10.1016/j.diabres.2010.11.019

639. Kim HK, Tyryshkin K, Elmi N, Dharsee M, Evans KR, Good J, Javadi M, McCormack S, Vaccarino AL, Zhang X, et al. Plasma microRNA expression levels and their targeted pathways in patients with major depressive disorder who are responsive to duloxetine treatment. J Psychiatr Res. 2019;110:38-44. doi:10.1016/j.jpsychires.2018.12.007

640. Long J, Tian L, Baranova A, Cao H, Yao Y, Rao S, Zhang F. Convergent lines of evidence supporting involvement of NFKB1 in schizophrenia. Psychiatry Res. 2022;312:114588. doi:10.1016/j.psychres.2022.114588

641. Fan Y, Zhang J, Zhuang X, Geng F, Jiang G, Yang X. Epigenetic transcripts of LINC01311 and hsa-miR-146a-5p regulate neural development in a cellular model of Alzheimer's disease. IUBMB Life. 2021;73(7):916-926. doi:10.1002/iub.2472

642. Dobricic V, Schilling M, Farkas I, Gveric DO, Ohlei O, Schulz J, Middleton L, Gentleman SM, Parkkinen L, Bertram L, et al. Common signatures of differential microRNA expression in Parkinson's and Alzheimer's disease brains. Brain Commun. 2022;4(6):fcac274. doi:10.1093/braincomms/fcac274

643. Petrović N, Essack M, Šami A, Perry G, Gojobori T, Isenović ER, Bajić VP. MicroRNA networks linked with BRCA1/2, PTEN, and common genes for Alzheimer's disease and breast cancer share highly enriched pathways that may unravel targets for the AD/BC comorbidity treatment.

Comput Biol Chem. 2023;106:107925. doi:10.1016/j.compbiolchem.2023.107925
644. Liu Q, Zhu L, Liu X, Zheng J, Liu Y, Ruan X, Cao S, Cai H, Li Z, Xue Y. TRA2A-induced upregulation of LINC00662 regulates blood-brain barrier permeability by affecting ELK4 mRNA stability in Alzheimer's microenvironment. RNA Biol. 2020;17(9):1293-1308. doi:10.1080/15476286.2020.1756055
645. Fredi BM, De Labio RW, Rasmussen LT, Chagas EFB, Chen ES, Turecki G, Smith MAC, Payão SLM. CDK10, CDK11, FOXO1, and FOXO3 Gene Expression in Alzheimer's Disease Encephalic Samples. Cell Mol Neurobiol. 2023;43(6):2953-2962. doi:10.1007/s10571-023-01341-9
646. Chida-Nagai A, Shintani M, Sato H, Nakayama T, Nii M, Akagawa H, Furukawa T, Rana A, Furutani Y, Inai K, et al. Role of BRCA1-associated protein (BRAP) variant in childhood pulmonary arterial hypertension. PLoS One. 2019;14(1):e0211450. doi:10.1371/journal.pone.0211450
647. Li Y, Zhang Z, Liu D. Intracranial Aneurysms Induced by RUNX1 Through Regulation of NFKB1 in Patients With Hypertension-An Integrated Analysis Based on Multiple Datasets and Algorithms. Front Neurol. 2022;13:877801. doi:10.3389/fneur.2022.877801
648. Ren Y, Shi J, Liu S, Zhu W, Shao A, Qiao Y, Li Y, Liu Y, Cheng Y, Liu Y. Transcription factor AP-2 gamma/Krüppel-like factor 10 axis is involved in miR-3656-related dysfunction of endothelial cells in hypertension. J Hypertens. 2023;41(4):554-563. doi:10.1097/HJH.0000000000003359
649. Nakagawa K, Chen R, Ross GW, Donlon TA, Allsopp RC, Willcox DC, Morris BJ, Willcox BJ, Masaki KH. FOXO3 longevity genotype attenuates the impact of hypertension on cerebral microinfarct risk. J Hypertens. 2023. doi:10.1097/HJH.0000000000003620
650. Yu XJ, Xiao T, Liu XJ, Li Y, Qi J, Zhang N, Fu LY, Liu KL, Li Y, Kang YM. Effects of Nrf1 in Hypothalamic Paraventricular Nucleus on Regulating the Blood Pressure During Hypertension. Front Neurosci. 2021;15:805070. doi:10.3389/fnins.2021.805070
651. Xie S, Niu W, Xu F, Wang Y, Hu S, Niu C. Differential expression and significance of miRNAs in plasma extracellular vesicles of patients with

Parkinson's disease. Int J Neurosci. 2022;132(7):673-688. doi:10.1080/00207454.2020.1835899
652. Santiago JA, Potashkin JA. Network-based metaanalysis identifies HNF4A and PTBP1 as longitudinally dynamic biomarkers for Parkinson's disease. Proc Natl Acad Sci U S A. 2015;112(7):2257-2262. doi:10.1073/pnas.1423573112
653. Li X, Deng Q, Kuang Y, Mao H, Yao M, Lin C, Luo X, Xu P. Identifying NFKB1, STAT3, and CDKN1A as Baicalein's Potential Hub Targets in Parkinson's Disease-related α-synuclein-mediated Pathways by Integrated Bioinformatics Strategies. Curr Pharm Des. 2023;29(30):2426-2437. doi:10.2174/0113816128259065231011114116
654. Walter J, Bolognin S, Poovathingal SK, Magni S, Gérard D, Antony PMA, Nickels SL, Salamanca L, Berger E, Smits LM, et al. The Parkinson's-disease-associated mutation LRRK2-G2019S alters dopaminergic differentiation dynamics via NR2F1. Cell Rep. 2021;37(3):109864. doi:10.1016/j.celrep.2021.109864
655. Zhang S, Ma Y, Feng J. Neuroprotective mechanisms of ε-viniferin in a rotenone-induced cell model of Parkinson's disease: significance of SIRT3-mediated FOXO3 deacetylation. Neural Regen Res. 2020;15(11):2143-2153. doi:10.4103/1673-5374.282264
656. Gong X, Huang M, Chen L. NRF1 mitigates motor dysfunction and dopamine neuron degeneration in mice with Parkinson's disease by promoting GLRX m6 A methylation through upregulation of METTL3 transcription. CNS Neurosci Ther. 2023. doi:10.1111/cns.14441
657. Noristani HN, Sabourin JC, Gerber YN, Teigell M, Sommacal A, Vivanco Md, Weber M, Perrin FE. Brca1 is expressed in human microglia and is dysregulated in human and animal model of ALS. Mol Neurodegener. 2015;10:34. doi:10.1186/s13024-015-0023-x
658. Noronha O, Mesarosovo L, Anink JJ, Iyer A, Aronica E, Mills JD. Differentially Expressed miRNAs in Age-Related Neurodegenerative Diseases: A Meta-Analysis. Genes (Basel). 2022;13(6):1034. doi:10.3390/genes13061034
659. Jeon GS, Kim KY, Hwang YJ, Jung MK, An S, Ouchi M, Ouchi T, Kowall N, Lee J, Ryu H. Deregulation of BRCA1 leads to impaired spatiotemporal dynamics of γ-H2AX and DNA damage responses in

Huntington's disease. Mol Neurobiol. 2012;45(3):550-563. doi:10.1007/s12035-012-8274-9

660. Santiago JA, Potashkin JA. Reply to Liu et al.: HNF4A and PTBP1 expression in the brain of neurodegenerative disease patients. Proc Natl Acad Sci U S A. 2015;112(30):E3976. doi:10.1073/pnas.1510113112

661. Shi C, Viccaro K, Lee HG, Shah K. Cdk5-Foxo3 axis: initially neuroprotective, eventually neurodegenerative in Alzheimer's disease models. J Cell Sci. 2016;129(9):1815-1830. doi:10.1242/jcs.185009

662. Yuan J, Zhang S, Zhang Y. Nrf1 is paved as a new strategic avenue to prevent and treat cancer, neurodegenerative and other diseases. Toxicol Appl Pharmacol. 2018;360:273-283. doi:10.1016/j.taap.2018.09.037

663. Zhang D, Yu D, Mei X, Lv G. Liraglutide provides neuroprotection by regulating autophagy through the AMPK-FOXO3 signaling pathway in a spinal contusion injury rat model. Neurosci Lett. 2020;720:134747. doi:10.1016/j.neulet.2020.134747

Tables

Tables

Table .1 Selected drug targets with their structural information.

Drug target	PDB Id	Resolution (Å)	Method of collection
LCK	2og8	2.30	X-RAY diffraction
CFTR	2pzg	1.8	X-RAY diffraction
CFTR	2bbs	2.05	X-RAY diffraction
CA9	5dvx	1.60	X-RAY diffraction
LHCGR	1qfw	3.50	X-RAY diffraction
CA14	4lu3	2.00	X-RAY diffraction
HGF	3hms	1.70	X-RAY diffraction
PRKCQ	1xjd	2.00	X-RAY diffraction

Table 2 The statistical metrics for key differentially expressed genes (DEGs)

Gene Symbol	logFC	pValue	adj.P.Val	tvalue	Regulation	Gene Name
IGLC3	10.06961	2.36E-36	9.29E-33	12.59107	Up	immunoglobulin lambda constant 3 (Kern-Oz+ marker)
IGLC2	9.980379	9.51E-42	5.14E-38	13.53658	Up	immunoglobulin lambda constant 2
IGKV4-1	9.853402	2.85E-43	2.02E-39	13.79185	Up	immunoglobulin kappa variable 4-1
RNA5SP202	9.73263	1.60E-07	5.17E-06	5.241145	Up	RNA, 5S ribosomal pseudogene 202

IGHG3	9.579062	3.62E-46	3.92E-42	14.26483	Up	immunoglobulin heavy constant gamma 3 (G3m marker)
IGHG1	9.086903	5.08E-82	2.19E-77	19.18358	Up	immunoglobulin heavy constant gamma 1 (G1m marker)
RNA5S9	9.009309	4.37E-10	3.59E-08	6.24025	Up	RNA, 5S ribosomal 9
IGHG2	8.987913	1.88E-44	1.63E-40	13.98661	Up	immunoglobulin heavy constant gamma 2 (G2m marker)
IGHV4-39	8.87895	9.53E-36	3.43E-32	12.48055	Up	immunoglobulin heavy variable 4-39
IGKV3-11	8.857399	2.23E-35	7.42E-32	12.41262	Up	immunoglobulin kappa variable 3-11
IGHV1-2	8.751044	6.38E-25	1.02E-21	10.30954	Up	immunoglobulin heavy variable 1-2
IGHV3-7	8.714308	1.78E-46	2.56E-42	14.31435	Up	immunoglobulin heavy variable 3-7
IGKV1-5	8.525895	2.19E-38	1.05E-34	12.9555	Up	immunoglobulin kappa variable 1-5
IGHV3-30	8.375043	3.33E-24	4.80E-21	10.14941	Up	immunoglobulin heavy variable 3-30
IGLV2-11	8.37053	1.55E-18	1.05E-15	8.786014	Up	immunoglobulin lambda variable 2-11
IGKC	8.317001	5.20E-70	1.12E-65	17.68786	Up	immunoglobulin kappa constant
IGHV4-34	8.216539	2.34E-21	2.57E-18	9.4887	Up	immunoglobulin heavy variable 4-34
IGLV3-21	8.215488	3.50E-19	2.70E-16	8.951673	Up	immunoglobulin lambda variable 3-21
IGKV3-15	8.163341	2.32E-22	2.87E-19	9.726642	Up	immunoglobulin kappa variable 3-15
IGLV1-44	8.146692	5.45E-21	5.61E-18	9.400075	Up	immunoglobulin lambda variable 1-44
IGHV3-23	8.105742	8.78E-32	2.23E-28	11.73159	Up	immunoglobulin heavy variable 3-23
IGHV4-59	8.097631	1.55E-32	4.48E-29	11.87728	Up	immunoglobulin heavy variable 4-59
IGHV2-5	8.052062	2.82E-26	5.53E-23	10.60531	Up	immunoglobulin heavy variable 2-5
IGKV3-20	7.830961	7.84E-27	1.61E-23	10.72411	Up	immunoglobulin kappa variable 3-20
IGHV3-21	7.705562	4.67E-14	1.14E-11	7.540844	Up	immunoglobulin heavy variable 3-21
IGKV1-9	7.499405	2.42E-17	1.36E-14	8.471443	Up	immunoglobulin kappa variable 1-9
JCHAIN	7.360576	4.95E-38	2.14E-34	12.89263	Up	joining chain of multimeric IgA and IgM
RNA5SP74	7.321259	5.89E-06	0.000107	4.530446	Up	RNA, 5S ribosomal pseudogene 74
MTND1P23	7.310865	2.46E-22	2.95E-19	9.720756	Up	MT-ND1 pseudogene 23
IGHM	7.2494	3.26E-43	2.02E-39	13.78214	Up	immunoglobulin heavy constant mu
RNA5-8SP6	7.226277	4.22E-07	1.17E-05	5.058973	Up	RNA, 5.8S ribosomal pseudogene 6
IGLV2-14	7.133414	2.58E-20	2.38E-17	9.234999	Up	immunoglobulin lambda variable 2-14
IGHA1	7.111494	4.58E-32	1.24E-28	11.78644	Up	immunoglobulin heavy constant alpha 1
IGHV1-18	7.103404	3.30E-16	1.44E-13	8.16198	Up	immunoglobulin heavy variable 1-18
IGHV1-3	6.909408	3.20E-13	6.34E-11	7.285773	Up	immunoglobulin heavy variable 1-3
IGLV3-19	6.895603	8.38E-16	3.20E-13	8.048572	Up	immunoglobulin lambda variable 3-19
RNA5-8SN4	6.885809	2.32E-08	1.03E-06	5.585954	Up	RNA, 5.8S ribosomal N4
IGHV4-4	6.749457	2.62E-16	1.17E-13	8.189652	Up	immunoglobulin heavy variable 4-4
IGHV1-69D	6.642154	1.14E-10	1.16E-08	6.446557	Up	immunoglobulin heavy variable 1-69D
IGHV4-30-2	6.631824	1.23E-22	1.56E-19	9.791384	Up	immunoglobulin heavy variable 4-30-2
IGHV1-46	6.62993	3.19E-17	1.75E-14	8.439262	Up	immunoglobulin heavy variable 1-46
IGKV1-12	6.564886	3.43E-17	1.83E-14	8.430757	Up	immunoglobulin kappa variable 1-12
FCRL5	6.47703	1.12E-31	2.68E-28	11.7112	Up	Fc receptor like 5
IGLV2-23	6.405091	3.33E-11	3.93E-09	6.631369	Up	immunoglobulin lambda variable 2-23
IGHV3-33	6.248309	3.50E-21	3.69E-18	9.446561	Up	immunoglobulin heavy variable 3-33
IGHV5-51	6.23901	2.51E-13	5.17E-11	7.318333	Up	immunoglobulin heavy variable 5-51

IGHV2-26	6.210374	6.52E-11	7.03E-09	6.531189	Up	immunoglobulin heavy variable 2-26
IGKV1-27	6.129594	3.83E-13	7.43E-11	7.261278	Up	immunoglobulin kappa variable 1-27
IGLV1-40	6.059396	2.40E-13	4.97E-11	7.324256	Up	immunoglobulin lambda variable 1-40
IGHV2-70	6.057597	1.97E-12	3.23E-10	7.036262	Up	immunoglobulin heavy variable 2-70
IGLV2-8	6.057078	6.45E-09	3.51E-07	5.804549	Up	immunoglobulin lambda variable 2-8
IGKV1-17	5.943759	9.14E-13	1.62E-10	7.142943	Up	immunoglobulin kappa variable 1-17
IGHV3-48	5.943452	5.17E-13	9.67E-11	7.220735	Up	immunoglobulin heavy variable 3-48
FAM30A	5.919962	1.33E-25	2.40E-22	10.45899	Up	family with sequence similarity 30 member A
IGHV3-53	5.875865	8.59E-10	6.43E-08	6.133671	Up	immunoglobulin heavy variable 3-53
IGKV1-16	5.84343	5.28E-11	5.81E-09	6.562845	Up	immunoglobulin kappa variable 1-16
IGLV2-18	5.815317	1.79E-06	3.95E-05	4.775712	Up	immunoglobulin lambda variable 2-18
IGHV4-61	5.766141	4.69E-13	8.97E-11	7.23396	Up	immunoglobulin heavy variable 4-61
IGHG4	5.744639	5.31E-19	3.96E-16	8.905529	Up	immunoglobulin heavy constant gamma 4 (G4m marker)
IGHV3-74	5.742772	6.28E-14	1.47E-11	7.5021	Up	immunoglobulin heavy variable 3-74
CCL18	5.700544	2.41E-06	5.07E-05	4.715676	Up	C-C motif chemokine ligand 18
IGKV2-24	5.557589	4.46E-08	1.79E-06	5.471597	Up	immunoglobulin kappa variable 2-24
IGKV5-2	5.547014	1.68E-06	3.74E-05	4.788956	Up	immunoglobulin kappa variable 5-2
IGKV1-6	5.49746	8.93E-07	2.20E-05	4.913766	Up	immunoglobulin kappa variable 1-6
IGHV3-15	5.492425	5.62E-17	2.89E-14	8.372986	Up	immunoglobulin heavy variable 3-15
IGHV3-49	5.480636	1.74E-08	8.11E-07	5.635571	Up	immunoglobulin heavy variable 3-49
IGHJ5	5.451962	8.30E-12	1.12E-09	6.833241	Up	immunoglobulin heavy joining 5
IGKV6-21	5.376049	8.08E-05	0.000954	3.941974	Up	immunoglobulin kappa variable 6-21 (non-functional)
IGHV3-11	5.364442	3.27E-08	1.37E-06	5.526245	Up	immunoglobulin heavy variable 3-11
IGHV3-20	5.350349	2.53E-05	0.000367	4.211688	Up	immunoglobulin heavy variable 3-20
IGLV6-57	5.334184	8.27E-07	2.05E-05	4.928818	Up	immunoglobulin lambda variable 6-57
IGLV3-10	5.332133	3.20E-05	0.000446	4.158513	Up	immunoglobulin lambda variable 3-10
IGKV3D-11	5.308549	3.99E-09	2.36E-07	5.88469	Up	immunoglobulin kappa variable 3D-11
IGKV2-30	5.270766	1.87E-08	8.60E-07	5.623272	Up	immunoglobulin kappa variable 2-30
IGHV4-55	5.181429	6.06E-08	2.29E-06	5.41712	Up	immunoglobulin heavy variable 4-55 (pseudogene)
IGLV1-47	5.13828	2.24E-09	1.43E-07	5.97945	Up	immunoglobulin lambda variable 1-47
IGHV4-28	5.13505	7.08E-11	7.58E-09	6.518881	Up	immunoglobulin heavy variable 4-28
LRRC37A2	5.113237	9.02E-11	9.37E-09	6.482541	Up	leucine rich repeat containing 37 member A2
IGHV7-4-1	5.089007	0.000321	0.002932	3.597749	Up	immunoglobulin heavy variable 7-4-1
RNA5SP336	5.078075	0.000197	0.001967	3.723358	Up	RNA, 5S ribosomal pseudogene 336
IGLV3-25	5.067368	8.14E-08	2.94E-06	5.363939	Up	immunoglobulin lambda variable 3-25
IGHV3-64D	5.059654	6.20E-06	0.000112	4.519591	Up	immunoglobulin heavy variable 3-64D
IGHJ3P	5.006431	2.65E-10	2.36E-08	6.318075	Up	immunoglobulin heavy joining 3P (pseudogene)
IGHA2	4.954369	1.33E-13	2.91E-11	7.402731	Up	immunoglobulin heavy constant alpha 2 (A2m marker)
IGLL5	4.908842	5.73E-09	3.18E-07	5.824311	Up	immunoglobulin lambda like polypeptide 5
IGLV10-54	4.847455	3.35E-07	9.65E-06	5.102469	Up	immunoglobulin lambda variable 10-54
IGHV2-70D	4.839897	9.56E-08	3.35E-06	5.334951	Up	immunoglobulin heavy variable 2-70D
IGHV1-69	4.839832	1.44E-06	3.31E-05	4.818946	Up	immunoglobulin heavy variable 1-69

STOML3	4.838278	3.22E-09	1.97E-07	5.920014	Up	stomatin like 3
MTCO1P53	4.789025	4.92E-08	1.93E-06	5.454246	Up	MT-CO1 pseudogene 53
IGKV1-8	4.778191	1.37E-06	3.17E-05	4.829013	Up	immunoglobulin kappa variable 1-8
IGHV3-43	4.751148	1.10E-05	0.000182	4.39621	Up	immunoglobulin heavy variable 3-43
IGLV4-69	4.749838	2.92E-06	5.97E-05	4.676391	Up	immunoglobulin lambda variable 4-69
IGLV7-46	4.656717	8.24E-06	0.000142	4.458826	Up	immunoglobulin lambda variable 7-46
IGLV7-43	4.647697	1.16E-05	0.000191	4.384866	Up	immunoglobulin lambda variable 7-43
SLAMF7	4.622828	1.03E-27	2.23E-24	10.91002	Up	SLAM family member 7
IGHJ6	4.543851	3.64E-08	1.50E-06	5.507313	Up	immunoglobulin heavy joining 6
RASSF6	4.517662	2.37E-17	1.35E-14	8.47416	Up	Ras association domain family member 6
IGLV8-61	4.460752	1.17E-05	0.000193	4.382357	Up	immunoglobulin lambda variable 8-61
IGKJ5	4.442739	6.83E-07	1.74E-05	4.966237	Up	immunoglobulin kappa joining 5
SHOX2	4.415867	1.04E-18	7.24E-16	8.830798	Up	short stature homeobox 2
FCRL2	4.355734	8.48E-11	8.85E-09	6.491869	Up	Fc receptor like 2
OR2U1P	4.351839	0.000349	0.003127	3.576222	Up	olfactory receptor family 2 subfamily U member 1 pseudogene
IGHV6-1	4.346739	9.49E-07	2.32E-05	4.901993	Up	immunoglobulin heavy variable 6-1
IGKV1D-13	4.331848	0.000309	0.002844	3.60765	Up	immunoglobulin kappa variable 1D-13
FAM216B	4.296144	1.10E-11	1.44E-09	6.793259	Up	family with sequence similarity 216 member B
IGLC7	4.273698	0.007229	0.034225	2.686091	Up	immunoglobulin lambda constant 7
IGHV3-72	4.267119	1.47E-06	3.34E-05	4.815936	Up	immunoglobulin heavy variable 3-72
OR2U2P	4.263762	8.85E-05	0.001029	3.920133	Up	olfactory receptor family 2 subfamily U member 2 pseudogene
IGKV2D-29	4.242053	0.000106	0.001192	3.877329	Up	immunoglobulin kappa variable 2D-29
IGKV3D-20	4.216622	6.63E-06	0.000118	4.505145	Up	immunoglobulin kappa variable 3D-20
NUGGC	4.21585	8.93E-18	5.51E-15	8.586927	Up	nuclear GTPase, germinal center associated
IGKV6D-21	4.187105	0.000299	0.002773	3.615749	Up	immunoglobulin kappa variable 6D-21 (non-functional)
IGHV3-13	4.126908	0.000308	0.002837	3.608343	Up	immunoglobulin heavy variable 3-13
PYHIN1	4.122934	2.38E-21	2.57E-18	9.487043	Up	pyrin and HIN domain family member 1
IGHJ4	4.114152	7.38E-06	0.000129	4.482513	Up	immunoglobulin heavy joining 4
MS4A1	4.099287	9.04E-20	8.14E-17	9.099923	Up	membrane spanning 4-domains A1
IGHV1-24	4.096599	9.49E-05	0.001091	3.903344	Up	immunoglobulin heavy variable 1-24
IGHV3-73	4.04934	0.000121	0.00132	3.844329	Up	immunoglobulin heavy variable 3-73
MS4A2	4.047018	1.86E-07	5.87E-06	5.212516	Up	membrane spanning 4-domains A2
P2RY10	4.044454	5.16E-13	9.67E-11	7.220951	Up	P2Y receptor family member 10
GPR174	4.03373	2.64E-12	4.22E-10	6.995816	Up	G protein-coupled receptor 174
PPIAP45	4.009258	3.28E-05	0.000454	4.153074	Up	peptidylprolyl isomerase A pseudogene 45
IGKJ4	3.963444	2.63E-07	7.90E-06	5.148218	Up	immunoglobulin kappa joining 4
OR2G1P	3.956149	9.61E-06	0.000162	4.425788	Up	olfactory receptor family 2 subfamily G member 1 pseudogene
FCRL3	3.954047	4.93E-11	5.49E-09	6.57309	Up	Fc receptor like 3
RN7SL472P	3.924574	1.01E-10	1.04E-08	6.465662	Up	RNA, 7SL, cytoplasmic 472, pseudogene
LY9	3.894804	5.19E-15	1.59E-12	7.822278	Up	lymphocyte antigen 9
IGKV1D-39	3.844402	5.11E-05	0.000657	4.050325	Up	immunoglobulin kappa variable 1D-39
IGHV3-66	3.82856	0.000175	0.001794	3.752313	Up	immunoglobulin heavy variable 3-66

ADGB	3.804221	8.77E-14	1.96E-11	7.458206	Up	androglobin
CLEC10A	3.791609	3.28E-13	6.47E-11	7.282393	Up	C-type lectin domain containing 10A
IGKJ3	3.790449	3.30E-07	9.53E-06	5.105588	Up	immunoglobulin kappa joining 3
DNAJC5B	3.787386	4.41E-14	1.08E-11	7.548378	Up	DnaJ heat shock protein family (Hsp40) member C5 beta
RPL13P12	3.769631	8.34E-16	3.20E-13	8.049139	Up	ribosomal protein L13 pseudogene 12
TRAV4	3.700919	1.15E-06	2.73E-05	4.864692	Up	T cell receptor alpha variable 4
AADACL2	3.693007	3.65E-13	7.13E-11	7.268053	Up	arylacetamide deacetylase like 2
FNDC1	3.666067	3.11E-15	1.02E-12	7.88639	Up	fibronectin type III domain containing 1
PALM3	3.647856	9.16E-25	1.41E-21	10.27472	Up	paralemmin 3
HOXB7	3.646834	1.40E-10	1.37E-08	6.415967	Up	homeobox B7
SLAMF6	3.620622	1.38E-21	1.61E-18	9.543929	Up	SLAM family member 6
OR2J2	3.603544	0.001357	0.009357	3.203636	Up	olfactory receptor family 2 subfamily J member 2
IGKV1D-16	3.587261	0.000242	0.002332	3.670803	Up	immunoglobulin kappa variable 1D-16
TRAT1	3.584333	5.06E-11	5.59E-09	6.569169	Up	T cell receptor associated transmembrane adaptor 1
IGLV3-9	3.578656	0.000674	0.005332	3.399775	Up	immunoglobulin lambda variable 3-9
TRAJ19	3.569176	4.70E-08	1.86E-06	5.462481	Up	T cell receptor alpha joining 19 (non-functional)
IGKV1-39	3.558538	0.000115	0.001267	3.856816	Up	immunoglobulin kappa variable 1-39
SBK3	3.557441	1.60E-05	0.000251	4.313795	Up	SH3 domain binding kinase family member 3
ISL1-DT	3.543877	3.38E-05	0.000466	4.145965	Up	ISL1 divergent transcript
STRIT1	3.540798	0.001724	0.011251	3.134135	Up	small transmembrane regulator of ion transport 1
OR2J4P	3.53933	0.002307	0.014191	3.047602	Up	olfactory receptor family 2 subfamily J member 4 pseudogene
ZBED2	3.536452	3.54E-08	1.46E-06	5.512586	Up	zinc finger BED-type containing 2
EOMES	3.53325	2.50E-14	6.48E-12	7.621738	Up	eomesodermin
ISL1	3.528071	0.009222	0.041161	2.60371	Up	ISL LIM homeobox 1
IGLV5-45	3.525068	0.000449	0.003839	3.509379	Up	immunoglobulin lambda variable 5-45
TTR	3.495699	2.57E-08	1.13E-06	5.568266	Up	transthyretin
OTX2	3.492617	7.18E-06	0.000126	4.488303	Up	orthodenticle homeobox 2
RAET1K	3.472459	2.17E-06	4.64E-05	4.73698	Up	retinoic acid early transcript 1K pseudogene
IGKV1D-12	3.456014	0.002777	0.016517	2.991368	Up	immunoglobulin kappa variable 1D-12
CCR4	3.454034	1.82E-08	8.38E-07	5.628614	Up	C-C motif chemokine receptor 4
GZMA	3.424963	4.71E-11	5.28E-09	6.579703	Up	granzyme A
NMRAL2P	3.40656	8.86E-09	4.57E-07	5.751261	Up	NmrA like redox sensor 2, pseudogene
C20orf85	3.401077	0.002022	0.012781	3.086996	Up	chromosome 20 open reading frame 85
SPAG17	3.397014	1.28E-15	4.59E-13	7.996966	Up	sperm associated antigen 17
POU4F2	3.37904	3.50E-06	6.95E-05	4.638842	Up	POU class 4 homeobox 2
IGKV3D-15	3.369577	0.00643	0.031388	2.724986	Up	immunoglobulin kappa variable 3D-15
CD79A	3.362021	3.47E-12	5.26E-10	6.957247	Up	CD79a molecule
CCR2	3.337673	9.44E-21	9.49E-18	9.342108	Up	C-C motif chemokine receptor 2
CD48	3.334282	1.10E-15	3.98E-13	8.015633	Up	CD48 molecule
GZMK	3.334223	3.07E-08	1.30E-06	5.537183	Up	granzyme K
IGKV1D-33	3.325079	0.00458	0.024266	2.835182	Up	immunoglobulin kappa variable 1D-33
MYLK3	3.314138	6.10E-16	2.53E-13	8.087355	Up	myosin light chain kinase 3

IGKV1-33	3.311733	0.001478	0.009994	3.17897	Up	immunoglobulin kappa variable 1-33
RGS21	3.310956	1.18E-06	2.78E-05	4.85949	Up	regulator of G protein signaling 21
CFAP107	3.290338	1.21E-09	8.55E-08	6.07912	Up	cilia and flagella associated protein 107
NEK2-DT	3.286039	1.07E-05	0.000177	4.403138	Up	NEK2 divergent transcript
PLEKHG4B	3.275951	2.07E-12	3.37E-10	7.029904	Up	pleckstrin homology and RhoGEF domain containing G4B
RPL36P11	3.261967	3.66E-14	9.30E-12	7.572599	Up	ribosomal protein L36 pseudogene 11
TRAV17	3.261329	0.00108	0.007797	3.268735	Up	T cell receptor alpha variable 17
CD3E	3.253453	9.68E-20	8.54E-17	9.092489	Up	CD3 epsilon subunit of T-cell receptor complex
CCL26	3.236983	3.18E-05	0.000443	4.160164	Up	C-C motif chemokine ligand 26
IGKV1D-8	3.235089	8.48E-05	0.000994	3.930382	Up	immunoglobulin kappa variable 1D-8
ITGAD	3.234555	4.78E-13	9.10E-11	7.231428	Up	integrin subunit alpha D
DOK2	3.227083	1.72E-12	2.86E-10	7.05538	Up	docking protein 2
OR5V1	3.226278	0.002043	0.012881	3.083934	Up	olfactory receptor family 5 subfamily V member 1
TDRD15	3.225782	5.50E-08	2.13E-06	5.43421	Up	tudor domain containing 15
IL2RB	3.2222	6.36E-13	1.16E-10	7.192572	Up	interleukin 2 receptor subunit beta
CCL4	3.204984	3.56E-18	2.33E-15	8.691929	Up	C-C motif chemokine ligand 4
MOGAT2	3.186868	2.52E-06	5.25E-05	4.706782	Up	monoacylglycerol O-acyltransferase 2
GZMH	3.172865	3.60E-11	4.19E-09	6.619505	Up	granzyme H
CCDC194	3.163823	1.49E-10	1.45E-08	6.406147	Up	coiled-coil domain containing 194
RNU6-968P	3.160787	2.02E-05	0.000304	4.262574	Up	RNA, U6 small nuclear 968, pseudogene
DYDC2	3.144851	1.31E-09	9.07E-08	6.066751	Up	DPY30 domain containing 2
CCL24	3.143753	0.00933	0.041495	2.599736	Up	C-C motif chemokine ligand 24
CFAP45	3.135547	1.94E-13	4.07E-11	7.352974	Up	cilia and flagella associated protein 45
TPSAB1	3.12225	0.000181	0.001841	3.74393	Up	tryptase alpha/beta 1
TRAJ18	3.117743	2.11E-07	6.53E-06	5.189219	Up	T cell receptor alpha joining 18
NRK	3.112536	1.99E-07	6.22E-06	5.200297	Up	Nik related kinase
IGHV3-69-1	3.106028	0.004192	0.022669	2.863372	Up	immunoglobulin heavy variable 3-69-1 (pseudogene)
PURPL	3.105211	5.41E-07	1.44E-05	5.011114	Up	p53 upregulated regulator of p53 levels
PELATON	3.096723	1.98E-11	2.45E-09	6.707322	Up	plaque enriched lncRNA in atherosclerotic and inflammatory bowel macrophage regulation
SIX3	3.086613	5.13E-06	9.54E-05	4.559224	Up	SIX homeobox 3
CIBAR2	3.086592	5.15E-06	9.56E-05	4.55856	Up	CBY1 interacting BAR domain containing 2
VWA5B1	3.081662	1.21E-10	1.21E-08	6.437767	Up	von Willebrand factor A domain containing 5B1
EPS8L3	3.07738	6.03E-15	1.78E-12	7.803265	Up	EPS8 like 3
TNFRSF13B	3.071467	3.72E-09	2.24E-07	5.895979	Up	TNF receptor superfamily member 13B
IGHD	3.042595	0.00049	0.004121	3.486128	Up	immunoglobulin heavy constant delta
TRAJ26	3.041591	6.00E-05	0.000747	4.012995	Up	T cell receptor alpha joining 26
FASLG	3.035234	9.82E-09	4.94E-07	5.733761	Up	Fas ligand
SLAMF1	3.032021	2.19E-10	2.00E-08	6.347082	Up	signaling lymphocytic activation molecule family member 1
OR9Q1	3.030789	0.000775	0.005971	3.361476	Up	olfactory receptor family 9 subfamily Q member 1
MZB1	3.023392	2.24E-11	2.75E-09	6.689692	Up	marginal zone B and B1 cell specific protein
RN7SKP24	3.0214	3.79E-05	0.000512	4.120084	Up	RN7SK pseudogene 24
SLC35D3	3.00786	0.000902	0.006744	3.319313	Up	solute carrier family 35 member D3

TRBV29-1	2.999279	6.67E-05	0.000814	3.987802	Up	T cell receptor beta variable 29-1
TRBV27	2.999151	1.90E-05	0.000289	4.276293	Up	T cell receptor beta variable 27
CD24	2.993973	1.27E-13	2.78E-11	7.409756	Up	CD24 molecule
IKZF3	2.986933	3.70E-26	6.95E-23	10.57983	Up	IKAROS family zinc finger 3
HMGB1P46	2.97631	2.71E-05	0.000388	4.196647	Up	high mobility group box 1 pseudogene 46
RPL31P11	2.953352	0.000173	0.001778	3.75499	Up	ribosomal protein L31 pseudogene 11
LAX1	2.951106	3.55E-15	1.15E-12	7.86994	Up	lymphocyte transmembrane adaptor 1
DAW1	2.949018	8.62E-14	1.94E-11	7.460532	Up	dynein assembly factor with WD repeats 1
TDGF1	2.948046	1.16E-13	2.57E-11	7.420777	Up	teratocarcinoma-derived growth factor 1
C6orf118	2.947575	1.67E-17	9.87E-15	8.514895	Up	chromosome 6 open reading frame 118
CD2	2.946345	3.31E-12	5.07E-10	6.963863	Up	CD2 molecule
CD28	2.934272	9.71E-12	1.28E-09	6.810744	Up	CD28 molecule
CDCA4P3	2.916556	0.000275	0.002601	3.637315	Up	cell division cycle associated 4 pseudogene 3
IGLV1-36	2.91503	0.000262	0.002501	3.64978	Up	immunoglobulin lambda variable 1-36
MTCO1P20	2.906685	1.71E-05	0.000264	4.299813	Up	MT-CO1 pseudogene 20
FCMR	2.905066	5.48E-16	2.32E-13	8.100306	Up	Fc mu receptor
CLIC6	2.90361	4.06E-10	3.40E-08	6.251579	Up	chloride intracellular channel 6
LYZ	2.894631	2.53E-17	1.40E-14	8.466434	Up	lysozyme
IL7R	2.891134	5.79E-18	3.68E-15	8.63658	Up	interleukin 7 receptor
DNAAF6	2.888379	8.83E-06	0.000151	4.444065	Up	dynein axonemal assembly factor 6
RPL19P18	2.868322	0.00018	0.001831	3.745787	Up	ribosomal protein L19 pseudogene 18
FTH1P22	2.867966	1.57E-06	3.54E-05	4.802458	Up	ferritin heavy chain 1 pseudogene 22
HSH2D	2.859222	1.23E-10	1.22E-08	6.435854	Up	hematopoietic SH2 domain containing
HLA-DRB5	2.858566	5.14E-19	3.90E-16	8.909132	Up	major histocompatibility complex, class II, DR beta 5
NPY2R	2.850473	1.48E-07	4.85E-06	5.254884	Up	neuropeptide Y receptor Y2
FCGR2B	2.846979	8.43E-15	2.40E-12	7.760976	Up	Fc gamma receptor IIb
TUBA4B	2.845888	8.14E-07	2.03E-05	4.93197	Up	tubulin alpha 4b
UBASH3A	2.843522	2.54E-10	2.27E-08	6.32425	Up	ubiquitin associated and SH3 domain containing A
RTP1	2.843383	6.43E-17	3.27E-14	8.357137	Up	receptor transporter protein 1
PLA2G2D	2.842058	1.24E-06	2.92E-05	4.848548	Up	phospholipase A2 group IID
RNU1-28P	2.837998	0.000198	0.001979	3.721723	Up	RNA, U1 small nuclear 28, pseudogene
SNORA20	2.837636	5.99E-08	2.28E-06	5.418984	Up	small nucleolar RNA, H/ACA box 20
VTRNA1-1	2.834068	6.85E-05	0.000832	3.98147	Up	vault RNA 1-1
TRAV13-1	2.826954	0.000183	0.001855	3.741495	Up	T cell receptor alpha variable 13-1
TPSB2	2.813938	1.35E-05	0.000218	4.351269	Up	tryptase beta 2
CYP11B1	2.809674	0.000243	0.00234	3.669596	Up	cytochrome P450 family 11 subfamily B member 1
RNU1-27P	2.799543	0.000306	0.002819	3.610416	Up	RNA, U1 small nuclear 27, pseudogene
TRAV19	2.793145	0.00054	0.004449	3.46011	Up	T cell receptor alpha variable 19
TRAJ24	2.792995	4.51E-05	0.000591	4.079457	Up	T cell receptor alpha joining 24
DRD3	2.779148	0.011431	0.048376	2.529247	Up	dopamine receptor D3
GLYATL1P1	2.772553	7.56E-08	2.77E-06	5.377354	Up	glycine-N-acyltransferase like 1 pseudogene 1
MTHFD2P1	2.770835	0.000606	0.004892	3.428857	Up	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase pseudogene 1

TRAJ40	2.767175	0.000847	0.006412	3.336948	Up	T cell receptor alpha joining 40
CD1C	2.764589	0.004532	0.024076	2.838512	Up	CD1c molecule
P2RY8	2.764298	5.82E-14	1.38E-11	7.51206	Up	P2Y receptor family member 8
FOXJ1	2.74989	3.20E-13	6.34E-11	7.285762	Up	forkhead box J1
CLECL1P	2.749365	5.06E-10	4.07E-08	6.21722	Up	C-type lectin like 1, pseudogene
MTATP8P1	2.747186	2.46E-06	5.16E-05	4.711101	Up	MT-ATP8 pseudogene 1
CEACAM16	2.742541	0.00066	0.005235	3.405872	Up	CEA cell adhesion molecule 16, tectorial membrane component
TRAJ48	2.740958	0.002142	0.013374	3.069795	Up	T cell receptor alpha joining 48
NLRP7	2.737118	0.000504	0.004212	3.478366	Up	NLR family pyrin domain containing 7
RNA5SP70	2.727898	0.001619	0.010722	3.152497	Up	RNA, 5S ribosomal pseudogene 70
LAIR2	2.714968	9.59E-08	3.36E-06	5.334241	Up	leukocyte associated immunoglobulin like receptor 2
TRAV12-3	2.712699	0.01031	0.044765	2.565246	Up	T cell receptor alpha variable 12-3
TRAJ7	2.711564	0.000206	0.002043	3.711376	Up	T cell receptor alpha joining 7
PRR32	2.70912	0.005376	0.027369	2.783599	Up	proline rich 32
TRAJ16	2.702491	7.77E-05	0.000924	3.951339	Up	T cell receptor alpha joining 16
TRAJ22	2.701987	4.44E-06	8.47E-05	4.589868	Up	T cell receptor alpha joining 22
RN7SL402P	2.699484	0.000205	0.002033	3.712903	Up	RNA, 7SL, cytoplasmic 402, pseudogene
PGBD3P4	2.69755	0.000265	0.00252	3.647307	Up	piggyBac transposable element derived 3 pseudogene 4
STMND1	2.696951	1.40E-13	3.02E-11	7.396773	Up	stathmin domain containing 1
TRBV20-1	2.691503	0.002456	0.014935	3.028758	Up	T cell receptor beta variable 20-1
XIRP2	2.688695	0.000442	0.003793	3.513666	Up	xin actin binding repeat containing 2
CD3D	2.683004	2.17E-08	9.75E-07	5.597557	Up	CD3 delta subunit of T-cell receptor complex
RNU6-511P	2.682155	0.002676	0.016024	3.002662	Up	RNA, U6 small nuclear 511, pseudogene
TRBC1	2.67945	4.39E-09	2.56E-07	5.868623	Up	T cell receptor beta constant 1
DNAI3	2.677946	6.71E-12	9.33E-10	6.86369	Up	dynein axonemal intermediate chain 3
TRBV28	2.676431	7.63E-05	0.000912	3.955707	Up	T cell receptor beta variable 28
C6orf141	2.671448	4.08E-07	1.14E-05	5.06539	Up	chromosome 6 open reading frame 141
TAB2	2.67141	1.32E-19	1.12E-16	9.058631	Up	TGF-beta activated kinase 1 (MAP3K7) binding protein 2
ICOS	2.667114	1.43E-07	4.71E-06	5.261213	Up	inducible T cell costimulator
CLEC12A	2.659187	3.08E-07	8.97E-06	5.11862	Up	C-type lectin domain family 12 member A
MGC4859	2.65776	2.92E-05	0.000412	4.179632	Up	uncharacterized LOC79150
PCP4	2.655991	8.68E-11	9.04E-09	6.488321	Up	Purkinje cell protein 4
LHCGR	2.655985	2.33E-15	7.79E-13	7.922579	Up	luteinizing hormone/choriogonadotropin receptor
IL24	2.647003	1.13E-08	5.55E-07	5.710622	Up	interleukin 24
PCAT19	2.633966	1.32E-15	4.70E-13	7.99318	Up	prostate cancer associated transcript 19
TRAJ11	2.625397	0.00062	0.004982	3.422847	Up	T cell receptor alpha joining 11
CD3G	2.62514	3.53E-10	3.04E-08	6.273298	Up	CD3 gamma subunit of T-cell receptor complex
SYNDIG1L	2.624628	1.93E-08	8.82E-07	5.617938	Up	synapse differentiation inducing 1 like
CCL5	2.624212	2.07E-19	1.69E-16	9.009623	Up	C-C motif chemokine ligand 5
CCL3	2.623699	0.000512	0.004264	3.474447	Up	C-C motif chemokine ligand 3
RNU7-156P	2.623599	0.000359	0.003202	3.568366	Up	RNA, U7 small nuclear 156 pseudogene
TNNI3	2.6183	9.47E-06	0.00016	4.428842	Up	troponin I3, cardiac type

TRAV12-2	2.61039	0.005577	0.028165	2.77165	Up	T cell receptor alpha variable 12-2
TRAJ13	2.60595	0.000403	0.003519	3.538071	Up	T cell receptor alpha joining 13
SIGLEC6	2.603157	0.007482	0.035107	2.674612	Up	sialic acid binding Ig like lectin 6
TRAJ6	2.601095	0.000117	0.001282	3.853341	Up	T cell receptor alpha joining 6
RNU6-35P	2.59925	0.004154	0.022517	2.866189	Up	RNA, U6 small nuclear 35, pseudogene
GPR101	2.592832	0.001003	0.007342	3.289802	Up	G protein-coupled receptor 101
EIF4BP8	2.591835	0.002684	0.01606	3.001769	Up	eukaryotic translation initiation factor 4B pseudogene 8
TRBV6-7	2.590423	0.0027	0.016141	3.000024	Up	T cell receptor beta variable 6-7 (non-functional)
LTF	2.588857	6.12E-09	3.35E-07	5.813371	Up	lactotransferrin
HISLA	2.588239	5.33E-15	1.62E-12	7.818945	Up	HIF1A stabilizing long noncoding RNA
ITK	2.587415	3.19E-12	4.90E-10	6.969221	Up	IL2 inducible T cell kinase
H4C13	2.586782	1.24E-10	1.23E-08	6.434549	Up	H4 clustered histone 13
AKR1C4	2.584239	0.004611	0.0244	2.832995	Up	aldo-keto reductase family 1 member C4
C1orf87	2.583897	1.29E-10	1.28E-08	6.42812	Up	chromosome 1 open reading frame 87
TRAJ10	2.582	5.61E-06	0.000103	4.54065	Up	T cell receptor alpha joining 10
SAGE1	2.581355	3.06E-06	6.19E-05	4.666984	Up	sarcoma antigen 1
CD52	2.577628	4.68E-10	3.82E-08	6.229474	Up	CD52 molecule
FAM183A	2.572989	6.72E-06	0.00012	4.502302	Up	family with sequence similarity 183 member A
TRAV8-2	2.570789	0.003151	0.018189	2.952654	Up	T cell receptor alpha variable 8-2
HOXB3	2.569759	1.23E-09	8.63E-08	6.076834	Up	homeobox B3
RN7SL193P	2.561035	3.74E-06	7.34E-05	4.625084	Up	RNA, 7SL, cytoplasmic 193, pseudogene
KRT17P6	2.560245	3.39E-05	0.000468	4.145302	Up	keratin 17 pseudogene 6
POTEF	2.556908	0.001515	0.010186	3.171751	Up	POTE ankyrin domain family member F
CATSPERD	2.554109	1.27E-06	2.97E-05	4.844565	Up	cation channel sperm associated auxiliary subunit delta
TRBV18	2.551622	0.001041	0.007568	3.279325	Up	T cell receptor beta variable 18
TRARG1	2.550504	6.54E-05	0.000801	3.992425	Up	trafficking regulator of GLUT4 (SLC2A4) 1
CD163	2.548294	2.86E-19	2.29E-16	8.97382	Up	CD163 molecule
HS3ST3A1	2.545491	4.47E-07	1.23E-05	5.047973	Up	heparan sulfate-glucosamine 3-sulfotransferase 3A1
GPNMB	2.538488	9.75E-16	3.63E-13	8.030017	Up	glycoprotein nmb
CTLA4	2.532196	9.04E-09	4.62E-07	5.747878	Up	cytotoxic T-lymphocyte associated protein 4
MTND4P24	2.531531	0.000135	0.001441	3.81732	Up	MT-ND4 pseudogene 24
SLC25A52	2.520769	3.79E-07	1.07E-05	5.079159	Up	solute carrier family 25 member 52
GZMAP1	2.509274	0.007505	0.035193	2.673572	Up	granzyme A pseudogene 1
MYO3A	2.506414	6.19E-08	2.33E-06	5.413334	Up	myosin IIIA
TFAP2D	2.506182	0.009684	0.042651	2.586905	Up	transcription factor AP-2 delta
IRF4	2.506033	4.39E-15	1.36E-12	7.843299	Up	interferon regulatory factor 4
GSDMA	2.505793	1.31E-05	0.000212	4.35768	Up	gasdermin A
MTATP6P13	2.495667	0.004151	0.022504	2.866451	Up	MT-ATP6 pseudogene 13
TRAV14DV4	2.490731	0.002978	0.017422	2.97	Up	T cell receptor alpha variable 14/delta variable 4
SDC1	2.489358	3.56E-09	2.15E-07	5.903655	Up	syndecan 1
FAM187B2P	2.484456	2.36E-06	4.99E-05	4.719493	Up	family with sequence similarity 187, member B pseudogene
FCGBP	2.483683	1.02E-14	2.83E-12	7.736488	Up	Fc gamma binding protein

TNFRSF9	2.483264	2.03E-07	6.34E-06	5.196241	Up	TNF receptor superfamily member 9
GOLGA2P1	2.481862	0.006786	0.032701	2.707148	Up	GOLGA2 pseudogene 1
LCK	2.478524	9.73E-12	1.28E-09	6.810462	Up	LCK proto-oncogene, Src family tyrosine kinase
TEKT4	2.475929	0.001821	0.011748	3.117976	Up	tektin 4
CD209	2.473703	1.45E-17	8.70E-15	8.531105	Up	CD209 molecule
TRBV5-6	2.473344	0.001131	0.008078	3.255731	Up	T cell receptor beta variable 5-6
IGLV1-51	2.471567	5.64E-09	3.15E-07	5.827198	Up	immunoglobulin lambda variable 1-51
ANKRD66	2.469538	1.96E-07	6.15E-06	5.202745	Up	ankyrin repeat domain 66
LIPM	2.465883	0.000101	0.001144	3.88933	Up	lipase family member M
MTCYBP34	2.465014	0.000516	0.004292	3.472334	Up	MT-CYB pseudogene 34
FNDC1-IT1	2.464882	0.003157	0.018214	2.952018	Up	FNDC1 intronic transcript 1
KRT18P38	2.462628	0.007763	0.03611	2.662228	Up	keratin 18 pseudogene 38
TRAJ3	2.459336	0.000135	0.001441	3.817419	Up	T cell receptor alpha joining 3
MAT1A	2.455929	7.26E-06	0.000127	4.486051	Up	methionine adenosyltransferase 1A
C6	2.455485	1.38E-09	9.56E-08	6.057323	Up	complement C6
IQGAP2	2.455181	5.84E-23	7.65E-20	9.866097	Up	IQ motif containing GTPase activating protein 2
NCR1	2.455156	4.27E-05	0.000564	4.092151	Up	natural cytotoxicity triggering receptor 1
TRBV5-5	2.45292	0.002186	0.013602	3.063716	Up	T cell receptor beta variable 5-5
TUBAL3	2.452748	1.63E-06	3.66E-05	4.794631	Up	tubulin alpha like 3
RNA5SP131	2.451042	0.000411	0.00357	3.533179	Up	RNA, 5S ribosomal pseudogene 131
RPS2P4	2.448819	1.68E-06	3.75E-05	4.78838	Up	ribosomal protein S2 pseudogene 4
GOLGA2P2Y	2.442343	0.011923	0.049989	2.514429	Up	GOLGA2 pseudogene 2 Y-linked
NUTM2E	2.431876	0.000339	0.003057	3.583589	Up	NUT family member 2E
MUC3A	2.430954	5.74E-08	2.20E-06	5.426803	Up	mucin 3A, cell surface associated
TRBV7-5	2.430215	0.000905	0.00676	3.31837	Up	T cell receptor beta variable 7-5 (pseudogene)
CDC20B	2.426913	1.07E-05	0.000177	4.402978	Up	cell division cycle 20B
HMGB3P25	2.416022	0.000209	0.002064	3.707642	Up	high mobility group box 3 pseudogene 25
CAPSL	2.414583	8.22E-08	2.96E-06	5.362138	Up	calcyphosine like
RNU6-1300P	2.41242	4.15E-06	8.00E-05	4.603615	Up	RNA, U6 small nuclear 1300, pseudogene
MTDHP3	2.408667	0.000129	0.001389	3.828466	Up	metadherin pseudogene 3
TRAC	2.399511	6.67E-13	1.21E-10	7.18597	Up	T cell receptor alpha constant
DNAH3	2.398772	1.42E-10	1.39E-08	6.413737	Up	dynein axonemal heavy chain 3
CDA	2.393538	8.51E-09	4.43E-07	5.758063	Up	cytidine deaminase
PRSS21	2.393048	1.54E-05	0.000242	4.3232	Up	serine protease 21
XCL2	2.391791	0.000731	0.005688	3.377769	Up	X-C motif chemokine ligand 2
TEKT1	2.390847	3.49E-10	3.00E-08	6.275413	Up	tektin 1
FOXL2	2.386873	1.15E-07	3.91E-06	5.301612	Up	forkhead box L2
MS4A14	2.385237	1.33E-20	1.31E-17	9.305517	Up	membrane spanning 4-domains A14
KRTDAP	2.374026	0.000643	0.005129	3.412752	Up	keratinocyte differentiation associated protein
B4GALNT2	2.370002	0.00018	0.001836	3.744989	Up	beta-1,4-N-acetyl-galactosaminyltransferase 2
GTF2A1L	2.368646	8.96E-05	0.001039	3.917096	Up	general transcription factor IIA subunit 1 like
TRAJ31	2.365751	0.00431	0.023139	2.854569	Up	T cell receptor alpha joining 31
MTCO1P22	2.365348	5.75E-06	0.000105	4.535255	Up	MT-CO1 pseudogene 22

C19orf84	2.364238	2.31E-07	7.06E-06	5.172245	Up	chromosome 19 open reading frame 84
ART5	2.364133	0.000751	0.005813	3.370403	Up	ADP-ribosyltransferase 5
CRABP1	2.358903	1.30E-06	3.04E-05	4.839467	Up	cellular retinoic acid binding protein 1
TRAJ20	2.357867	0.001601	0.010619	3.155711	Up	T cell receptor alpha joining 20
TTLL10	2.355612	0.000288	0.002691	3.625933	Up	tubulin tyrosine ligase like 10
RNU6-1061P	2.352412	0.011441	0.0484	2.528932	Up	RNA, U6 small nuclear 1061, pseudogene
TRIML2	2.351192	0.00055	0.004519	3.455087	Up	tripartite motif family like 2
MCIDAS	2.348837	0.010757	0.046234	2.550493	Up	multiciliate differentiation and DNA synthesis associated cell cycle protein
GSTO3P	2.348156	0.008548	0.03889	2.629632	Up	glutathione S-transferase omega 3, pseudogene
PRPH	2.347791	6.58E-09	3.56E-07	5.801376	Up	peripherin
AOC1	2.347765	1.55E-10	1.49E-08	6.400321	Up	amine oxidase copper containing 1
IL5RA	2.34749	1.90E-10	1.78E-08	6.3695	Up	interleukin 5 receptor subunit alpha
RN7SL219P	2.34365	2.37E-06	5.00E-05	4.719207	Up	RNA, 7SL, cytoplasmic 219, pseudogene
MYH2	2.34313	0.000574	0.004681	3.443796	Up	myosin heavy chain 2
NDUFB4P12	2.342175	0.000186	0.001877	3.737979	Up	NADH:ubiquinone oxidoreductase subunit B4 pseudogene 12
RNU6-1148P	2.338507	0.006894	0.033122	2.701939	Up	RNA, U6 small nuclear 1148, pseudogene
KRT42P	2.338178	0.000638	0.005097	3.414928	Up	keratin 42, pseudogene
TRGV5P	2.336804	0.000153	0.0016	3.786682	Up	T cell receptor gamma variable 5P (pseudogene)
SIK1	2.33675	1.63E-05	0.000253	4.310826	Up	salt inducible kinase 1
TUBB6P1	2.335907	0.000688	0.005416	3.394155	Up	tubulin beta 6 class V pseudogene 1
F13A1	2.335434	4.04E-15	1.29E-12	7.853544	Up	coagulation factor XIII A chain
RN7SKP13	2.335324	0.007426	0.034922	2.677113	Up	RN7SK pseudogene 13
WT1	2.335307	0.007073	0.033715	2.693375	Up	WT1 transcription factor
TRAJ27	2.331792	0.010904	0.046741	2.545769	Up	T cell receptor alpha joining 27
RNU1-136P	2.330118	0.000521	0.004328	3.469568	Up	RNA, U1 small nuclear 136, pseudogene
MAPK15	2.328436	4.35E-06	8.32E-05	4.593858	Up	mitogen-activated protein kinase 15
CD8B	2.325886	1.22E-06	2.88E-05	4.851934	Up	CD8b molecule
TRAJ9	2.325496	0.00099	0.007271	3.293281	Up	T cell receptor alpha joining 9
MS4A7	2.323466	6.42E-16	2.64E-13	8.080988	Up	membrane spanning 4-domains A7
TRBJ1-3	2.322928	0.001232	0.008648	3.231414	Up	T cell receptor beta joining 1-3
PPIAP75	2.322255	0.008801	0.039728	2.61969	Up	peptidylprolyl isomerase A pseudogene 75
OR2T6	2.32019	0.000615	0.004953	3.424955	Up	olfactory receptor family 2 subfamily T member 6
RPL29P2	2.315552	0.00056	0.004582	3.450492	Up	ribosomal protein L29 pseudogene 2
MSR1	2.314735	4.26E-15	1.34E-12	7.847069	Up	macrophage scavenger receptor 1
ALOX15B	2.312127	2.87E-08	1.23E-06	5.549073	Up	arachidonate 15-lipoxygenase type B
PTGDR	2.310319	3.59E-11	4.18E-09	6.620262	Up	prostaglandin D2 receptor
LPAR3	2.308994	4.29E-14	1.07E-11	7.551827	Up	lysophosphatidic acid receptor 3
CFAP157	2.306183	3.27E-09	1.99E-07	5.917616	Up	cilia and flagella associated protein 157
RNU6-959P	2.305238	0.005255	0.026928	2.79099	Up	RNA, U6 small nuclear 959, pseudogene
GML	2.304102	0.004183	0.022632	2.864052	Up	glycosylphosphatidylinositol anchored molecule like
CDHR4	2.302566	7.92E-05	0.000939	3.946747	Up	cadherin related family member 4
CRNN	2.301304	0.000364	0.003238	3.56489	Up	cornulin

JSRP1	2.295409	6.15E-06	0.000111	4.521046	Up	junctional sarcoplasmic reticulum protein 1
RNU6-657P	2.290608	0.010939	0.046853	2.544651	Up	RNA, U6 small nuclear 657, pseudogene
JAML	2.289737	3.55E-17	1.87E-14	8.426856	Up	junction adhesion molecule like
MTCYBP41	2.287487	0.000642	0.005125	3.413158	Up	MT-CYB pseudogene 41
HMGB3P18	2.286238	0.001475	0.009982	3.179617	Up	high mobility group box 3 pseudogene 18
TMIE	2.284492	1.04E-17	6.32E-15	8.569709	Up	transmembrane inner ear
H2BL1P	2.280991	5.65E-05	0.000713	4.027136	Up	H2B.L histone variant 1, pseudogene
PIWIL3	2.279502	0.001176	0.00834	3.244689	Up	piwi like RNA-mediated gene silencing 3
DNAH11	2.278761	1.70E-14	4.55E-12	7.671124	Up	dynein axonemal heavy chain 11
GBP5	2.278653	1.06E-19	9.18E-17	9.082386	Up	guanylate binding protein 5
CORO1CP1	2.277287	0.006374	0.031172	2.727898	Up	CORO1C pseudogene 1
NTS	2.275531	1.40E-05	0.000223	4.344611	Up	neurotensin
NMRK2	2.270988	3.93E-05	0.000526	4.111797	Up	nicotinamide riboside kinase 2
HGF	2.268418	1.66E-24	2.47E-21	10.21721	Up	hepatocyte growth factor
RNASE10	2.267054	0.001389	0.009522	3.196931	Up	ribonuclease A family member 10 (inactive)
HPAT5	2.266209	0.009324	0.041482	2.599926	Up	human pluripotency-associated transcript 5
TRAJ45	2.265859	0.001591	0.010573	3.157624	Up	T cell receptor alpha joining 45
LCN8	2.265686	0.003233	0.018567	2.944636	Up	lipocalin 8
RIBC2	2.26544	1.86E-11	2.32E-09	6.716557	Up	RIB43A domain with coiled-coils 2
RNA5SP488	2.264995	0.000493	0.00414	3.48428	Up	RNA, 5S ribosomal pseudogene 488
TRBV7-7	2.263429	0.002496	0.015135	3.023849	Up	T cell receptor beta variable 7-7
C11orf86	2.262763	0.008643	0.039199	2.625867	Up	chromosome 11 open reading frame 86
CDRT15P3	2.262597	0.000493	0.004136	3.484634	Up	CDRT15 pseudogene 3
SLC22A31	2.261314	0.008327	0.038137	2.63853	Up	solute carrier family 22 member 31
ZBBX	2.259523	9.53E-13	1.68E-10	7.137187	Up	zinc finger B-box domain containing
DPRXP6	2.258929	0.010238	0.044526	2.567697	Up	divergent-paired related homeobox pseudogene 6
SNORA70F	2.258601	0.000905	0.006757	3.318612	Up	small nucleolar RNA, H/ACA box 70F
RNA5SP435	2.258059	0.000386	0.003394	3.549721	Up	RNA, 5S ribosomal pseudogene 435
POM121L2	2.257763	0.000632	0.005062	3.417396	Up	POM121 transmembrane nucleoporin like 2
MICB	2.255347	1.56E-15	5.43E-13	7.972207	Up	MHC class I polypeptide-related sequence B
TRPM8	2.245189	3.57E-09	2.15E-07	5.903173	Up	transient receptor potential cation channel subfamily M member 8
MYB	2.244675	9.27E-08	3.27E-06	5.340392	Up	MYB proto-oncogene, transcription factor
FOXF2	2.243871	1.56E-10	1.50E-08	6.399118	Up	forkhead box F2
OR1J1	2.243868	0.000766	0.005912	3.364943	Up	olfactory receptor family 1 subfamily J member 1
RNU6-908P	2.240717	0.002102	0.013177	3.075371	Up	RNA, U6 small nuclear 908, pseudogene
ADGRG6	2.240372	8.19E-18	5.13E-15	8.596877	Up	adhesion G protein-coupled receptor G6
C1orf141	2.239853	1.49E-07	4.87E-06	5.254042	Up	chromosome 1 open reading frame 141
RNU1-18P	2.234506	0.000102	0.00116	3.885486	Up	RNA, U1 small nuclear 18, pseudogene
TRBC2	2.231132	1.32E-12	2.23E-10	7.091838	Up	T cell receptor beta constant 2
IL2RG	2.230515	1.94E-20	1.82E-17	9.265833	Up	interleukin 2 receptor subunit gamma
MTND2P28	2.227591	2.20E-08	9.81E-07	5.595516	Up	MT-ND2 pseudogene 28
MRC1	2.221527	7.32E-17	3.64E-14	8.341755	Up	mannose receptor C-type 1

TRBV5-4	2.218166	0.001092	0.007855	3.26561	Up	T cell receptor beta variable 5-4
FOLR2	2.217489	3.12E-12	4.85E-10	6.972088	Up	folate receptor beta
RNU6-194P	2.217308	4.30E-06	8.24E-05	4.596379	Up	RNA, U6 small nuclear 194, pseudogene
DIO3	2.216404	3.82E-06	7.46E-05	4.620962	Up	iodothyronine deiodinase 3
LRRC77P	2.214253	5.16E-06	9.58E-05	4.55817	Up	leucine rich repeat containing 77, pseudogene
CD96	2.214213	3.69E-14	9.33E-12	7.571419	Up	CD96 molecule
SIGLEC1	2.212265	5.50E-13	1.02E-10	7.212406	Up	sialic acid binding Ig like lectin 1
UCN3	2.207121	0.001763	0.01145	3.127513	Up	urocortin 3
TRBV7-9	2.205271	0.000171	0.001762	3.757925	Up	T cell receptor beta variable 7-9
CHIT1	2.204519	1.96E-08	8.93E-07	5.615236	Up	chitinase 1
POTEI	2.203428	0.004518	0.02403	2.839531	Up	POTE ankyrin domain family member I
MROH2B	2.202867	0.009771	0.042954	2.583835	Up	maestro heat like repeat family member 2B
OR4G6P	-25.5969	2.95E-15	9.72E-13	-7.89321	Down	olfactory receptor family 4 subfamily G member 6 pseudogene
ADGRG7	-8.58446	1.25E-09	8.77E-08	-6.07346	Down	adhesion G protein-coupled receptor G7
OR4F4	-5.85182	4.62E-05	0.000603	-4.07412	Down	olfactory receptor family 4 subfamily F member 4
FAM138E	-5.09552	0.004962	0.025791	-2.80949	Down	family with sequence similarity 138 member E
NKX2-4	-2.4967	7.16E-06	0.000126	-4.48897	Down	NK2 homeobox 4
PLAC8	-2.43595	1.09E-12	1.86E-10	-7.11872	Down	placenta associated 8
RXFP4	-2.31739	4.79E-09	2.74E-07	-5.85445	Down	relaxin family peptide/INSL5 receptor 4
ICOSLG	-2.26241	6.48E-08	2.42E-06	-5.40495	Down	inducible T cell costimulator ligand
SFN	-2.18937	2.38E-06	5.03E-05	-4.71783	Down	stratifin
PLAC9P1	-2.17385	5.14E-10	4.11E-08	-6.21474	Down	placenta associated 9 pseudogene 1
CIROP	-2.15476	4.28E-15	1.34E-12	-7.84642	Down	ciliated left-right organizer metallopeptidase
GRHL3	-2.15109	8.85E-10	6.59E-08	-6.12882	Down	grainyhead like transcription factor 3
UGT2B17	-2.0886	0.003996	0.021856	-2.8785	Down	UDP glucuronosyltransferase family 2 member B17
IL9	-2.0504	2.48E-11	3.02E-09	-6.67429	Down	interleukin 9
TMEM88B	-2.02877	1.63E-10	1.56E-08	-6.39237	Down	transmembrane protein 88B
ADAMTS14	-1.98454	2.04E-10	1.89E-08	-6.35815	Down	ADAM metallopeptidase with thrombospondin type 1 motif 14
TMEFF1	-1.96678	0.000496	0.004154	-3.48293	Down	transmembrane protein with EGF like and two follistatin like domains 1
STC2	-1.95851	1.40E-09	9.58E-08	-6.05591	Down	stanniocalcin 2
GJC2	-1.94723	4.47E-09	2.60E-07	-5.86577	Down	gap junction protein gamma 2
C11orf96	-1.89951	5.87E-07	1.54E-05	-4.9953	Down	chromosome 11 open reading frame 96
PPP1R12BP1	-1.87007	4.35E-06	8.32E-05	-4.5938	Down	protein phosphatase 1 regulatory subunit 12B pseudogene 1
TEX44	-1.86075	0.000975	0.007184	-3.29758	Down	testis expressed 44
NPPC	-1.85514	2.39E-05	0.00035	-4.22482	Down	natriuretic peptide C
DAO	-1.85111	2.48E-09	1.58E-07	-5.96267	Down	D-amino acid oxidase
CPAMD8	-1.81242	2.23E-10	2.03E-08	-6.34426	Down	C3 and PZP like alpha-2-macroglobulin domain containing 8
CIR1P2	-1.78812	4.72E-10	3.85E-08	-6.22817	Down	CIR1 pseudogene 2
VEGFA	-1.77755	9.36E-09	4.76E-07	-5.74197	Down	vascular endothelial growth factor A
RASAL1	-1.75144	2.18E-10	1.99E-08	-6.34826	Down	RAS protein activator like 1
SYS1-DBNDD2	-1.74965	2.18E-08	9.76E-07	-5.5967	Down	SYS1-DBNDD2 readthrough (NMD candidate)

ADM	-1.74493	1.85E-10	1.75E-08	-6.37338	Down	adrenomedullin
SMIM32	-1.72996	0.000227	0.002209	-3.68712	Down	small integral membrane protein 32
IL31RA	-1.71948	3.16E-05	0.000441	-4.16133	Down	interleukin 31 receptor A
CHRM5	-1.70513	0.000132	0.001419	-3.82215	Down	cholinergic receptor muscarinic 5
CA9	-1.6961	0.00052	0.00432	-3.47013	Down	carbonic anhydrase 9
CTSV	-1.67945	4.15E-09	2.45E-07	-5.8779	Down	cathepsin V
SLC25A48	-1.67882	2.73E-12	4.32E-10	-6.99105	Down	solute carrier family 25 member 48
KCNG4	-1.67471	1.46E-07	4.80E-06	-5.25699	Down	potassium voltage-gated channel modifier subfamily G member 4
SAA2	-1.67305	6.51E-05	0.000798	-3.99357	Down	serum amyloid A2
HILPDA	-1.66926	1.50E-07	4.90E-06	-5.25282	Down	hypoxia inducible lipid droplet associated
ZNF705G	-1.66674	0.002099	0.013167	-3.07583	Down	zinc finger protein 705G
LIPC	-1.65244	1.92E-14	5.09E-12	-7.65593	Down	lipase C, hepatic type
C8orf74	-1.63296	0.004414	0.023601	-2.84698	Down	chromosome 8 open reading frame 74
MAP6D1	-1.62728	8.99E-08	3.18E-06	-5.34601	Down	MAP6 domain containing 1
COL9A3	-1.61567	6.37E-10	4.92E-08	-6.18102	Down	collagen type IX alpha 3 chain
CARNS1	-1.60946	2.28E-08	1.01E-06	-5.5892	Down	carnosine synthase 1
CR2	-1.59638	3.99E-09	2.36E-07	-5.88464	Down	complement C3d receptor 2
GACAT3	-1.58916	1.62E-05	0.000253	-4.31132	Down	gastric cancer associated transcript 3
COL9A2	-1.5776	8.27E-10	6.24E-08	-6.13958	Down	collagen type IX alpha 2 chain
HOXD1	-1.57645	0.000192	0.001932	-3.72954	Down	homeobox D1
RPS2P1	-1.57446	2.27E-05	0.000335	-4.23686	Down	ribosomal protein S2 pseudogene 1
EXD1	-1.57368	9.89E-08	3.45E-06	-5.32869	Down	exonuclease 3'-5' domain containing 1
RNU6-1160P	-1.56615	4.63E-07	1.27E-05	-5.0409	Down	RNA, U6 small nuclear 1160, pseudogene
SEMA3B	-1.56577	3.81E-11	4.38E-09	-6.61132	Down	semaphorin 3B
SAPCD2	-1.55972	4.14E-09	2.44E-07	-5.87865	Down	suppressor APC domain containing 2
INSM1	-1.55295	8.21E-07	2.04E-05	-4.9304	Down	INSM transcriptional repressor 1
USP17L1	-1.54908	1.02E-05	0.000171	-4.41202	Down	ubiquitin specific peptidase 17 like family member 1
ANGPTL4	-1.54676	3.85E-10	3.26E-08	-6.25993	Down	angiopoietin like 4
CHI3L1	-1.52703	2.86E-05	0.000406	-4.18397	Down	chitinase 3 like 1
DBNDD2	-1.51549	2.63E-08	1.15E-06	-5.56424	Down	dysbindin domain containing 2
C1orf116	-1.50814	1.31E-06	3.05E-05	-4.83869	Down	chromosome 1 open reading frame 116
TUBB4A	-1.50726	6.02E-13	1.11E-10	-7.19997	Down	tubulin beta 4A class IVa
SOX3	-1.50447	1.06E-05	0.000176	-4.40462	Down	SRY-box transcription factor 3
MAG	-1.49487	9.59E-09	4.87E-07	-5.73789	Down	myelin associated glycoprotein
TACSTD2	-1.49391	6.27E-06	0.000113	-4.51714	Down	tumor associated calcium signal transducer 2
SCNN1G	-1.4925	0.000323	0.002946	-3.59583	Down	sodium channel epithelial 1 subunit gamma
AATK	-1.48396	4.36E-07	1.20E-05	-5.05236	Down	apoptosis associated tyrosine kinase
GCM1	-1.47853	0.000469	0.003975	-3.49777	Down	glial cells missing transcription factor 1
PRODH	-1.47777	0.000856	0.006465	-3.33407	Down	proline dehydrogenase 1
SCART1	-1.46813	3.45E-12	5.26E-10	-6.95791	Down	scavenger receptor family member expressed on T cells 1
RPS2P30	-1.46804	2.80E-06	5.76E-05	-4.68509	Down	ribosomal protein S2 pseudogene 30
CHP2	-1.46103	6.24E-05	0.000772	-4.00345	Down	calcineurin like EF-hand protein 2

CYP1D1P	-1.45656	9.56E-06	0.000162	-4.42679	Down	cytochrome P450 family 1 subfamily D member 1, pseudogene
CHADL	-1.45485	4.76E-06	8.95E-05	-4.57529	Down	chondroadherin like
GPR142	-1.44715	0.002327	0.014298	-3.04493	Down	G protein-coupled receptor 142
LDB3	-1.44172	5.69E-09	3.17E-07	-5.82568	Down	LIM domain binding 3
CNP	-1.43958	4.57E-09	2.64E-07	-5.86196	Down	2',3'-cyclic nucleotide 3' phosphodiesterase
GPD1	-1.43924	1.66E-06	3.71E-05	-4.79136	Down	glycerol-3-phosphate dehydrogenase 1
FAM53A	-1.43394	7.66E-08	2.79E-06	-5.37493	Down	family with sequence similarity 53 member A
SCHIP1	-1.4323	5.93E-10	4.67E-08	-6.19224	Down	schwannomin interacting protein 1
PRR18	-1.43204	1.47E-11	1.87E-09	-6.75125	Down	proline rich 18
PKD1L2	-1.43021	2.05E-10	1.89E-08	-6.35734	Down	polycystin 1 like 2 (gene/pseudogene)
BMP8A	-1.42783	6.42E-06	0.000115	-4.51205	Down	bone morphogenetic protein 8a
TBATA	-1.42227	0.005126	0.026449	-2.79899	Down	thymus, brain and testes associated
ACP7	-1.42143	6.42E-06	0.000115	-4.51206	Down	acid phosphatase 7, tartrate resistant (putative)
CPB1	-1.41151	1.18E-10	1.18E-08	-6.44218	Down	carboxypeptidase B1
DMBT1	-1.40963	4.05E-07	1.13E-05	-5.06664	Down	deleted in malignant brain tumors 1
KBTBD11-OT1	-1.40851	5.83E-14	1.38E-11	-7.5119	Down	KBTBD11 overlapping transcript 1
BTG4	-1.39705	1.19E-05	0.000196	-4.37852	Down	BTG anti-proliferation factor 4
ZP3P1	-1.39348	0.000496	0.004154	-3.48297	Down	ZP3 pseudogene 1
FOXE1	-1.39161	5.34E-05	0.000682	-4.04025	Down	forkhead box E1
HMGB1P43	-1.39063	0.011328	0.048074	-2.53241	Down	high mobility group box 1 pseudogene 43
MAP1LC3B2	-1.39043	9.11E-10	6.71E-08	-6.12423	Down	microtubule associated protein 1 light chain 3 beta 2
PDIA2	-1.39039	4.72E-05	0.000614	-4.06884	Down	protein disulfide isomerase family A member 2
OR2K2	-1.38589	0.000106	0.001192	-3.87698	Down	olfactory receptor family 2 subfamily K member 2
WASH8P	-1.38517	3.11E-10	2.72E-08	-6.29321	Down	WAS protein family homolog 8, pseudogene
OPLAH	-1.37796	3.15E-07	9.16E-06	-5.1142	Down	5-oxoprolinase, ATP-hydrolysing
HES6	-1.37734	2.85E-06	5.85E-05	-4.68151	Down	hes family bHLH transcription factor 6
COL11A2	-1.37719	3.97E-09	2.36E-07	-5.8855	Down	collagen type XI alpha 2 chain
RPL26P18	-1.37191	0.003986	0.021822	-2.87923	Down	ribosomal protein L26 pseudogene 18
TRPV6	-1.37042	1.53E-15	5.38E-13	-7.97437	Down	transient receptor potential cation channel subfamily V member 6
RNU6-913P	-1.36459	0.000116	0.001273	-3.85534	Down	RNA, U6 small nuclear 913, pseudogene
CDH1	-1.35955	2.46E-06	5.15E-05	-4.71141	Down	cadherin 1
RABGEF1	-1.35858	6.90E-14	1.60E-11	-7.48975	Down	RAB guanine nucleotide exchange factor 1
FTCD	-1.35811	5.92E-06	0.000107	-4.52907	Down	formimidoyltransferase cyclodeaminase
ARC	-1.35638	0.000132	0.001418	-3.82262	Down	activity regulated cytoskeleton associated protein
RN7SL520P	-1.35291	2.78E-05	0.000395	-4.19115	Down	RNA, 7SL, cytoplasmic 520, pseudogene
SREBF1	-1.35236	3.84E-10	3.26E-08	-6.26023	Down	sterol regulatory element binding transcription factor 1
TMTC4	-1.35104	2.82E-12	4.45E-10	-6.98634	Down	transmembrane O-mannosyltransferase targeting cadherins 4
GDF2	-1.35047	0.00945	0.041907	-2.59532	Down	growth differentiation factor 2
RN7SKP145	-1.34966	0.007267	0.034367	-2.68438	Down	RN7SK pseudogene 145
CPHXL	-1.34658	9.52E-10	6.94E-08	-6.11722	Down	cytoplasmic polyadenylated homeobox like
ABCF2P1	-1.34609	6.24E-05	0.000772	-4.00338	Down	ATP binding cassette subfamily F member 2 pseudogene 1

RNU6-871P	-1.3446	5.86E-05	0.000733	-4.01851	Down	RNA, U6 small nuclear 871, pseudogene
PYY2	-1.34242	0.001853	0.011924	-3.11276	Down	peptide YY 2 (pseudogene)
LIPE	-1.33945	6.74E-08	2.49E-06	-5.39807	Down	lipase E, hormone sensitive type
RN7SL808P	-1.33791	0.005177	0.026632	-2.79578	Down	RNA, 7SL, cytoplasmic 808, pseudogene
FAM178B	-1.33665	1.47E-07	4.80E-06	-5.25679	Down	family with sequence similarity 178 member B
COL16A1	-1.33577	2.73E-08	1.18E-06	-5.5578	Down	collagen type XVI alpha 1 chain
TXNDC8	-1.3356	0.008816	0.039772	-2.6191	Down	thioredoxin domain containing 8
CNDP1	-1.32376	3.30E-09	2.01E-07	-5.91585	Down	carnosine dipeptidase 1
DHCR7	-1.31902	1.10E-09	7.89E-08	-6.0937	Down	7-dehydrocholesterol reductase
GLOD5	-1.31444	0.008251	0.037863	-2.64162	Down	glyoxalase domain containing 5
FXYD4	-1.3054	1.96E-05	0.000296	-4.26995	Down	FXYD domain containing ion transport regulator 4
RNU6-448P	-1.29755	0.000886	0.006645	-3.32442	Down	RNA, U6 small nuclear 448, pseudogene
KIF19	-1.29668	9.09E-06	0.000155	-4.4378	Down	kinesin family member 19
SSPOP	-1.28665	1.82E-06	4.00E-05	-4.77245	Down	SCO-spondin, pseudogene
KCNE5	-1.28331	0.000132	0.001419	-3.82237	Down	potassium voltage-gated channel subfamily E regulatory subunit 5
GALNT6	-1.28089	7.63E-08	2.78E-06	-5.37557	Down	polypeptide N-acetylgalactosaminyltransferase 6
MARCKSL1	-1.27718	2.96E-13	5.96E-11	-7.29603	Down	MARCKS like 1
PTPRVP	-1.27707	0.000509	0.004249	-3.47574	Down	protein tyrosine phosphatase receptor type V, pseudogene
LLCFC1	-1.27694	2.58E-07	7.78E-06	-5.15203	Down	LLLL and CFNLAS motif containing 1
SEC14L5	-1.27009	2.77E-08	1.20E-06	-5.55509	Down	SEC14 like lipid binding 5
ZNF536	-1.26683	9.24E-10	6.78E-08	-6.12198	Down	zinc finger protein 536
HAGHL	-1.26683	2.35E-06	4.97E-05	-4.72094	Down	hydroxyacylglutathione hydrolase like
CMTM5	-1.26256	8.45E-06	0.000145	-4.45353	Down	CKLF like MARVEL transmembrane domain containing 5
MAP1LC3A	-1.26085	2.02E-08	9.14E-07	-5.61058	Down	microtubule associated protein 1 light chain 3 alpha
KCNH8	-1.25847	8.45E-10	6.34E-08	-6.13626	Down	potassium voltage-gated channel subfamily H member 8
KRT8P7	-1.25462	0.001897	0.012139	-3.10594	Down	keratin 8 pseudogene 7
GJB1	-1.25104	1.61E-06	3.62E-05	-4.79718	Down	gap junction protein beta 1
PLXNB3	-1.25085	1.30E-05	0.000211	-4.35928	Down	plexin B3
HSF4	-1.24951	7.66E-08	2.79E-06	-5.375	Down	heat shock transcription factor 4
AGPAT4	-1.2483	2.57E-14	6.60E-12	-7.61852	Down	1-acylglycerol-3-phosphate O-acyltransferase 4
OLIG2	-1.2468	6.55E-09	3.55E-07	-5.80216	Down	oligodendrocyte transcription factor 2
FAM66B	-1.2459	1.27E-09	8.83E-08	-6.07177	Down	family with sequence similarity 66 member B
MT1X	-1.24513	4.34E-09	2.54E-07	-5.87081	Down	metallothionein 1X
MAL	-1.24447	3.18E-09	1.95E-07	-5.92201	Down	mal, T cell differentiation protein
HIP1R	-1.24233	3.09E-09	1.91E-07	-5.92669	Down	huntingtin interacting protein 1 related
RAB7B	-1.23808	5.56E-09	3.13E-07	-5.82942	Down	RAB7B, member RAS oncogene family
SLC16A8	-1.23674	2.52E-05	0.000365	-4.213	Down	solute carrier family 16 member 8
KLK8	-1.23402	0.009277	0.041343	-2.60167	Down	kallikrein related peptidase 8
C5orf64	-1.2318	3.15E-12	4.89E-10	-6.9707	Down	chromosome 5 putative open reading frame 64
PLCH2	-1.23176	4.91E-07	1.33E-05	-5.02999	Down	phospholipase C eta 2
PLLP	-1.23035	3.30E-09	2.01E-07	-5.91604	Down	plasmolipin
RPL21P87	-1.22842	7.77E-05	0.000924	-3.95131	Down	ribosomal protein L21 pseudogene 87

CUEDC1	-1.22447	4.17E-08	1.69E-06	-5.48359	Down	CUE domain containing 1
SLC36A3	-1.20856	0.003125	0.018073	-2.95512	Down	solute carrier family 36 member 3
GTSCR1	-1.20661	1.31E-06	3.05E-05	-4.83825	Down	Gilles de la Tourette syndrome chromosome region, candidate 1
SLC5A11	-1.20504	2.04E-06	4.40E-05	-4.74955	Down	solute carrier family 5 member 11
USH1C	-1.20258	4.00E-07	1.12E-05	-5.06895	Down	USH1 protein network component harmonin
IGSF8	-1.2002	1.63E-06	3.66E-05	-4.79464	Down	immunoglobulin superfamily member 8
AQP6	-1.19959	4.38E-05	0.000576	-4.0865	Down	aquaporin 6
TRPV5	-1.19788	9.50E-08	3.34E-06	-5.336	Down	transient receptor potential cation channel subfamily V member 5
SAA1	-1.19714	0.011799	0.049583	-2.51809	Down	serum amyloid A1
PACSIN3	-1.19589	7.99E-09	4.18E-07	-5.76869	Down	protein kinase C and casein kinase substrate in neurons 3
CDKN1C	-1.18913	8.26E-08	2.97E-06	-5.36142	Down	cyclin dependent kinase inhibitor 1C
RPS17P2	-1.18857	0.00053	0.004384	-3.46497	Down	ribosomal protein S17 pseudogene 2
TMEM125	-1.18801	7.43E-06	0.00013	-4.48097	Down	transmembrane protein 125
CDC42EP1	-1.18648	3.05E-05	0.000427	-4.16995	Down	CDC42 effector protein 1
SH3BP5	-1.18398	1.02E-10	1.05E-08	-6.46359	Down	SH3 domain binding protein 5
NKX6-2	-1.18193	5.91E-06	0.000107	-4.52958	Down	NK6 homeobox 2
GREB1L	-1.18126	1.52E-13	3.24E-11	-7.38512	Down	GREB1 like retinoic acid receptor coactivator
ADSS1	-1.18068	5.13E-09	2.92E-07	-5.84296	Down	adenylosuccinate synthase 1
SNHG18	-1.18066	4.72E-12	6.84E-10	-6.91373	Down	small nucleolar RNA host gene 18
TKTL1	-1.18012	0.002703	0.016157	-2.99969	Down	transketolase like 1
ACSBG1	-1.17794	3.08E-11	3.68E-09	-6.64263	Down	acyl-CoA synthetase bubblegum family member 1
TSC22D4	-1.17652	1.37E-06	3.16E-05	-4.8299	Down	TSC22 domain family member 4
CFTR	-1.17646	8.77E-10	6.54E-08	-6.13031	Down	CF transmembrane conductance regulator
INSIG1	-1.17271	2.88E-12	4.52E-10	-6.98354	Down	insulin induced gene 1
NDUFB4P10	-1.17243	4.01E-06	7.76E-05	-4.61107	Down	NADH:ubiquinone oxidoreductase subunit B4 pseudogene 10
ZNF775	-1.16714	2.67E-05	0.000383	-4.19988	Down	zinc finger protein 775
OXCT2P1	-1.16652	6.87E-05	0.000833	-3.9809	Down	3-oxoacid CoA-transferase 2 pseudogene 1
OR13A1	-1.16053	0.00028	0.002632	-3.63357	Down	olfactory receptor family 13 subfamily A member 1
SRCIN1	-1.15582	1.39E-06	3.21E-05	-4.82642	Down	SRC kinase signaling inhibitor 1
MTCO2P16	-1.15506	0.001228	0.00863	-3.23224	Down	MT-CO2 pseudogene 16
HSD17B3	-1.15395	1.27E-08	6.17E-07	-5.69005	Down	hydroxysteroid 17-beta dehydrogenase 3
TNFAIP6	-1.15327	2.08E-09	1.36E-07	-5.99131	Down	TNF alpha induced protein 6
TMEM151A	-1.15207	0.000192	0.001933	-3.72916	Down	transmembrane protein 151A
SMG1P5	-1.15115	2.88E-10	2.54E-08	-6.30498	Down	SMG1 pseudogene 5
ACADS	-1.15036	6.18E-05	0.000765	-4.00585	Down	acyl-CoA dehydrogenase short chain
TMCO5A	-1.14873	0.000199	0.001989	-3.72015	Down	transmembrane and coiled-coil domains 5A
RPL21P98	-1.14841	0.001034	0.007526	-3.28099	Down	ribosomal protein L21 pseudogene 98
CALB2	-1.1453	0.000608	0.004905	-3.42785	Down	calbindin 2
ALDOC	-1.14393	9.75E-09	4.92E-07	-5.73495	Down	aldolase, fructose-bisphosphate C
PTPRH	-1.14327	1.61E-06	3.63E-05	-4.79659	Down	protein tyrosine phosphatase receptor type H
GREM1	-1.14058	2.91E-07	8.57E-06	-5.12917	Down	gremlin 1, DAN family BMP antagonist
VWA1	-1.13959	1.87E-05	0.000284	-4.2803	Down	von Willebrand factor A domain containing 1

SEPHS1P6	-1.13752	8.58E-08	3.06E-06	-5.35454	Down	selenophosphate synthetase 1 pseudogene 6
CES4A	-1.13652	5.61E-08	2.17E-06	-5.43093	Down	carboxylesterase 4A
CT69	-1.13517	1.61E-08	7.58E-07	-5.64948	Down	cancer/testis associated transcript 69
DUXB	-1.13504	2.91E-08	1.24E-06	-5.54674	Down	double homeobox B
CERCAM	-1.13131	6.41E-05	0.000789	-3.9971	Down	cerebral endothelial cell adhesion molecule
RBP7	-1.13025	2.93E-09	1.83E-07	-5.93556	Down	retinol binding protein 7
ADAP1	-1.13024	0.000467	0.003964	-3.4988	Down	ArfGAP with dual PH domains 1
ATF3	-1.1283	5.77E-05	0.000725	-4.02211	Down	activating transcription factor 3
ABCA2	-1.12624	6.76E-07	1.73E-05	-4.96812	Down	ATP binding cassette subfamily A member 2
USP17L8	-1.12353	0.001162	0.008267	-3.24797	Down	ubiquitin specific peptidase 17 like family member 8
SGK2	-1.12215	4.14E-11	4.71E-09	-6.59897	Down	serum/glucocorticoid regulated kinase 2
PLEKHG3	-1.12182	8.96E-08	3.17E-06	-5.34667	Down	pleckstrin homology and RhoGEF domain containing G3
HK2	-1.11819	5.19E-07	1.39E-05	-5.01908	Down	hexokinase 2
MCAM	-1.11676	1.87E-08	8.57E-07	-5.6239	Down	melanoma cell adhesion molecule
CLUHP6	-1.1163	0.000212	0.002092	-3.70383	Down	clustered mitochondria homolog pseudogene 6
GLDN	-1.116	2.24E-06	4.78E-05	-4.73018	Down	gliomedin
GPR37	-1.11385	3.94E-09	2.35E-07	-5.88683	Down	G protein-coupled receptor 37
RAB33A	-1.11375	8.65E-08	3.08E-06	-5.35304	Down	RAB33A, member RAS oncogene family
EFS	-1.11365	7.10E-06	0.000125	-4.49068	Down	embryonal Fyn-associated substrate
IFNA2	-1.11336	0.001008	0.007372	-3.28835	Down	interferon alpha 2
OR1L4	-1.11121	0.000382	0.003368	-3.55215	Down	olfactory receptor family 1 subfamily L member 4
KLK10	-1.11115	0.001556	0.010385	-3.16409	Down	kallikrein related peptidase 10
SPINK14	-1.10969	0.001417	0.009666	-3.19123	Down	serine peptidase inhibitor Kazal type 14 (putative)
ADAT3	-1.10248	0.00613	0.030286	-2.74077	Down	adenosine deaminase tRNA specific 3
HPDL	-1.09775	0.000373	0.003301	-3.55838	Down	4-hydroxyphenylpyruvate dioxygenase like
SEMA4D	-1.09761	9.11E-12	1.22E-09	-6.81991	Down	semaphorin 4D
TAS2R40	-1.09749	3.29E-08	1.37E-06	-5.5254	Down	taste 2 receptor member 40
SCD	-1.09633	1.55E-09	1.05E-07	-6.03958	Down	stearoyl-CoA desaturase
NGFR	-1.09596	0.000633	0.005065	-3.41718	Down	nerve growth factor receptor
FFAR1	-1.09551	0.000539	0.004445	-3.46048	Down	free fatty acid receptor 1
NTNG2	-1.09364	1.86E-07	5.87E-06	-5.21246	Down	netrin G2
ATP8B5P	-1.09325	6.11E-07	1.59E-05	-4.98778	Down	ATPase phospholipid transporting 8B5, pseudogene
HAS1	-1.08963	0.001462	0.00991	-3.18214	Down	hyaluronan synthase 1
BOLA3P4	-1.0893	0.000269	0.002552	-3.64336	Down	bolA family member 3 pseudogene 4
SCAND1	-1.08879	0.000102	0.001155	-3.88687	Down	SCAN domain containing 1
KEL	-1.08795	9.34E-07	2.29E-05	-4.90498	Down	Kell metallo-endopeptidase (Kell blood group)
TF	-1.08614	4.45E-06	8.49E-05	-4.58907	Down	transferrin
GLUL	-1.08529	3.35E-13	6.59E-11	-7.27937	Down	glutamate-ammonia ligase
DMRTA2	-1.08454	0.00027	0.002555	-3.64292	Down	DMRT like family A2
HCN2	-1.08452	1.22E-05	0.000199	-4.37429	Down	hyperpolarization activated cyclic nucleotide gated potassium and sodium channel 2
KREMEN2	-1.08396	0.008639	0.039188	-2.62603	Down	kringle containing transmembrane protein 2
PCBP4	-1.08211	8.02E-07	2.00E-05	-4.93481	Down	poly(rC) binding protein 4

GNG8	-1.07967	0.001042	0.007573	-3.279	Down	G protein subunit gamma 8
PET117	-1.07921	0.005362	0.027322	-2.78442	Down	PET117 cytochrome c oxidase chaperone
ARSI	-1.0763	0.000273	0.002582	-3.63973	Down	arylsulfatase family member I
VN1R83P	-1.07587	9.23E-12	1.23E-09	-6.81808	Down	vomeronasal 1 receptor 83 pseudogene
DMRT2	-1.07541	1.45E-06	3.33E-05	-4.81741	Down	doublesex and mab-3 related transcription factor 2
AOX1	-1.07437	3.88E-13	7.49E-11	-7.25956	Down	aldehyde oxidase 1
VN1R12P	-1.07392	0.000468	0.003966	-3.49847	Down	vomeronasal 1 receptor 12, pseudogene
PALM2AKAP2	-1.07266	0.004208	0.022746	-2.86215	Down	PALM2 and AKAP2 fusion
TM7SF2	-1.07245	8.68E-08	3.09E-06	-5.35232	Down	transmembrane 7 superfamily member 2
OR2AE1	-1.07197	0.000663	0.005256	-3.40454	Down	olfactory receptor family 2 subfamily AE member 1
S1PR5	-1.07064	1.03E-06	2.49E-05	-4.88548	Down	sphingosine-1-phosphate receptor 5
SKOR1	-1.07037	5.11E-07	1.37E-05	-5.02203	Down	SKI family transcriptional corepressor 1
ROGDI	-1.06973	4.00E-06	7.76E-05	-4.61115	Down	rogdi atypical leucine zipper
C1orf122	-1.06792	0.000133	0.001425	-3.82084	Down	chromosome 1 open reading frame 122
ELF3	-1.06694	0.006759	0.032606	-2.70851	Down	E74 like ETS transcription factor 3
GLULP1	-1.06518	0.00391	0.021524	-2.88533	Down	glutamate-ammonia ligase pseudogene 1
RNU5D-1	-1.06486	0.000254	0.002435	-3.65774	Down	RNA, U5D small nuclear 1
PLEKHG4	-1.06471	7.68E-05	0.000916	-3.95429	Down	pleckstrin homology and RhoGEF domain containing G4
TPRN	-1.06362	0.000202	0.002014	-3.71595	Down	taperin
ZNF367	-1.06358	2.10E-08	9.47E-07	-5.60353	Down	zinc finger protein 367
NACAD	-1.06132	1.53E-05	0.00024	-4.32504	Down	NAC alpha domain containing
HMSD	-1.06044	5.81E-09	3.20E-07	-5.82213	Down	histocompatibility minor serpin domain containing
HAPLN2	-1.05998	0.000179	0.001822	-3.74747	Down	hyaluronan and proteoglycan link protein 2
LLGL2	-1.05978	5.41E-05	0.000689	-4.03729	Down	LLGL scribble cell polarity complex component 2
SYNJ2	-1.0597	2.16E-09	1.39E-07	-5.98562	Down	synaptojanin 2
GOLGA6A	-1.05921	0.00096	0.007093	-3.30197	Down	golgin A6 family member A
MYCN	-1.05745	1.41E-09	9.61E-08	-6.05467	Down	MYCN proto-oncogene, bHLH transcription factor
HPN	-1.05702	7.64E-05	0.000913	-3.95536	Down	hepsin
SHC2	-1.05563	0.000168	0.001731	-3.76322	Down	SHC adaptor protein 2
FN3K	-1.05529	2.10E-09	1.37E-07	-5.99005	Down	fructosamine 3 kinase
IFNA13	-1.05056	0.002515	0.015217	-3.02148	Down	interferon alpha 13
SERPINE3	-1.04996	8.55E-07	2.12E-05	-4.92236	Down	serpin family E member 3
TLE2	-1.04971	1.42E-05	0.000227	-4.34026	Down	TLE family member 2, transcriptional corepressor
MYRF	-1.04962	2.41E-06	5.07E-05	-4.71565	Down	myelin regulatory factor
GAMT	-1.04568	5.35E-06	9.88E-05	-4.55057	Down	guanidinoacetate N-methyltransferase
TREH	-1.04504	7.17E-05	0.000865	-3.97041	Down	trehalase
MEIS1	-1.04497	1.45E-13	3.11E-11	-7.39188	Down	Meis homeobox 1
COL6A4P1	-1.04494	0.002048	0.012905	-3.08321	Down	collagen type VI alpha 4 pseudogene 1
OR5C1	-1.04369	0.000393	0.003449	-3.54464	Down	olfactory receptor family 5 subfamily C member 1
DUXAP9	-1.04104	0.001512	0.010169	-3.17238	Down	double homeobox A pseudogene 9
SPANXA2-OT1	-1.0401	2.18E-05	0.000324	-4.24578	Down	SPANXA2 overlapping transcript 1
BNC1	-1.03976	0.001374	0.009453	-3.19997	Down	basonuclin 1

HCRTR1	-1.03799	0.00132	0.009159	-3.21168	Down	hypocretin receptor 1
MOG	-1.03632	4.45E-06	8.48E-05	-4.5894	Down	myelin oligodendrocyte glycoprotein
SBF1	-1.03609	1.35E-05	0.000217	-4.35224	Down	SET binding factor 1
ADAMTS4	-1.03468	1.91E-05	0.00029	-4.27468	Down	ADAM metallopeptidase with thrombospondin type 1 motif 4
CA14	-1.03434	1.20E-05	0.000196	-4.37831	Down	carbonic anhydrase 14
INF2	-1.03405	4.82E-05	0.000625	-4.06405	Down	inverted formin 2
RPS7P6	-1.02978	0.007576	0.035453	-2.67041	Down	ribosomal protein S7 pseudogene 6
TMEM171	-1.02953	0.000624	0.005007	-3.42099	Down	transmembrane protein 171
OSBPL5	-1.02719	1.63E-06	3.66E-05	-4.79442	Down	oxysterol binding protein like 5
BIN1	-1.02589	8.26E-06	0.000142	-4.45834	Down	bridging integrator 1
NME3	-1.02561	0.000868	0.006538	-3.33023	Down	NME/NM23 nucleoside diphosphate kinase 3
CDK18	-1.02418	6.65E-07	1.71E-05	-4.97123	Down	cyclin dependent kinase 18
RAB6C	-1.02323	6.07E-07	1.59E-05	-4.98886	Down	RAB6C, member RAS oncogene family
PTPDC1	-1.02128	4.67E-16	2.02E-13	-8.11983	Down	protein tyrosine phosphatase domain containing 1
ARL2BP	-1.02123	0.009939	0.043518	-2.57796	Down	ADP ribosylation factor like GTPase 2 binding protein
FSCN1	-1.02095	4.83E-06	9.07E-05	-4.57224	Down	fascin actin-bundling protein 1
TEX45	-1.01757	0.000455	0.00388	-3.50599	Down	testis expressed 45
F11	-1.01421	0.006907	0.033157	-2.70129	Down	coagulation factor XI
RNU6-539P	-1.01311	0.008659	0.039248	-2.62523	Down	RNA, U6 small nuclear 539, pseudogene
TP53TG5	-1.01256	7.85E-11	8.30E-09	-6.50339	Down	TP53 target 5
BNIP3P30	-1.01107	0.00119	0.008419	-3.24138	Down	BCL2 interacting protein 3 pseudogene 30
MTFR2	-1.01087	0.001029	0.007494	-3.28244	Down	mitochondrial fission regulator 2
RHOU	-1.01083	1.94E-10	1.81E-08	-6.36576	Down	ras homolog family member U
STMN4	-1.01036	5.09E-06	9.49E-05	-4.561	Down	stathmin 4
GOLGA6B	-1.01012	0.003058	0.017791	-2.96182	Down	golgin A6 family member B
ACAA2P1	-1.00787	0.000293	0.002727	-3.62156	Down	ACAA2 pseudogene 1
DIPK1C	-1.00776	6.63E-08	2.47E-06	-5.40089	Down	divergent protein kinase domain 1C
PAQR4	-1.00722	0.000513	0.00427	-3.47391	Down	progestin and adipoQ receptor family member 4
RNASE1	-1.00569	5.03E-06	9.41E-05	-4.56333	Down	ribonuclease A family member 1, pancreatic
RN7SKP112	-1.00383	0.011031	0.04716	-2.54171	Down	RN7SK pseudogene 112
GNLY	-1.00246	0.00111	0.007953	-3.26115	Down	granulysin
MVK	-1.00215	2.64E-07	7.92E-06	-5.14755	Down	mevalonate kinase
SH3PXD2B	-1.00066	4.24E-08	1.71E-06	-5.48036	Down	SH3 and PX domains 2B
MKRN3	-0.99835	6.32E-11	6.83E-09	-6.53594	Down	makorin ring finger protein 3
BMP2	-0.99813	1.39E-06	3.21E-05	-4.8262	Down	bone morphogenetic protein 2
HSPA2	-0.99499	2.36E-05	0.000347	-4.2275	Down	heat shock protein family A (Hsp70) member 2
GPIHBP1	-0.99465	0.000366	0.003255	-3.56314	Down	glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1
CUTALP	-0.99364	4.70E-11	5.28E-09	-6.5801	Down	cutA divalent cation tolerance like, pseudogene
LMNA	-0.99073	4.46E-06	8.49E-05	-4.58883	Down	lamin A/C
FAM21FP	-0.99019	0.000411	0.003574	-3.53276	Down	family with sequence similarity 21 member F, pseudogene
PLA2G4C	-0.98917	1.28E-08	6.21E-07	-5.68874	Down	phospholipase A2 group IVC
ERBB3	-0.98788	7.80E-08	2.83E-06	-5.37173	Down	erb-b2 receptor tyrosine kinase 3

KIRREL2	-0.9864	0.001412	0.009651	-3.1921	Down	kirre like nephrin family adhesion molecule 2
EQTN	-0.98575	3.23E-05	0.000449	-4.15668	Down	equatorin
HSD11B1	-0.98561	1.31E-05	0.000212	-4.35873	Down	hydroxysteroid 11-beta dehydrogenase 1
GCAWKR	-0.98395	2.96E-07	8.68E-06	-5.12591	Down	gastric cancer associated WDR5 and KAT2A binding lncRNA
HTRA1	-0.98379	6.06E-08	2.29E-06	-5.41709	Down	HtrA serine peptidase 1
DLL1	-0.98191	1.74E-06	3.85E-05	-4.78204	Down	delta like canonical Notch ligand 1
C22orf23	-0.98123	0.000159	0.001654	-3.77704	Down	chromosome 22 open reading frame 23
EEPD1	-0.98041	5.70E-08	2.19E-06	-5.42782	Down	endonuclease/exonuclease/phosphatase family domain containing 1
RHBG	-0.97935	0.000155	0.001625	-3.78216	Down	Rh family B glycoprotein
NKX2-2	-0.97848	2.50E-05	0.000363	-4.21466	Down	NK2 homeobox 2
BNIP3P22	-0.97812	0.002088	0.013104	-3.07747	Down	BCL2 interacting protein 3 pseudogene 22
PTGDS	-0.97717	8.64E-05	0.001009	-3.92579	Down	prostaglandin D2 synthase
PFKL	-0.9767	3.38E-08	1.40E-06	-5.52059	Down	phosphofructokinase, liver type
CPHXL2	-0.97544	2.43E-05	0.000354	-4.22153	Down	cytoplasmic polyadenylated homeobox like 2
RNU6-883P	-0.9742	0.001176	0.00834	-3.24469	Down	RNA, U6 small nuclear 883, pseudogene
EVA1A	-0.97408	0.000787	0.006044	-3.35718	Down	eva-1 homolog A, regulator of programmed cell death
LMF1	-0.97228	7.95E-06	0.000138	-4.46645	Down	lipase maturation factor 1
THBS2	-0.96985	4.42E-07	1.22E-05	-5.04971	Down	thrombospondin 2
SH3TC2	-0.96976	1.00E-06	2.44E-05	-4.89076	Down	SH3 domain and tetratricopeptide repeats 2
NHLH2	-0.96855	4.32E-10	3.56E-08	-6.24193	Down	nescient helix-loop-helix 2
IGSF1	-0.96849	3.90E-06	7.59E-05	-4.6165	Down	immunoglobulin superfamily member 1
SH3TC2-DT	-0.96743	8.97E-08	3.17E-06	-5.34653	Down	SH3TC2 divergent transcript
SDCBPP1	-0.96429	0.000598	0.004835	-3.43258	Down	syndecan binding protein pseudogene 1
PEBP4	-0.96338	0.005803	0.029036	-2.75872	Down	phosphatidylethanolamine binding protein 4
PIWIL2	-0.96277	2.52E-12	4.07E-10	-7.00245	Down	piwi like RNA-mediated gene silencing 2
PLEKHH1	-0.96265	2.32E-07	7.07E-06	-5.17191	Down	pleckstrin homology, MyTH4 and FERM domain containing H1
CDR2L	-0.96189	2.61E-05	0.000376	-4.20535	Down	cerebellar degeneration related protein 2 like
MT1G	-0.96078	0.006926	0.033214	-2.70038	Down	metallothionein 1G
GADD45B	-0.96044	0.00068	0.005367	-3.39734	Down	growth arrest and DNA damage inducible beta
APLP1	-0.95975	1.23E-06	2.90E-05	-4.85033	Down	amyloid beta precursor like protein 1
ST3GAL4	-0.95865	2.32E-06	4.92E-05	-4.72321	Down	ST3 beta-galactoside alpha-2,3-sialyltransferase 4
PHLDB1	-0.95847	1.10E-05	0.000183	-4.39583	Down	pleckstrin homology like domain family B member 1
GASK1A	-0.95807	2.90E-08	1.23E-06	-5.54764	Down	golgi associated kinase 1A
IFNA11P	-0.9562	0.006539	0.031756	-2.71946	Down	interferon alpha 11, pseudogene
FGF11	-0.95394	3.13E-05	0.000437	-4.16414	Down	fibroblast growth factor 11
CELP	-0.9536	0.006239	0.030684	-2.73497	Down	carboxyl ester lipase pseudogene
OR7M1P	-0.95184	0.000328	0.002978	-3.59229	Down	olfactory receptor family 7 subfamily M member 1 pseudogene
SHB	-0.95102	5.54E-07	1.47E-05	-5.00661	Down	SH2 domain containing adaptor protein B
UNC5B	-0.95086	7.25E-06	0.000127	-4.48629	Down	unc-5 netrin receptor B
ENOSF1	-0.95059	2.07E-07	6.44E-06	-5.19266	Down	enolase superfamily member 1
RPL18AP11	-0.95045	0.000115	0.001267	-3.85682	Down	ribosomal protein L18a pseudogene 11

MYH6	-0.94772	0.000502	0.004193	-3.47992	Down	myosin heavy chain 6
CPA2	-0.94756	0.001466	0.009934	-3.18136	Down	carboxypeptidase A2
KIAA0087	-0.94673	0.000496	0.004154	-3.48286	Down	KIAA0087 lncRNA
CNPY1	-0.94622	0.008357	0.03822	-2.63728	Down	canopy FGF signaling regulator 1
SNX22	-0.94612	1.54E-05	0.000242	-4.32328	Down	sorting nexin 22
NKAIN4	-0.94576	9.87E-05	0.001126	-3.89383	Down	sodium/potassium transporting ATPase interacting 4
TRAPPC13P1	-0.94569	0.004002	0.021882	-2.87797	Down	trafficking protein particle complex 13 pseudogene 1
ASPA	-0.94357	7.00E-09	3.73E-07	-5.79102	Down	aspartoacylase
CIRBP	-0.94321	5.90E-08	2.26E-06	-5.4218	Down	cold inducible RNA binding protein
CYP26C1	-0.94295	0.001299	0.009041	-3.21617	Down	cytochrome P450 family 26 subfamily C member 1
FASN	-0.94282	9.91E-06	0.000166	-4.41909	Down	fatty acid synthase
MRI1	-0.94276	7.70E-07	1.93E-05	-4.94285	Down	methylthioribose-1-phosphate isomerase 1
RASSF2	-0.94155	7.28E-10	5.53E-08	-6.15981	Down	Ras association domain family member 2
PPP2R2B-IT1	-0.94033	5.79E-09	3.20E-07	-5.82274	Down	PPP2R2B intronic transcript 1
CRB2	-0.93983	0.000441	0.003791	-3.51407	Down	crumbs cell polarity complex component 2
MAN1B1-DT	-0.93874	4.92E-05	0.000635	-4.05954	Down	MAN1B1 divergent transcript
GIPC1	-0.93779	1.39E-07	4.60E-06	-5.26592	Down	GIPC PDZ domain containing family member 1
PNPLA3	-0.93702	0.000457	0.003893	-3.5046	Down	patatin like phospholipase domain containing 3
LSS	-0.93642	1.41E-07	4.64E-06	-5.26417	Down	lanosterol synthase
BTBD16	-0.9358	9.04E-06	0.000154	-4.43891	Down	BTB domain containing 16
DHRS13	-0.93563	0.000134	0.001436	-3.81845	Down	dehydrogenase/reductase 13
GPR62	-0.93533	0.000184	0.001868	-3.7394	Down	G protein-coupled receptor 62
FAM170A	-0.93455	0.011451	0.048423	-2.52861	Down	family with sequence similarity 170 member A
LGI3	-0.93188	4.12E-06	7.95E-05	-4.60543	Down	leucine rich repeat LGI family member 3
ACTN2	-0.93164	1.81E-08	8.36E-07	-5.62918	Down	actinin alpha 2
PRKCQ	-0.93126	3.06E-08	1.30E-06	-5.53787	Down	protein kinase C theta
MMP15	-0.93064	7.82E-05	0.000928	-3.94991	Down	matrix metallopeptidase 15
CLUL1	-0.92888	0.000432	0.003727	-3.51962	Down	clusterin like 1
LLGL1	-0.92882	3.44E-05	0.000474	-4.14203	Down	LLGL scribble cell polarity complex component 1
CBR1	-0.92716	6.69E-10	5.12E-08	-6.17335	Down	carbonyl reductase 1
PRODH	-0.92655	0.000754	0.005832	-3.36927	Down	proline dehydrogenase 1
MT1M	-0.92632	3.89E-05	0.000523	-4.11397	Down	metallothionein 1M
ARHGAP23	-0.92549	4.34E-06	8.30E-05	-4.59464	Down	Rho GTPase activating protein 23
SAMMSON	-0.92401	0.003759	0.020876	-2.8977	Down	survival associated mitochondrial melanoma specific oncogenic non-coding RNA
PADI2	-0.924	8.93E-06	0.000152	-4.44152	Down	peptidyl arginine deiminase 2
PCDHA7	-0.92362	3.29E-06	6.58E-05	-4.65161	Down	protocadherin alpha 7
EDIL3	-0.9236	3.62E-07	1.03E-05	-5.0879	Down	EGF like repeats and discoidin domains 3
MPP2	-0.92176	5.07E-06	9.47E-05	-4.56169	Down	MAGUK p55 scaffold protein 2
SVEP1	-0.92159	1.68E-05	0.00026	-4.30418	Down	sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1
PPEF1	-0.91856	0.000379	0.003347	-3.55414	Down	protein phosphatase with EF-hand domain 1
SLC45A3	-0.91757	0.000551	0.004521	-3.45481	Down	solute carrier family 45 member 3
NOXA1	-0.91728	0.008565	0.038948	-2.62895	Down	NADPH oxidase activator 1

EEF1B2P8	-0.91725	0.007005	0.033474	-2.69663	Down	eukaryotic translation elongation factor 1 beta 2 pseudogene 8
MT3	-0.91628	4.13E-06	7.98E-05	-4.6045	Down	metallothionein 3
ADORA1	-0.91619	1.17E-05	0.000192	-4.38366	Down	adenosine A1 receptor
ALDH1A1	-0.91544	8.65E-08	3.08E-06	-5.353	Down	aldehyde dehydrogenase 1 family member A1
ANGPTL2	-0.91525	3.50E-07	1.00E-05	-5.09406	Down	angiopoietin like 2
GLIDR	-0.91428	2.50E-10	2.24E-08	-6.32676	Down	glioblastoma down-regulated RNA
DISP3	-0.91261	0.000376	0.003326	-3.55619	Down	dispatched RND transporter family member 3
TAS2R39	-0.91223	1.82E-06	4.00E-05	-4.77277	Down	taste 2 receptor member 39
PSG6	-0.90903	0.00306	0.017796	-2.96167	Down	pregnancy specific beta-1-glycoprotein 6
IRF5P1	-0.90851	0.008743	0.039546	-2.62193	Down	interferon regulatory factor 5 pseudogene 1
NENF	-0.90814	2.30E-06	4.87E-05	-4.72554	Down	neudesin neurotrophic factor
EVI5L	-0.90753	4.71E-06	8.87E-05	-4.57728	Down	ecotropic viral integration site 5 like
TNFSF9	-0.90646	3.81E-05	0.000514	-4.11868	Down	TNF superfamily member 9
PAQR6	-0.9052	2.09E-05	0.000314	-4.2547	Down	progestin and adipoQ receptor family member 6
ITPRID1	-0.90499	0.000288	0.002691	-3.62598	Down	ITPR interacting domain containing 1
PDE8A	-0.90395	6.96E-16	2.79E-13	-8.07119	Down	phosphodiesterase 8A
TTYH1	-0.90289	7.17E-06	0.000126	-4.4887	Down	tweety family member 1
GPC2	-0.90266	0.000203	0.002017	-3.71541	Down	glypican 2
CPB2	-0.90204	3.49E-08	1.44E-06	-5.51504	Down	carboxypeptidase B2
KAZN	-0.90149	1.47E-09	1.00E-07	-6.04722	Down	kazrin, periplakin interacting protein
DYSF	-0.89981	3.49E-05	0.000479	-4.13874	Down	dysferlin
TRIM61	-0.89943	8.58E-06	0.000147	-4.45025	Down	tripartite motif containing 61
PCCB	-0.89936	8.92E-09	4.59E-07	-5.75013	Down	propionyl-CoA carboxylase subunit beta
CAPN13	-0.89908	0.000436	0.003752	-3.51734	Down	calpain 13
SEMA4C	-0.89797	4.27E-05	0.000563	-4.09261	Down	semaphorin 4C
MATN1	-0.89776	0.000536	0.004426	-3.46184	Down	matrilin 1
NEU4	-0.89766	0.006026	0.029899	-2.74634	Down	neuraminidase 4
IPO13	-0.89766	4.63E-06	8.76E-05	-4.58092	Down	importin 13
SLC25A13	-0.89677	4.58E-11	5.17E-09	-6.58403	Down	solute carrier family 25 member 13
ERF	-0.89652	0.001857	0.011941	-3.11216	Down	ETS2 repressor factor
RTKN	-0.8965	7.00E-06	0.000124	-4.4937	Down	rhotekin
KCNIP1-OT1	-0.89637	0.006228	0.030643	-2.73552	Down	KCNIP1 overlapping transcript 1
MTCO1P47	-0.89621	0.000818	0.00624	-3.34668	Down	MT-CO1 pseudogene 47
ZNF146	-0.89503	6.54E-16	2.66E-13	-8.07883	Down	zinc finger protein 146
TSPAN15	-0.89296	5.27E-07	1.41E-05	-5.01621	Down	tetraspanin 15
MEIOB	-0.89275	0.000114	0.001257	-3.85887	Down	meiosis specific with OB-fold
ZNF784	-0.89191	3.11E-05	0.000436	-4.16497	Down	zinc finger protein 784
TMEM229A	-0.89108	1.41E-06	3.25E-05	-4.82326	Down	transmembrane protein 229A
MAPK8IP1	-0.88969	7.77E-06	0.000135	-4.47147	Down	mitogen-activated protein kinase 8 interacting protein 1
CYCSP23	-0.88942	0.000119	0.001307	-3.8474	Down	CYCS pseudogene 23
CAPN8	-0.88907	0.00809	0.037301	-2.6483	Down	calpain 8
TRAPPC6A	-0.88601	0.000414	0.00359	-3.53122	Down	trafficking protein particle complex subunit 6A

SPON1	-0.88559	1.87E-07	5.88E-06	-5.21197	Down	spondin 1
SLC24A4	-0.88531	6.23E-08	2.34E-06	-5.41205	Down	solute carrier family 24 member 4
RPS2P32	-0.88508	0.000264	0.002512	-3.64846	Down	ribosomal protein S2 pseudogene 32
EGLN3	-0.88502	4.15E-14	1.04E-11	-7.55626	Down	egl-9 family hypoxia inducible factor 3
FAM86B2	-0.88456	0.000477	0.00403	-3.4933	Down	family with sequence similarity 86 member B2
MRPS26	-0.88435	6.59E-05	0.000806	-3.99071	Down	mitochondrial ribosomal protein S26
ADAMTSL2	-0.88353	9.87E-05	0.001126	-3.8937	Down	ADAMTS like 2
LCTL	-0.88352	6.74E-05	0.000821	-3.98516	Down	lactase like
MARCOL	-0.88232	3.85E-05	0.000519	-4.11641	Down	MARCO like
TST	-0.88163	0.000585	0.004755	-3.43833	Down	thiosulfate sulfurtransferase
CHPF	-0.88086	0.000174	0.001788	-3.75338	Down	chondroitin polymerizing factor
SEPTIN4	-0.8808	4.09E-07	1.14E-05	-5.06469	Down	septin 4
CYP2A6	-0.88079	7.68E-07	1.93E-05	-4.94339	Down	cytochrome P450 family 2 subfamily A member 6
ZNF837	-0.88038	0.001954	0.01243	-3.09717	Down	zinc finger protein 837
C20orf202	-0.87967	2.13E-05	0.000318	-4.25048	Down	chromosome 20 open reading frame 202
RHOB	-0.87907	1.15E-07	3.91E-06	-5.30158	Down	ras homolog family member B
ROM1	-0.87831	6.53E-06	0.000117	-4.50848	Down	retinal outer segment membrane protein 1
CTNNA3	-0.87727	8.85E-08	3.14E-06	-5.34884	Down	catenin alpha 3
F3	-0.87671	0.000162	0.001684	-3.77164	Down	coagulation factor III, tissue factor
NINJ2	-0.876	0.000193	0.001941	-3.72783	Down	ninjurin 2
LRP2	-0.87593	4.22E-07	1.17E-05	-5.05873	Down	LDL receptor related protein 2
POLR2F	-0.87591	3.10E-05	0.000434	-4.16576	Down	RNA polymerase II, I and III subunit F
CADM4	-0.87402	5.99E-08	2.28E-06	-5.41924	Down	cell adhesion molecule 4
MEX3D	-0.87287	0.000207	0.00205	-3.71028	Down	mex-3 RNA binding family member D
OR1L6	-0.87124	0.002826	0.016744	-2.98606	Down	olfactory receptor family 1 subfamily L member 6
BEST1	-0.87099	4.50E-09	2.61E-07	-5.86453	Down	bestrophin 1
WNT7A	-0.87051	0.00124	0.008697	-3.22948	Down	Wnt family member 7A
ASPHD1	-0.87041	0.000103	0.001172	-3.88266	Down	aspartate beta-hydroxylase domain containing 1
ABHD17A	-0.8695	0.001751	0.01139	-3.12956	Down	abhydrolase domain containing 17A, depalmitoylase
JAKMIP3	-0.86832	7.19E-07	1.82E-05	-4.95616	Down	Janus kinase and microtubule interacting protein 3
PHLDA3	-0.86654	0.000843	0.006387	-3.33833	Down	pleckstrin homology like domain family A member 3
LGALS3BP	-0.86636	1.17E-05	0.000192	-4.38371	Down	galectin 3 binding protein
RASA3	-0.86609	1.35E-11	1.74E-09	-6.76331	Down	RAS p21 protein activator 3

Table 3 The enriched GO terms of the up and down regulated differentially expressed genes

GO ID	CATEGORY	GO Name	adjusted_p_value	negative_log10_of_adjusted_p_value	Gene Count	Gene
				Up regulated genes		
GO:0002376	BP	immune system	1.48E-86	85.8309114	199	IGLC3,IGLC2,IGKV4-1,IGHG1,IGHG2,IGHV4-39,IGKV3-11,IGHV1-2,IGHV3-7,IGKV1-

process	5,IGHV3-30,IGLV2-11,IGHV4-34,IGLV3-21,IGKV3-15,IGLV1-44,IGHV3-23,IGHV4-59,IGHV2-5,IGKV3-20,IGHV3-21,IGKV1-9,JCHAIN,IGHM,IGLV2-14,IGHA1,IGHV1-18,IGHV1-3,IGLV3-19,IGHV4-4,IGHV1-69D,IGHV4-30-2,IGHV1-46,IGKV1-12,IGLV2-23,IGHV3-33,IGHV5-51,IGHV2-26,IGKV1-27,IGLV1-40,IGHV2-70,IGLV2-8,IGKV1-17,IGHV3-48,IGHV3-53,IGKV1-16,IGLV2-18,IGHV4-61,IGHG4,IGHV3-74,CCL18,IGKV2-24,IGKV5-2,IGKV1-6,IGHV3-15,IGHV3-49,IGKV6-21,IGHV3-11,IGHV3-20,IGLV6-57,IGLV3-10,IGKV3D-11,IGKV2-30,IGLV1-47,IGHV4-28,IGHV7-4-1,IGLV3-25,IGHV3-64D,IGHA2,IGLL5,IGLV10-54,IGHV2-70D,IGHV1-69,IGKV1-8,IGHV3-43,IGLV4-69,IGLV7-46,IGLV7-43,SLAMF7,IGLV8-61,IGHV6-1,IGKV1D-13,IGHV3-72,IGKV2D-29,IGKV3D-20,IGKV6D-21,IGHV3-13,PYHIN1,MS4A1,IGHV1-24,IGHV3-73,MS4A2,GPR174,FCRL3,LY9,IGKV1D-39,IGHV3-66,CLEC10A,TRAV4,SLAMF6,IGKV1D-16,TRAT1,IGLV3-9,IGKV1-39,EOMES,IGLV5-45,IGKV1D-12,CCR4,GZMA,POU4F2,IGKV3D-15,CD79A,CCR2,CD48,IGKV1D-33,IGKV1-33,TRAV17,CD3E,CCL26,IGKV1D-8,ITGAD,IL2RB,CCL4,CCL24,TNFRSF13B,FASLG,SLAMF1,MZB1,TRBV29-1,TRBV27,CD24,IKZF3,LAX1,TDGF1,CD2,CD28,IGLV1-36,FCMR,LYZ,IL7R,HSH2D,HLA-DRB5,FCGR2B,UBASH3A,PLA2G2D,TRAV13-1,CYP11B1,TRAV19,CD1C,FOXJ1,TRAV12-3,TRBV20-1,CD3D,TRBC1,TRBV28,ICOS,CD3G,CCL5,CCL3,TRAV12-2,TRBV6-7,LTF,ITK,H4C13,TRAV8-2,TRBV18,GPNMB,CTLA4,IRF4,TRAV14DV4,TNFRSF9,LCK,CD209,TRBV5-6,IGLV1-51,TRAJ3,C6,NCR1,TRBV5-5,TRAC,XCL2,TRAJ31,TRIML2,IL5RA,CD8B,TRBJ1-3,PTGDR,JAML,GBP5,TRBV7-7,MICB,MYB,TRBC2,IL2RG,MRC1,TRBV5-4,CD96,TRBV7-9,CHIT1

GO:0050896	BP	response to stimulus	5.48E-37	36.26088329	264	IGLC3,IGLC2,IGKV4-1,IGHG1,IGHG2,IGHV4-39,IGKV3-11,IGHV1-2,IGHV3-7,IGKV1-5,IGHV3-30,IGLV2-11,IGHV4-34,IGLV3-21,IGKV3-15,IGLV1-44,IGHV3-23,IGHV4-59,IGHV2-5,IGKV3-20,IGHV3-21,IGKV1-9,JCHAIN,IGHM,IGLV2-14,IGHA1,IGHV1-18,IGHV1-3,IGLV3-19,IGHV4-4,IGHV1-69D,IGHV4-30-2,IGHV1-46,IGKV1-12,FCRL5,IGLV2-23,IGHV3-33,IGHV5-51,IGHV2-26,IGKV1-27,IGLV1-40,IGHV2-70,IGLV2-8,IGKV1-17,IGHV3-48,IGHV3-53,IGKV1-16,IGLV2-18,IGHV4-61,IGHG4,IGHV3-74,CCL18,IGKV2-24,IGKV5-2,IGKV1-6,IGHV3-15,IGHV3-49,IGKV6-21,IGHV3-11,IGHV3-20,IGLV6-57,IGLV3-10,IGKV3D-11,IGKV2-30,IGLV1-47,IGHV4-28,IGHV7-4-1,IGLV3-25,IGHV3-64D,IGHA2,IGLL5,IGLV10-54,IGHV2-70D,IGHV1-69,STOML3,IGKV1-8,IGHV3-43,IGLV4-69,IGLV7-46,IGLV7-43,SLAMF7,RASSF6,IGLV8-61,SHOX2,FCRL2,IGHV6-1,IGKV1D-13,IGHV3-72,IGKV2D-29,IGKV3D-20,NUGGC,IGKV6D-21,IGHV3-13,PYHIN1,MS4A1,IGHV1-24,IGHV3-73,MS4A2,P2RY10,GPR174,FCRL3,LY9,IGKV1D-39,IGHV3-66,CLEC10A,TRAV4,PALM3,SLAMF6,OR2J2,IGKV1D-16,TRAT1,IGLV3-9,IGKV1-39,EOMES,ISL1,IGLV5-45,TTR,OTX2,IGKV1D-12,CCR4,GZMA,POU4F2,IGKV3D-15,CD79A,CCR2,CD48,IGKV1D-33,MYLK3,IGKV1-33,RGS21,PLEKHG4B,TRAV17,CD3E,CCL26,IGKV1D-8,ITGAD,DOK2,OR5V1,IL2RB,CCL4,CCL24,TPSAB1,NRK,EPS8L3,TNFRSF13B,FASLG,SLAMF1,OR9Q1,MZB1,TRBV29-1,TRBV27,CD24,IKZF3,LAX1,TDGF1,CD2,CD28,IGLV1-36,FCMR,LYZ,IL7R,HSH2D,HLA-DRB5,NPY2R,FCGR2B,UBASH3A,RTP1,PLA2G2D,TRAV13-1,CYP11B1,TRAV19,DRD3,CD1C,P2RY8,FOXJ1,NLRP7,TRAV12-3,TRBV20-1,CD3D,TRBC1,TRBV28,TAB2,ICOS,CLEC12A,PCP4,LHCGR,IL24,CD3G,CCL5,CCL3,TNNI3,TRAV12-

						2,GPR101,TRBV6-7,LTF,ITK,AKR1C4,TRAV8-2,TRBV18,TRARG1,CD163,GPNMB,CTLA4,MYO3A,IRF4,GSDMA,TRAV14DV4,SDC1,LCK,CD209,TRBV5-6,IGLV1-51,TRAJ3,C6,IQGAP2,NCR1,TRBV5-5,TRAC,CDA,XCL2,MS4A14,TRAJ31,CRABP1,TRIML2,AOC1,IL5RA,SIK1,F13A1,WT1,MAPK15,CD8B,MS4A7,TRBJ1-3,OR2T6,MSR1,ALOX15B,PTGDR,LPAR3,GML,CRNN,JAML,GBP5,NTS,HGF,RNASE10,LCN8,TRBV7-7,MICB,TRPM8,MYB,OR1J1,ADGRG6,TRBC2,IL2RG,MRC1,TRBV5-4,FOLR2,DIO3,CD96,SIGLEC1,UCN3,TRBV7-9,CHIT1,MROH2B
GO:0016020	CC	membrane	5.40E-18	17.26794982	246	IGLC3,IGLC2,IGKV4-1,IGHG3,IGHG1,IGHG2,IGHV4-39,IGKV3-11,IGHV1-2,IGHV3-7,IGKV1-5,IGHV3-30,IGLV2-11,IGHV4-34,IGLV3-21,IGKV3-15,IGLV1-44,IGHV3-23,IGHV4-59,IGHV2-5,IGKV3-20,IGHV3-21,IGKV1-9,IGHM,IGLV2-14,IGHA1,IGHV1-18,IGHV1-3,IGLV3-19,IGHV4-4,IGHV1-69D,IGHV4-30-2,IGHV1-46,IGKV1-12,FCRL5,IGLV2-23,IGHV3-33,IGHV5-51,IGHV2-26,IGKV1-27,IGLV1-40,IGHV2-70,IGLV2-8,IGKV1-17,IGHV3-48,IGHV3-53,IGKV1-16,IGLV2-18,IGHV4-61,IGHG4,IGHV3-74,IGKV2-24,IGKV5-2,IGKV1-6,IGHV3-15,IGHV3-49,IGKV6-21,IGHV3-11,IGHV3-20,IGLV6-57,IGLV3-10,IGKV3D-11,IGKV2-30,IGLV1-47,IGHV4-28,LRRC37A2,IGHV7-4-1,IGLV3-25,IGHV3-64D,IGHA2,IGLL5,IGLV10-54,IGHV2-70D,IGHV1-69,STOML3,IGKV1-8,IGHV3-43,IGLV4-69,IGLV7-46,IGLV7-43,SLAMF7,IGLV8-61,FCRL2,IGHV6-1,IGKV1D-13,IGHV3-72,IGKV2D-29,IGKV3D-20,IGKV6D-21,IGHV3-13,MS4A1,IGHV1-24,IGHV3-73,MS4A2,P2RY10,GPR174,FCRL3,LY9,IGKV1D-39,IGHV3-66,CLEC10A,DNAJC5B,TRAV4,AADACL2,PALM3,SLAMF6,OR2J2,IGKV1D-16,TRAT1,IGLV3-9,IGKV1-39,STRIT1,IGLV5-45,IGKV1D-12,CCR4,GZMA,IGKV3D-

						15,CD79A,CCR2,CD48,IGKV1D-33,IGKV1-33,RGS21,TRAV17,CD3E,IGKV1D-8,ITGAD,OR5V1,IL2RB,MOGAT2,GZMH,NRK,EPS8L3,TNFRSF13B,IGHD,FASLG,SLAMF1,OR9Q1,SLC35D3,TRBV29-1,TRBV27,CD24,LAX1,TDGF1,CD2,CD28,IGLV1-36,FCMR,CLIC6,IL7R,HLA-DRB5,NPY2R,FCGR2B,RTP1,TRAV13-1,CYP11B1,TRAV19,DRD3,CD1C,P2RY8,LAIR2,TRAV12-3,TRBV20-1,CD3D,TRBC1,TRBV28,TAB2,ICOS,CLEC12A,LHCGR,CD3G,SYNDIG1L,TRAV12-2,SIGLEC6,GPR101,TRBV6-7,LTF,ITK,H4C13,CD52,TRAV8-2,CATSPERD,TRBV18,TRARG1,CD163,HS3ST3A1,GPNMB,CTLA4,SLC25A52,IRF4,GSDMA,TRAV14DV4,SDC1,TNFRSF9,LCK,CD209,TRBV5-6,IGLV1-51,TRAJ3,C6,IQGAP2,NCR1,TRBV5-5,MUC3A,TRAC,PRSS21,MS4A14,B4GALNT2,TRAJ31,PRPH,AOC1,IL5RA,CD8B,MS4A7,TRBJ1-3,OR2T6,MSR1,ALOX15B,PTGDR,LPAR3,CFAP157,GML,CDHR4,CRNN,JSRP1,JAML,TMIE,GBP5,NMRK2,HGF,TRBV7-7,SLC22A31,MICB,TRPM8,MYB,OR1J1,ADGRG6,TRBC2,IL2RG,MRC1,TRBV5-4,FOLR2,DIO3,CD96,SIGLEC1,TRBV7-9
GO:0032991	CC	protein-containing complex	8.21E-09	8.085775725	188	IGLC3,IGLC2,IGKV4-1,IGHG1,IGHG2,IGHV4-39,IGKV3-11,IGHV1-2,IGHV3-7,IGKV1-5,IGHV3-30,IGLV2-11,IGHV4-34,IGLV3-21,IGKV3-15,IGLV1-44,IGHV3-23,IGHV4-59,IGHV2-5,IGKV3-20,IGHV3-21,IGKV1-9,JCHAIN,IGHM,IGLV2-14,IGHA1,IGHV1-18,IGHV1-3,IGLV3-19,IGHV4-4,IGHV1-69D,IGHV4-30-2,IGHV1-46,IGKV1-12,FCRL5,IGLV2-23,IGHV3-33,IGHV5-51,IGHV2-26,IGKV1-27,IGLV1-40,IGHV2-70,IGLV2-8,IGKV1-17,IGHV3-48,IGHV3-53,IGKV1-16,IGLV2-18,IGHV4-61,IGHG4,IGHV3-74,IGKV2-24,IGKV5-2,IGKV1-6,IGHV3-15,IGHV3-49,IGKV6-21,IGHV3-11,IGHV3-20,IGLV6-57,IGLV3-10,IGKV3D-11,IGKV2-30,IGLV1-47,IGHV4-28,IGHV7-4-

						1,IGLV3-25,IGHV3-64D,IGHA2,IGLL5,IGLV10-54,IGHV2-70D,IGHV1-69,IGKV1-8,IGHV3-43,IGLV4-69,IGLV7-46,IGLV7-43,IGLV8-61,IGHV6-1,IGKV1D-13,IGHV3-72,IGKV2D-29,IGKV3D-20,IGKV6D-21,IGHV3-13,PYHIN1,IGHV1-24,IGHV3-73,MS4A2,IGKV1D-39,IGHV3-66,TRAV4,IGKV1D-16,TRAT1,IGLV3-9,IGKV1-39,ISL1,IGLV5-45,TTR,OTX2,IGKV1D-12,POU4F2,IGKV3D-15,CD79A,IGKV1D-33,IGKV1-33,TRAV17,CD3E,IGKV1D-8,ITGAD,IL2RB,RNU6-968P,DYDC2,SIX3,MZB1,TRBV29-1,TRBV27,DAW1,CD2,CD28,IGLV1-36,CLIC6,HLA-DRB5,RNU1-28P,TRAV13-1,RNU1-27P,TRAV19,TRAV12-3,TRBV20-1,CD3D,RNU6-511P,TRBC1,DNAI3,TRBV28,PCP4,LHCGR,CD3G,TNNI3,TRAV12-2,RNU6-35P,GPR101,TRBV6-7,LTF,H4C13,SAGE1,TRAV8-2,CATSPERD,TRBV18,CTLA4,MYO3A,TFAP2D,IRF4,TRAV14DV4,SDC1,TRBV5-6,IGLV1-51,TRAJ3,MAT1A,C6,NCR1,TRBV5-5,CDC20B,RNU6-1300P,TRAC,DNAH3,GTF2A1L,RNU6-1061P,IL5RA,MYH2,F13A1,RNU1-136P,CD8B,TRBJ1-3,MSR1,RNU6-959P,RNU6-657P,DNAH11,TRBV7-7,POM121L2,MYB,FOXF2,RNU1-18P,TRBC2,IL2RG,TRBV5-4,RNU6-194P,TRBV7-9
GO:0003823	MF	antigen binding	3.83E-117	116.4163807	90	IGLC3,IGLC2,IGKV4-1,IGHG1,IGHG2,IGHV4-39,IGKV3-11,IGHV1-2,IGHV3-7,IGKV1-5,IGHV3-30,IGLV2-11,IGHV4-34,IGLV3-21,IGKV3-15,IGLV1-44,IGHV3-23,IGHV4-59,IGHV2-5,IGKV3-20,IGHV3-21,JCHAIN,IGHM,IGLV2-14,IGHA1,IGHV1-18,IGHV1-3,IGLV3-19,IGHV4-4,IGHV1-69D,IGHV4-30-2,IGHV1-46,IGLV2-23,IGHV3-33,IGHV5-51,IGHV2-26,IGLV1-40,IGHV2-70,IGLV2-8,IGKV1-17,IGHV3-48,IGHV3-53,IGKV1-16,IGHV4-61,IGHG4,IGHV3-74,IGKV5-2,IGHV3-15,IGHV3-49,IGHV3-11,IGHV3-20,IGLV6-57,IGKV2-30,IGLV1-47,IGHV4-28,IGHV7-4-1,IGLV3-25,IGHV3-

						64D,IGHA2,IGLL5,IGHV2-70D,IGHV1-69,IGHV3-43,IGLV7-43,IGHV6-1,IGHV3-72,IGHV3-13,IGHV1-24,IGHV3-73,IGKV1D-39,IGHV3-66,IGKV1D-16,IGKV1-39,IGKV1D-12,CD48,IGKV1D-33,IGKV1-33,SLAMF1,IL7R,HLA-DRB5,TRAV19,CD1C,TRAV12-3,TRBC1,TRBV28,TRAV12-2,CD209,IGLV1-51,TRBC2,TRBV7-9
GO:0005102	MF	signaling receptor binding	5.32E-22	21.27396289	83	IGLC3,IGLC2,IGHG1,IGHG2,IGHV4-39,IGHV1-2,IGHV3-7,IGHV3-30,IGHV4-34,IGHV3-23,IGHV4-59,IGHV2-5,IGHV3-21,JCHAIN,IGHM,IGHA1,IGHV1-18,IGHV1-3,IGHV4-4,IGHV1-69D,IGHV4-30-2,IGHV1-46,IGHV3-33,IGHV5-51,IGHV2-26,IGHV2-70,IGHV3-48,IGHV3-53,IGHV4-61,IGHG4,IGHV3-74,CCL18,IGHV3-15,IGHV3-49,IGHV3-11,IGHV3-20,IGHV4-28,IGHV7-4-1,IGHV3-64D,IGHA2,IGLL5,IGHV2-70D,IGHV1-69,IGHV3-43,IGHV6-1,IGHV3-72,IGHV3-13,MS4A1,IGHV1-24,IGHV3-73,IGHV3-66,TRAT1,TTR,CCR2,CD3E,CCL26,ITGAD,DOK2,CCL4,CCL24,FASLG,TDGF1,CD2,CLIC6,RTP1,TRAV19,DRD3,TRBC1,IL24,CD3G,CCL5,CCL3,GPNMB,LCK,XCL2,CD8B,JAML,NTS,HGF,MICB,TRBC2,UCN3,TRBV7-9
			Down regulated genes			
GO:0032502	BP	developmental process	7.18E-09	8.144080437	176	NKX2-4,PLAC8,SFN,CIROP,GRHL3,IL9,TMEFF1,STC2,GJC2,NPPC,CPAMD8,VEGFA,RASAL1,ADM,IL31RA,CA9,COL9A3,CR2,COL9A2,HOXD1,SEMA3B,SAPCD2,INSM1,ANGPTL4,CHI3L1,SOX3,MAG,TACSTD2,AATK,GCM1,CHADL,LDB3,CNP,BMP8A,TBATA,DMBT1,BTG4,FOXE1,HES6,COL11A2,CDH1,ARC,SREBF1,GDF2,TXNDC8,MARCKSL1,ZNF536,CMTM5,GJB1,PLXNB3,HSF4,OLIG2,MT1X,MAL,HIP1R,RAB7B,KLK8,PLLP,USH1C,IGSF8,AQP6,CDKN1C,CDC42EP1,NKX6-2,GREB1L,ACSBG1,TSC22D4,CFTR,INSIG1,SRCIN1,HSD17B3,TNFAIP6,ALDOC,GREM1,ATF3,ABCA2,HK2,MCAM,GLDN,GPR37,IFNA2,SEMA4D,NGFR,NTNG2,KEL,TF,GLUL,DMRTA2,KREMEN2,GNG8,D

						MRT2,PALM2AKAP2,S1PR5,ROGDI,ELF3,TPRN,HAPLN2,SYNJ2,MYCN,HPN,FN3K,IFNA13,TLE2,MYRF,GAMT,TREH,MEIS1,BNC1,MOG,SBF1,ADAMTS4,INF2,BIN1,RHOU,STMN4,SH3PXD2B,BMP2,HSPA2,LMNA,ERBB3,HSD11B1,HTRA1,DLL1,NKX2-2,THBS2,SH3TC2,NHLH2,PIWIL2,MT1G,GADD45B,APLP1,PHLDB1,FGF11,SHB,UNC5B,MYH6,ASPA,CYP26C1,FASN,RASSF2,CRB2,PNPLA3,ACTN2,PRKCQ,MMP15,LLGL1,CBR1,PADI2,PCDHA7,SVEP1,SLC45A3,MT3,ADORA1,DISP3,TNFSF9,GPC2,CPB2,KAZN,DYSF,SEMA4C,MATN1,NEU4,ERF,ZNF784,SLC24A4,ADAMTSL2,LCTL,TST,SEPTIN4,RHOB,ROM1,F3,NINJ2,LRP2,WNT7A,PHLDA3
GO:0032501	BP	multicellular organismal process	2.67E-08	7.573717421	197	OR4F4,PLAC8,RXFP4,ICOSLG,SFN,CIROP,GRHL3,IL9,TMEFF1,STC2,GJC2,NPPC,CPAMD8,VEGFA,RASAL1,ADM,IL31RA,CHRM5,HILPDA,LIPC,COL9A3,CR2,COL9A2,HOXD1,SEMA3B,INSM1,ANGPTL4,CHI3L1,SOX3,MAG,TACSTD2,SCNN1G,AATK,GCM1,CHADL,LDB3,CNP,BMP8A,TBATA,BTG4,FOXE1,OR2K2,HES6,COL11A2,TRPV6,CDH1,RABGEF1,ARC,SREBF1,TMTC4,GDF2,COL16A1,TXNDC8,KCNE5,MARCKSL1,LLCFC1,ZNF536,GJB1,PLXNB3,HSF4,OLIG2,MT1X,MAL,HIP1R,RAB7B,KLK8,PLLP,USH1C,IGSF8,AQP6,TRPV5,SAA1,CDKN1C,NKX6-2,GREB1L,ACSBG1,TSC22D4,CFTR,INSIG1,OR13A1,SRCIN1,HSD17B3,TNFAIP6,GREM1,VWA1,ABCA2,HK2,MCAM,GLDN,GPR37,IFNA2,OR1L4,SEMA4D,TAS2R40,SCD,NGFR,FFAR1,NTNG2,KEL,TF,GLUL,DMRTA2,HCN2,KREMEN2,GNG8,DMRT2,OR2AE1,S1PR5,ROGDI,ELF3,TPRN,HMSD,HAPLN2,SYNJ2,MYCN,HPN,IFNA13,MYRF,GAMT,MEIS1,OR5C1,BNC1,HCRTR1,MOG,SBF1,ADAMTS4,BIN1,F11,STMN4,SH3PXD2B,BMP2,HSPA2,GPIHBP1,LMNA,PLA2G4C,ERBB3,EQTN,HSD11B1,DLL1,NKX2-2,THBS2,SH3TC2,NHLH2,PIWIL2,MT1G,APLP1,ST3GAL4,PHLDB1,FGF11,SHB,UNC5B,MYH6,ASPA,CYP26C1,FASN,RASSF2,CRB2,GIPC1,ACTN2,PRKCQ,MMP15,LLGL1,PADI2,PCDHA7,MPP2,SVEP1,PPEF1,SLC45A3,MT3,ADORA1,ALDH1A1,DISP3,TAS2R39,PSG6,TNFSF9

						,GPC2,CPB2,KAZN,DYSF,SEMA4C,MATN1,NEU4,MAPK8IP1,CAPN8,SLC24A4,ADAMTSL2,LCTL,SEPTIN4,RHOB,ROM1,CTNNA3,F3,NINJ2,LRP2,OR1L6,BEST1,WNT7A
GO:0110165	CC	cellular anatomical entity	0.067162031	1.17287618	386	ADGRG7,OR4F4,NKX2-4,PLAC8,RXFP4,ICOSLG,SFN,CIROP,GRHL3,UGT2B17,IL9,TMEM88B,ADAMTS14,TMEFF1,STC2,GJC2,TEX44,NPPC,DAO,CPAMD8,VEGFA,RASAL1,SYS1-DBNDD2,ADM,SMIM32,IL31RA,CHRM5,CA9,CTSV,SLC25A48,KCNG4,SAA2,HILPDA,ZNF705G,LIPC,MAP6D1,COL9A3,CARNS1,CR2,COL9A2,HOXD1,EXD1,RNU6-1160P,SEMA3B,SAPCD2,INSM1,ANGPTL4,CHI3L1,DBNDD2,C1ORF116,TUBB4A,SOX3,MAG,TACSTD2,SCNN1G,AATK,GCM1,PRODH,SCART1,CHP2,CHADL,GPR142,LDB3,CNP,GPD1,FAM53A,PKD1L2,BMP8A,TBATA,ACP7,CPB1,DMBT1,BTG4,FOXE1,MAP1LC3B2,PDIA2,OR2K2,OPLAH,HES6,COL11A2,TRPV6,RNU6-913P,CDH1,RABGEF1,FTCD,ARC,SREBF1,TMTC4,GDF2,CPHXL,RNU6-871P,LIPE,COL16A1,TXNDC8,CNDP1,DHCR7,FXYD4,RNU6-448P,KIF19,KCNE5,GALNT6,MARCKSL1,LLCFC1,SEC14L5,ZNF536,CMTM5,MAP1LC3A,KCNH8,GJB1,PLXNB3,HSF4,AGPAT4,OLIG2,MT1X,MAL,HIP1R,RAB7B,SLC16A8,KLK8,PLCH2,PLLP,SLC36A3,SLC5A11,USH1C,IGSF8,AQP6,TRPV5,SAA1,PACSIN3,CDKN1C,TMEM125,CDC42EP1,SH3BP5,NKX6-2,GREB1L,ADSS1,TKTL1,ACSBG1,TSC22D4,CFTR,INSIG1,ZNF775,OR13A1,SRCIN1,HSD17B3,TNFAIP6,TMEM151A,ACADS,TMCO5A,CALB2,ALDOC,PTPRH,GREM1,VWA1,CES4A,DUXB,CERCAM,RBP7,ADAP1,ATF3,ABCA2,SGK2,PLEKHG3,HK2,MCAM,GLDN,GPR37,RAB33A,EFS,IFNA2,OR1L4,KLK10,SPINK14,HPDL,SEMA4D,TAS2R40,SCD,NGFR,FFAR1,NTNG2,HAS1,SCAND1,KEL,TF,GLUL,DMRTA2,HCN2,KREMEN2,PCBP4,GNG8,PET117,ARSI,DMRT2,AOX1,PALM2AKAP2,TM7SF2,OR2AE1,S1PR5,SKOR1,ROGDI,ELF3,RNU5D-1,PLEKHG4,TPRN,ZNF367,NACAD,HMSD,HAPLN2,LLGL2,SYNJ2,GOLGA6A,MYCN,HPN,SHC2,FN3K,IFNA13,SERPINE3,TLE2,MYRF,

						GAMT,TREH,MEIS1,OR5C1,BNC1,HCRTR1,MOG,SBF1,ADAMTS4,CA14,INF2,TMEM171,OSBPL5,BIN1,NME3,CDK18,RAB6C,PTPDC1,ARL2BP,FSCN1,F11,RNU6-539P,TP53TG5,MTFR2,RHOU,STMN4,GOLGA6B,DIPK1C,PAQR4,RNASE1,GNLY,MVK,SH3PXD2B,BMP2,HSPA2,GPIHBP1,LMNA,PLA2G4C,ERBB3,KIRREL2,EQTN,HSD11B1,HTRA1,DLL1,EEPD1,RHBG,NKX2-2,PFKL,CPHXL2,RNU6-883P,EVA1A,LMF1,THBS2,SH3TC2,NHLH2,IGSF1,PEBP4,PIWIL2,PLEKHH1,MT1G,GADD45B,APLP1,ST3GAL4,PHLDB1,GASK1A,FGF11,SHB,UNC5B,ENOSF1,MYH6,CPA2,SNX22,NKAIN4,ASPA,CIRBP,CYP26C1,FASN,MRI1,RASSF2,CRB2,GIPC1,PNPLA3,LSS,DHRS13,GPR62,FAM170A,LGI3,ACTN2,PRKCQ,MMP15,CLUL1,LLGL1,CBR1,MT1M,ARHGAP23,PADI2,PCDHA7,EDIL3,MPP2,SVEP1,PPEF1,SLC45A3,NOXA1,MT3,ADORA1,ALDH1A1,ANGPTL2,DISP3,TAS2R39,PSG6,NENF,EVI5L,TNFSF9,PAQR6,PDE8A,TTYH1,GPC2,CPB2,KAZN,DYSF,TRIM61,PCCB,CAPN13,SEMA4C,MATN1,NEU4,IPO13,SLC25A13,ERF,RTKN,ZNF146,TSPAN15,ZNF784,TMEM229A,MAPK8IP1,CAPN8,TRAPPC6A,SPON1,SLC24A4,EGLN3,MRPS26,ADAMTSL2,LCTL,MARCOL,TST,CHPF,SEPTIN4,CYP2A6,ZNF837,RHOB,ROM1,CTNNA3,F3,NINJ2,LRP2,POLR2F,CADM4,MEX3D,OR1L6,BEST1,WNT7A,ASPHD1,ABHD17A,JAKMIP3,PHLDA3,LGALS3BP,RASA3
GO:0005737	CC	cytoplasm	0.067885536	1.168222749	243	PLAC8,ICOSLG,SFN,CIROP,UGT2B17,STC2,TEX44,NPPC,DAO,VEGFA,RASAL1,ADM,CTSV,SLC25A48,HILPDA,LIPC,MAP6D1,COL9A3,CARNS1,COL9A2,EXD1,SEMA3B,SAPCD2,CHI3L1,DBNDD2,C1ORF116,TUBB4A,MAG,TACSTD2,AATK,PRODH,SCART1,CHP2,GPR142,LDB3,CNP,GPD1,TBATA,CPB1,DMBT1,BTG4,MAP1LC3B2,PDIA2,OPLAH,COL11A2,CDH1,RABGEF1,FTCD,ARC,SREBF1,TMTC4,LIPE,COL16A1,TXNDC8,CNDP1,DHCR7,KIF19,GALNT6,MARCKSL1,SEC14L5,MAP1LC3A,GJB1,AGPAT4,OLIG2,MT1X,MAL,HIP1R,RAB7B,KLK8,PLCH2,USH1C,AQP6,SAA1,PACSIN3,CDKN1C,CDC42EP1,SH3BP5,ADSS1,TKTL1,ACSBG1,TSC22D4,CFTR,INSIG1,SRCIN1,HSD1

						7B3,TNFAIP6,ACADS,CALB2,ALDOC,PTPRH,VWA1,CERCAM,RBP7,ADAP1,ABCA2,SGK2,PLEKHG3,HK2,GPR37,RAB33A,EFS,KLK10,HPDL,SCD,NGFR,HAS1,KEL,TF,GLUL,KREMEN2,PCBP4,PET117,ARSI,AOX1,TM7SF2,S1PR5,ROGDI,ELF3,PLEKHG4,NACAD,LLGL2,SYNJ2,GOLGA6A,HPN,SHC2,FN3K,MYRF,GAMT,BNC1,SBF1,INF2,OSBPL5,BIN1,NME3,CDK18,RAB6C,PTPDC1,ARL2BP,FSCN1,TP53TG5,MTFR2,RHOU,STMN4,GOLGA6B,DIPK1C,GNLY,MVK,SH3PXD2B,HSPA2,LMNA,PLA2G4C,EQTN,HSD11B1,HTRA1,DLL1,RHBG,PFKL,EVA1A,LMF1,THBS2,SH3TC2,PIWIL2,MT1G,GADD45B,APLP1,ST3GAL4,PHLDB1,GASK1A,FGF11,SHB,ENOSF1,MYH6,CPA2,SNX22,ASPA,CIRBP,CYP26C1,FASN,MRI1,RASSF2,CRB2,GIPC1,PNPLA3,LSS,DHRS13,GPR62,LGI3,ACTN2,PRKCQ,LLGL1,CBR1,MT1M,ARHGAP23,PADI2,MPP2,SVEP1,PPEF1,NOXA1,MT3,ADORA1,ALDH1A1,DISP3,NENF,PDE8A,TTYH1,GPC2,KAZN,DYSF,TRIM61,PCCB,CAPN13,SEMA4C,NEU4,IPO13,SLC25A13,ERF,RTKN,ZNF146,TSPAN15,MAPK8IP1,CAPN8,TRAPPC6A,SPON1,SLC24A4,EGLN3,MRPS26,LCTL,TST,CHPF,SEPTIN4,CYP2A6,RHOB,CTNNA3,LRP2,POLR2F,MEX3D,BEST1,WNT7A,ABHD17A,JAKMIP3,PHLDA3,LGALS3BP,RASA3
GO:0098772	MF	molecular function regulator activity	0.047007711	1.327830892	63	SFN,IL9,STC2,NPPC,CPAMD8,VEGFA,RASAL1,ADM,CA9,SEMA3B,ANGPTL4,BMP8A,RABGEF1,GDF2,FXYD4,KCNE5,CMTM5,MAL,PACSIN3,CDKN1C,SH3BP5,CFTR,GREM1,ADAP1,ABCA2,SGK2,PLEKHG3,IFNA2,SPINK14,SEMA4D,FFAR1,PLEKHG4,HMSD,LLGL2,IFNA13,SERPINE3,SBF1,BIN1,ARL2BP,RHOU,SH3PXD2B,BMP2,GPIHBP1,ERBB3,HTRA1,DLL1,IGSF1,FGF11,CRB2,MMP15,LLGL1,ARHGAP23,NOXA1,MT3,ALDH1A1,NENF,EVI5L,TNFSF9,SEMA4C,RTKN,MAPK8IP1,WNT7A,RASA3
GO:0140677	MF	molecular function activator activity	0.047007711	1.327830892	44	IL9,STC2,NPPC,VEGFA,RASAL1,ADM,CA9,SEMA3B,BMP8A,RABGEF1,GDF2,CMTM5,MAL,SH3BP5,GREM1,ADAP1,PLEKHG3,IFNA2,SEMA4D,FFAR1,PLEKHG4,LLGL2,IFNA13,SBF1,RHOU,SH3PXD2B,BMP2,GPIHBP1,ERBB3,HTRA1,DLL1,FGF11,MMP15,LLGL1,ARHG

					AP23,NOXA1,MT3,ALDH1A1,NENF,EVI5L,TNFSF9,SEMA4C,WNT7A,RASA3

Table 4 The enriched pathway terms of the up and down regulated differentially expressed genes

Pathway ID	Pathway Name	adjusted_p_value	negative_log10_of_adjusted_p_value	Gene Count	Gene
			Up regulated genes		
REAC:R-HSA-168256	Immune System	7.08E-38	37.15022242	113	IGLC3,IGLC2,IGKV4-1,IGHG1,IGHG2,IGHV4-39,IGKV3-11,IGHV1-2,IGHV3-7,IGKV1-5,IGHV3-30,IGLV2-11,IGHV4-34,IGLV3-21,IGKV3-15,IGLV1-44,IGHV3-23,IGHV4-59,IGHV2-5,IGKV3-20,IGHM,IGLV2-14,IGLV3-19,IGHV1-46,IGKV1-12,IGLV2-23,IGHV3-33,IGLV1-40,IGHV2-70,IGLV2-8,IGKV1-17,IGHV3-48,IGHV3-53,IGKV1-16,IGHG4,IGKV5-2,IGHV3-11,IGLV6-57,IGKV2-30,IGLV1-47,IGLV3-25,IGHV1-69,IGLV7-43,SLAMF7,IGKV3D-20,IGHV3-13,MS4A2,IGKV1D-39,CLEC10A,SLAMF6,IGKV1D-16,TRAT1,IGKV1-39,TTR,IGKV1D-12,CD79A,CCR2,IGKV1D-33,IGKV1-33,CD3E,IL2RB,CCL4,TNFRSF13B,FASLG,CD28,LYZ,IL7R,HLA-DRB5,FCGR2B,TUBA4B,TRAV19,CD1C,LAIR2,CD3D,TRBC1,TAB2,CLEC12A,IL24,CD3G,CCL5,CCL3,SIGLEC6,LTF,ITK,CTLA4,IRF4,SDC1,TNFRSF9,LCK,CD209,IGLV1-51,C6,IQGAP2,NCR1,TUBAL3,MUC3A,TRAC,CDA,AOC1,IL5RA,MYH2,F13A1,CD8B,JAML,GBP5,HGF,MICB,IL2RG,MRC1,CD96,SIGLEC1,TRBV7-9,CHIT1
REAC:R-HSA-202403	TCR signaling	9.31E-06	5.031017738	12	TRAT1,CD3E,HLA-DRB5,TRAV19,CD3D,TRBC1,TAB2,CD3G,ITK,LCK,TRAC,T

					RBV7-9
REAC:R-HSA-449147	Signaling by Interleukins	0.009177632	2.037269376	18	IGHG1,IGHG4,CCR2,IL2RB,CCL4,FASLG,IL7R,TAB2,IL24,CCL5,CCL3,IRF4,SDC1,LCK,IL5RA,F13A1,HGF,IL2RG
REAC:R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	0.033564699	1.474117249	13	P2RY10,CCR4,CCR2,CCL4,NPY2R,DRD3,LHCGR,CCL5,CCL3,XCL2,PTGDR,LPAR3,NTS
REAC:R-HSA-1280215	Cytokine Signaling in Immune system	0.036661634	1.435788182	22	IGHG1,IGHG4,CCR2,IL2RB,CCL4,TNFRSF13B,FASLG,IL7R,HLA-DRB5,TAB2,IL24,CCL5,CCL3,IRF4,SDC1,TNFRSF9,LCK,IL5RA,F13A1,GBP5,HGF,IL2RG
REAC:R-HSA-500792	GPCR ligand binding	0.164500063	0.783833932	14	P2RY10,CCR4,CCR2,CCL4,NPY2R,DRD3,LHCGR,CCL5,CCL3,XCL2,PTGDR,LPAR3,NTS,UCN3
			Down regulated genes		
REAC:R-HSA-1655829	Regulation of cholesterol biosynthesis by SREBP (SREBF)	0.020632763	1.68544262	7	DHCR7,INSIG1,SCD,TM7SF2,MVK,FASN,LSS
REAC:R-HSA-1474228	Degradation of the extracellular matrix	0.020632763	1.68544262	11	CTSV,COL9A3,COL9A2,COL11A2,CDH1,COL16A1,ADAMTS4,HTRA1,MMP15,CAPN13,CAPN8
REAC:R-HSA-8957322	Metabolism of steroids	0.032317344	1.490564341	11	SREBF1,DHCR7,INSIG1,HSD17B3,SCD,TM7SF2,MVK,HSD11B1,FASN,LSS,LRP2
REAC:R-HSA-1474244	Extracellular matrix organization	0.230258584	0.63778417	14	ADAMTS14,CTSV,COL9A3,COL9A2,COL11A2,CDH1,COL16A1,ADAMTS4,BMP2,HTRA1,MMP15,CAPN13,MATN1,CAPN8
REAC:R-HSA-556833	Metabolism of lipids	0.240535296	0.618821186	26	HILPDA,ANGPTL4,GPD1,SREBF1,LIPE,DHCR7,AGPAT4,ACSBG1,INSIG1,HSD17B3,ACADS,SCD,ARSI,TM7SF2,SYNJ2,SBF1,OSBPL5,MVK,PLA2G4C,HSD11B1,FASN,PNPLA3,LSS,CBR1,PCCB,LRP2
REAC:R-HSA-1430728	Metabolism	0.324955932	0.488175531	58	UGT2B17,DAO,CA9,HILPDA,CARNS1,ANGPTL4,PRODH,GPD1,OPLAH,FTCD,SREBF1,LIPE,DHCR7,AGPAT4,SLC16A8,PLCH2,ADSS1,ACSBG1,INSIG1,HSD17B3,ACADS,ALDOC,HK2,SCD,FFAR1,HAS1,GLUL,GNG8,ARSI,AOX1,TM7SF2,SYN

J2,GAMT,SBF1,CA14,OSBPL5,
NME3,MVK,GPIHBP1,PLA2G4
C,HSD11B1,PFKL,ST3GAL4,A
SPA,CYP26C1,FASN,MRI1,PN
PLA3,LSS,CBR1,ALDH1A1,GP
C2,PCCB,SLC25A13,TST,CHP
F,CYP2A6,LRP2

Table 5 Topology table for up and down regulated genes

Regulation	Node	Degree	Betweenness	Stress	Closeness
Up	LCK	140	0.058833	16807950	0.307962
Up	PYHIN1	126	0.052288	14469590	0.28918
Up	SLAMF1	93	0.043579	6854232	0.274257
Up	DOK2	92	0.028643	6940372	0.287996
Up	TAB2	83	0.038875	9755578	0.310568
Up	C6orf141	72	0.024145	6150196	0.26301
Up	IKZF3	61	0.027978	4317696	0.263618
Up	POTEF	56	0.021911	5211510	0.250074
Up	NPY2R	56	0.022163	4152490	0.252513
Up	FOXL2	48	0.015502	2987768	0.259676
Up	SDC1	47	0.021521	2719126	0.274329
Up	CCR2	42	0.013268	4601914	0.250282
Up	FASLG	41	0.012687	1582940	0.275241
Up	CD79A	41	0.015733	4708198	0.245121
Up	IGHG1	40	0.00989	3641634	0.262781
Up	IGHA1	39	0.012825	2142462	0.268995
Up	CCR4	35	0.012921	3385226	0.248806
Up	IGHG2	33	0.006747	2674868	0.248616
Up	LTF	32	0.007394	1952246	0.24638
Up	TNFRSF13B	31	0.009736	2745188	0.234327
Up	ITK	30	0.004789	847972	0.279322
Up	IGKC	30	0.007807	2266182	0.253317
Up	HGF	29	0.00803	1507282	0.26043
Up	POTEI	29	0.010191	2696488	0.237292
Up	IGHA2	27	0.005708	3642692	0.220584
Up	P2RY8	25	0.00726	1510550	0.225971
Up	ZBBX	25	0.00844	825726	0.254877
Up	MYB	24	0.006732	1591432	0.252106
Up	CLEC12A	24	0.007916	2190268	0.221546
Up	GML	24	0.007403	1542574	0.244538
Up	TTR	21	0.005401	1289472	0.265576
Up	CD3E	21	0.005	822592	0.256707
Up	CCL5	21	0.006503	628572	0.23117
Up	ISL1	20	0.006034	1101492	0.241668
Up	IL2RB	20	0.004493	463700	0.267851
Up	TDGF1	20	0.008132	1032370	0.224947
Up	LYZ	19	0.004719	1308102	0.254416
Up	CRNN	19	0.004615	1699386	0.214018
Up	JCHAIN	19	0.002072	1086114	0.224971
Up	IQGAP2	18	0.00411	1091974	0.249793
Up	WT1	18	0.004077	1563748	0.238918
Up	CDA	18	0.005444	1258070	0.215724
Up	TEKT4	18	0.006382	836454	0.233136
Up	IL2RG	16	0.002901	291022	0.248279
Up	CTLA4	16	0.00267	370240	0.252695
Up	MAPK15	16	0.003406	820796	0.24729
Up	FOXJ1	15	0.004646	699482	0.238297
Up	IGLL5	15	0.003041	1619426	0.216866
Up	IRF4	14	0.004554	911852	0.223813
Up	TRIML2	14	0.003726	745092	0.229898
Up	SLAMF7	14	0.003102	658976	0.244638
Up	FOXF2	14	0.003977	970700	0.217874

Up	PRPH	14	0.00387	667282	0.240264
Up	CD2	13	0.002636	285328	0.255959
Up	TNNI3	11	1	110	1
Up	TUBAL3	11	0.001148	432370	0.250119
Up	RIBC2	11	0.003753	482112	0.22895
Up	DRD3	10	0.002836	245256	0.249188
Up	CDC20B	10	0.001734	432434	0.218732
Up	IGHM	10	0.001962	771212	0.259421
Up	TUBA4B	10	3.81E-04	146958	0.244439
Up	PLEKHG4B	10	0.002575	439176	0.228677
Up	TNFRSF9	9	0.001472	194238	0.217818
Up	FCGR2B	9	0.001661	223634	0.239732
Up	CD3D	9	0.001659	395762	0.238068
Up	UBASH3A	9	0.001652	322436	0.246856
Up	ICOS	8	0.00148	240124	0.2304
Up	CD28	8	9.20E-04	300772	0.227432
Up	CD209	8	0.001913	624752	0.174561
Up	HOXB7	8	0.001334	573180	0.2304
Up	TRARG1	8	0.002105	371424	0.193223
Up	IGHG3	8	8.36E-04	230950	0.21568
Up	SIK1	7	0.001327	404776	0.237867
Up	TRAT1	7	4.69E-04	65264	0.254003
Up	XIRP2	7	0.001263	101636	0.235926
Up	IL7R	6	2.94E-04	36312	0.233008
Up	IL5RA	6	0.001036	224104	0.204815
Up	CCL3	6	0.00102	264856	0.199301
Up	SLAMF6	6	2.94E-05	9606	0.204368
Up	F13A1	6	9.51E-04	178910	0.222644
Up	HSH2D	6	9.54E-04	223244	0.220504
Up	OTX2	6	0.001421	140220	0.183128
Up	MYH2	6	4.43E-04	116614	0.22614
Up	NCR1	5	9.67E-04	237432	0.221116
Up	GSDMA	5	3.69E-04	127942	0.213844
Up	PRSS21	5	0.001421	119730	0.239215
Up	TEKT1	5	9.78E-04	219492	0.196069
Up	MS4A1	4	9.51E-04	195172	0.241253
Up	IGHG4	4	2.00E-04	21808	0.212274
Up	IL24	4	9.98E-04	136230	0.210474
Up	PCP4	4	5.07E-04	62300	0.201567
Up	CD48	3	1.54E-04	17404	0.237586
Up	ITGAD	3	9.48E-04	106298	0.212906
Up	CLEC10A	3	1	6	1
Up	NLRP7	3	0	0	0.191609
Up	CD3G	2	0	0	0.212798
Up	GTF2A1L	2	4.74E-04	113092	0.185552
Up	CCL18	2	4.74E-04	97832	0.224432
Up	TFAP2D	2	8.04E-05	19550	0.230425
Up	LAIR2	2	8.88E-06	4128	0.193003
Up	GPR101	2	4.74E-04	84402	0.214355
Up	DNAJC5B	2	4.74E-04	63948	0.208066
Up	UCN3	1	0	0	1
Up	CLIC6	1	0	0	0.199489
Up	POU4F2	1	0	0	0.227297
Up	FCGBP	1	0	0	0.191748
Up	ART5	1	0	0	0.19167
Up	LHCGR	1	0	0	0.212584
Up	CD8B	1	0	0	0.161303
Up	IGLC7	1	0	0	0.178225
Up	IGLC2	1	0	0	0.209025
Up	LPAR3	1	0	0	1
Down	CFTR	448	0.23294	51911534	0.355249
Down	RHOB	310	0.15555	38047904	0.326878
Down	LMNA	234	0.131093	28009940	0.33655
Down	EGLN3	218	0.089938	27288494	0.300527
Down	ERBB3	164	0.07109	20481052	0.305288
Down	SFN	151	0.063891	14207304	0.312361
Down	CDH1	99	0.045914	9295142	0.323496
Down	LGALS3BP	96	0.041894	6685572	0.314245
Down	LLGL2	85	0.029632	6429240	0.269322
Down	MAP1LC3A	80	0.027842	8446748	0.288804

Down	MRPS26	80	0.02894	2657506	0.278585
Down	FOXE1	74	0.024085	8242508	0.261495
Down	POLR2F	69	0.024818	5551166	0.235767
Down	LRP2	62	0.025207	2775392	0.265426
Down	GPR37	62	0.021578	8569080	0.250386
Down	FASN	62	0.018313	4007430	0.303248
Down	TSC22D4	60	0.022958	4955946	0.269545
Down	HSPA2	51	0.017989	2628066	0.303248
Down	RABGEF1	48	0.016655	4511302	0.270495
Down	ACTN2	47	0.015872	1936132	0.261122
Down	DYSF	46	0.016541	2367264	0.266095
Down	CDK18	44	0.015072	4414490	0.268039
Down	TMEM171	44	0.016979	2402824	0.260671
Down	HIP1R	43	0.01693	2178882	0.287192
Down	BIN1	43	0.013341	2910812	0.262814
Down	GIPC1	41	0.015352	2965838	0.269959
Down	PFKL	41	0.017113	2200404	0.297016
Down	SLC25A13	41	0.012474	2982996	0.285154
Down	CA14	38	0.012126	3428272	0.22986
Down	PACSIN3	36	0.008301	1977144	0.264411
Down	NGFR	35	0.010558	2189410	0.266061
Down	SREBF1	35	0.012699	1366254	0.265559
Down	CMTM5	35	0.012218	2566464	0.225922
Down	CIRBP	32	0.010017	1802488	0.2613
Down	MAPK8IP1	30	0.012444	1435146	0.263635
Down	TF	30	0.009455	2568540	0.260542
Down	SBF1	30	0.012372	1266794	0.27754
Down	CBR1	30	0.013504	1693874	0.296974
Down	HK2	29	0.008798	1761438	0.253728
Down	IPO13	28	0.010874	1797866	0.256441
Down	TNFSF9	28	0.008188	1801388	0.230475
Down	INF2	28	0.003516	1545810	0.249247
Down	LLGL1	27	0.009508	1070324	0.282823
Down	FSCN1	27	0.010468	1439798	0.286724
Down	ATF3	26	0.005532	1667062	0.248835
Down	MARCKSL1	26	0.007311	1435148	0.24605
Down	SCAND1	26	0.010071	2109302	0.212359
Down	SHB	26	0.007591	964476	0.277449
Down	CTNNA3	25	0.00672	834614	0.263816
Down	PLEKHG3	25	0.006247	1054996	0.280473
Down	TSPAN15	24	0.008179	1096016	0.229722
Down	ERF	24	0.006312	1775804	0.248177
Down	MKRN3	24	0.007051	890546	0.252362
Down	ARHGAP23	24	0.007333	1371270	0.258025
Down	ADAMTS4	23	0.007022	1763788	0.237105
Down	IGSF8	22	0.006733	1435756	0.223695
Down	CUEDC1	22	0.007581	2106760	0.246107
Down	MYH6	22	0.006908	1582100	0.238418
Down	PHLDA3	22	0.004658	1584334	0.240785
Down	MEIS1	21	0.006568	1318744	0.218347
Down	CERCAM	21	0.00931	747112	0.230538
Down	APLP1	20	0.004911	829966	0.230715
Down	PRKCQ	20	0.006504	735740	0.278382
Down	AATK	20	0.003035	692730	0.264876
Down	PTPDC1	20	0.003353	1160564	0.253256
Down	ABCA2	20	0.008648	1517904	0.260349
Down	GALNT6	20	0.006483	3415268	0.206934
Down	VEGFA	19	0.004622	1026228	0.232507
Down	NME3	19	0.005723	1121392	0.23615
Down	ELF3	19	0.002774	768426	0.243832
Down	CTSV	19	0.005403	1153110	0.217101
Down	TLE2	18	0.003774	2368808	0.22454
Down	HTRA1	18	0.005805	918226	0.209232
Down	GLUL	17	0.003346	592544	0.243762
Down	DMBT1	16	0.001848	609084	0.239039
Down	EVI5L	16	0.005983	869332	0.233008
Down	CNP	16	0.004968	644810	0.27189
Down	CDC42EP1	15	0.004362	481862	0.271295
Down	INSIG1	15	0.002963	1520474	0.224623
Down	ST3GAL4	15	0.004884	545722	0.184006

Down	MCAM	15	0.00422	477230	0.268807
Down	MYCN	14	0.003305	769538	0.227776
Down	KLK10	14	0.001971	1124350	0.204666
Down	ALDOC	13	0.003062	1091856	0.242976
Down	TRAPPC6A	13	0.004934	312962	0.22769
Down	SEMA4C	12	0.00317	479158	0.247667
Down	RHOU	12	0.001547	375864	0.239868
Down	ZNF146	12	0.004459	843410	0.235137
Down	HSF4	11	0.002579	251034	0.20733
Down	CA9	11	9.11E-04	113280	0.258959
Down	DHCR7	10	0.002641	362558	0.258246
Down	CDR2L	9	0.002382	406166	0.216444
Down	MAL	9	0.00305	533156	0.219084
Down	PLLP	9	0.002396	255530	0.22801
Down	PLEKHG4	8	0.001024	145762	0.212466
Down	PCCB	7	0.001531	206160	0.221348
Down	GJB1	7	6.42E-04	160668	0.240579
Down	AGPAT4	7	0.001284	240210	0.202534
Down	RTKN	6	0.001641	132644	0.263224
Down	UNC5B	6	0.001445	200958	0.223849
Down	NOXA1	6	0.002369	378880	0.214115
Down	SCD	6	6.70E-04	111220	0.23965
Down	SCHIP1	5	9.48E-04	170190	0.199991
Down	GCM1	5	0.001021	282572	0.216355
Down	TACSTD2	5	0.001036	180184	0.236547
Down	TTYH1	5	0.001011	145006	0.212306
Down	PTPRH	5	5.11E-04	42036	0.263388
Down	GNG8	4	9.55E-04	132524	0.214148
Down	NENF	4	0.001421	188832	0.207851
Down	FGF11	4	5.52E-04	129372	0.215691
Down	SEMA3B	3	1	6	1
Down	PPEF1	2	3.02E-06	3356	0.226845
Down	GOLGA6A	2	4.74E-04	73866	0.206751
Down	SYNJ2	2	2.56E-04	79302	0.242808
Down	ICOSLG	1	0	0	0.187264
Down	LDB3	1	0	0	0.207066
Down	GPIHBP1	1	0	0	0.173413
Down	CNDP1	1	0	0	0.200057
Down	THBS2	1	0	0	0.178905
Down	TNFAIP6	1	0	0	0.187773
Down	EDIL3	1	0	0	0.206701
Down	EEPD1	1	0	0	0.215284
Down	MT3	1	0	0	0.209856
Down	EFS	1	0	0	0.18547
Down	HSD17B3	1	0	0	0.191792
Down	MPP2	1	0	0	0.177453
Down	PRODH	1	0	0	0.232699
Down	NTNG2	1	0	0	0.20019
Down	NINJ2	1	0	0	1
Down	MTFR2	1	0	0	0.201615
Down	LSS	1	0	0	0.196498
Down	S1PR5	1	0	0	0.20019
Down	TUBB4A	1	0	0	0.236985
Down	KREMEN2	1	0	0	0.25182
Down	HPN	1	0	0	0.169716
Down	PHLDB1	1	0	0	0.231094

Table 6 MiRNA - hub gene and TF – hub gene topology table

Regulation	Hub Genes	Degree	MicroRNA	Regulation	Hub Genes	Degree	TF
Up	IKZF3	147	hsa-mir-6794-3p	Up	LTF	15	BRCA1
Up	TAB2	118	hsa-mir-3689a-3p	Up	CD79A	10	HNF4A
Up	C6orf141	59	hsa-mir-4449	Up	LCK	10	NFKB1
Up	SDC1	47	hsa-mir-146a-5p	Up	IKZF3	9	TEAD1
Up	CCR4	45	hsa-mir-4695-5p	Up	TAB2	8	ELK4
Up	SLAMF1	30	hsa-mir-4778-3p	Up	PYHIN1	8	JUND
Up	FASLG	25	hsa-mir-362-3p	Up	DOK2	8	USF2

Up	FOXL2	19	hsa-mir-3915	Up	POTEF	7	STAT3
Up	CCR2	11	hsa-mir-6514-3p	Up	CCR4	6	MEF2A
Up	CD79A	7	hsa-mir-520f-3p	Up	SLAMF1	6	YY1
Up	PYHIN1	7	hsa-mir-1277-5p	Up	SDC1	6	PPARG
Up	LCK	6	hsa-mir-520c-3p	Up	FASLG	5	ARID3A
Up	DOK2	5	hsa-mir-365b-3p	Up	NPY2R	5	ELF5
Up	NPY2R	4	hsa-mir-302f	Up	FOXL2	4	CEBPB
Up	POTEF	2	hsa-mir-16-5p	Up	CCR2	4	TP53
Down	RHOB	216	hsa-mir-4651	Down	MAP1LC3A	14	TFAP2C
Down	LGALS3BP	99	hsa-mir-548q	Down	CFTR	10	NR2F1
Down	SFN	91	hsa-mir-8485	Down	LLGL2	8	FOXO3
Down	CDH1	75	hsa-mir-195-5p	Down	POLR2F	8	NRF1
Down	POLR2F	68	hsa-mir-4739	Down	FOXE1	8	NFYA
Down	EGLN3	58	hsa-mir-122-5p	Down	LGALS3BP	8	HOXA5
Down	ERBB3	53	hsa-mir-6842-5p	Down	MRPS26	8	SOX17
Down	LMNA	50	hsa-mir-744-5p	Down	LRP2	8	E2F6
Down	LLGL2	40	hsa-mir-200c-3p	Down	CDH1	7	ESR1
Down	FOXE1	29	hsa-mir-4723-3p	Down	SFN	6	FOS
Down	GPR37	22	hsa-mir-186-5p	Down	RHOB	5	RELA
Down	CFTR	16	hsa-mir-154-5p	Down	EGLN3	4	POU2F2
Down	LRP2	15	hsa-mir-196a-5p	Down	ERBB3	4	GATA2
Down	MRPS26	14	hsa-mir-3065-5p	Down	LMNA	4	JUN
Down	MAP1LC3A	6	hsa-mir-22-3p	Down	GPR37	4	FOXL1

Table 7 Drug- hub gene topology table

Categeory	Gene	Degree	Drug (one examples)
UP	FCGR2B	20	Palivizumab
UP	LYZ	15	Cu-Bicyclam
UP	LCK	14	Nintedanib
UP	LHCGR	7	Goserelin
UP	MS4A1	5	Ofatumumab
UP	IL2RB	4	Basiliximab
UP	HGF	4	N,O6-Disulfo-Glucosamine
UP	NPY2R	3	Cysteamine
UP	CCR2	3	CCX915
UP	CD3D	2	Blinatumomab
UP	IL2RG	2	Aldesleukin
UP	ITK	2	Pazopanib
UP	F13A1	2	N-Acetyl-Serine
UP	CDA	2	DN-101
UP	CD2	1	Alefacept
UP	CD3E	1	Muromonab
UP	CD3G	1	Muromonab
Down	CFTR	8	Lumacaftor
Down	CA9	6	Zonisamide
Down	HPN	5	Bentiromide
Down	PRKCQ	4	Tamoxifen
Down	LRP2	4	Urokinase
Down	TUBB4A	4	Epothilone D
Down	MAPK8IP1	4	2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One

Down	CA14	3	Acetazolamide
Down	FASN	2	Cerulenin
Down	GLUL	2	L-Glutamine
Down	LSS	2	Lanosterol
Down	CBR1	2	3-(4-Amino-1-Tert-Butyl-1h-Pyrazolo[3,4-D]Pyrimidin-3-Yl)Phenol
Down	CTSV	2	3-amino-5-phenylpentane
Down	DHCR7	1	NADH
Down	HSD17B3	1	NADH

Table 8. Binding affinity and amino acid interactions of receptors and ligands

Compound and gene name (Receptor pdb id)	Affinity (kcal/mol)	Amino acid interactions			
		Hydrogen bonding interactions	Electrostatic interactions	Hydrophobic interactions	Ionic interactions
Nintedanib LCK (2og8)	-9.7	MET A: 319, LYS A: 273, GLY A: 322, ASN A: 321	--	TYR A: 318, LEU A: 371, PHE A: 383, LEU A: 251, ALA A: 271, Val A: 259	--
Glyburide and CFTR (2pzg)	-8.5	ARG A: 250, ILE A: 482	SER 485	PRO A: 477, HIS A: 484, LYS A: 483, LEU A: 387	--
Glyburide and CFTR (2bbs)	-7.5	SER A: 466, GLY A: 461	--	ALA A: 551, VAL A: 603	--
Caffeine and CA9 (5dvx)	-6.7	PHE A: 173, PHE A: 390, PRO A: 391, ALA A: 171, ARG A: 151	--	ALA A: 388, ALA A: 392, GLN A: 169, ARG A: 234, GLU A: 305, LEU A: 380	--
Goserelin and LHCGR (1qfw)	-6.6	CYS A: 28, THR A: 58, CYS A: 32, SER A: 34, CYS A: 60, SER A: 55, GLN A: 27, ASN A: 15	GLU A: 77	CYS A:59, HIS A: 79	GLU A: 77
Caffeine and CA14 (4lu3)	-5.6	THR A: 200	HIS A: 94, ASN A: 62	LEU A: 198, VAL A: 121, ALA A: 143	--
Glucosamine 6-sulfate HGF (3hms)	-5.2	TYR A: 124, THR A: 75, CYS A: 74, CYS A: 84, ARG A: 76, GLU A: 41	--	--	--

Figures

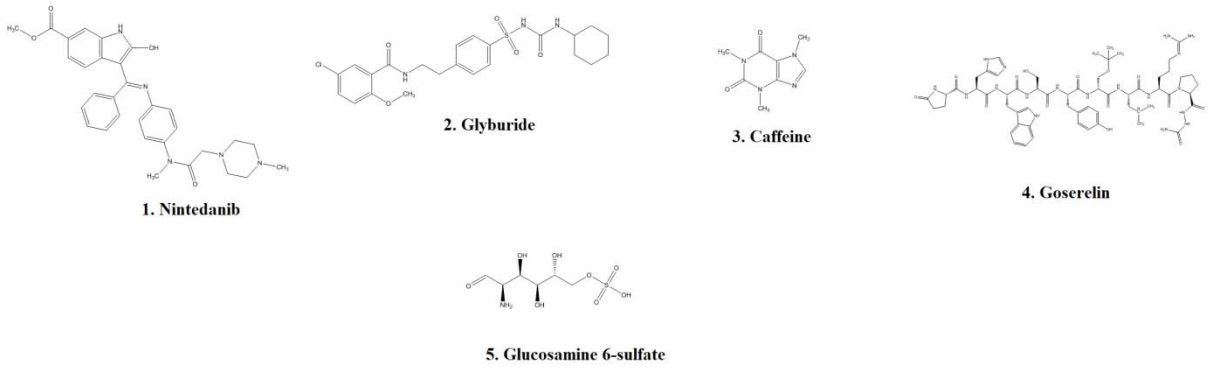


Fig. 1. Chemical structures of drug molecules.

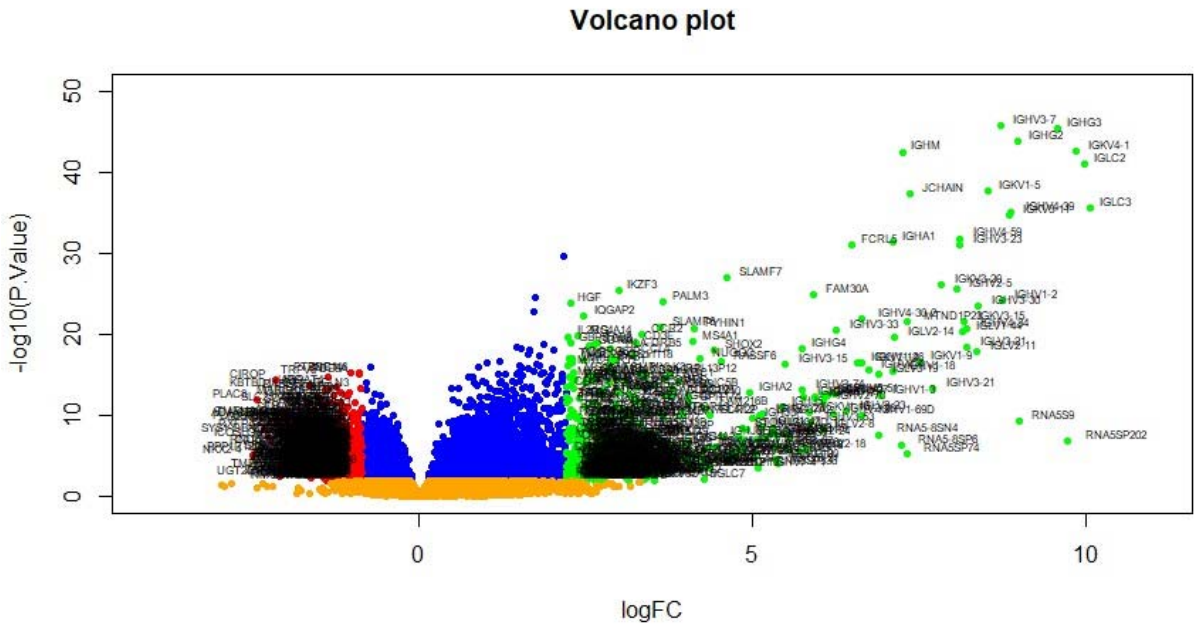


Fig. 2. Volcano plot of differentially expressed genes. Genes with a significant change of more than two-fold were selected. Green dot represented up regulated significant genes and red dot represented down regulated significant genes.

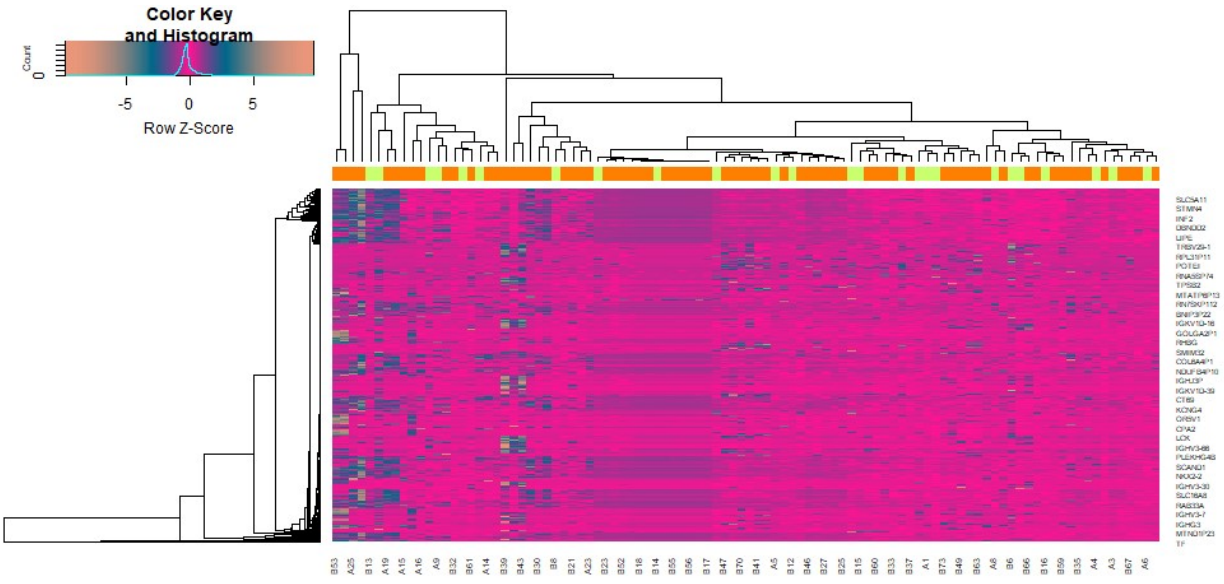
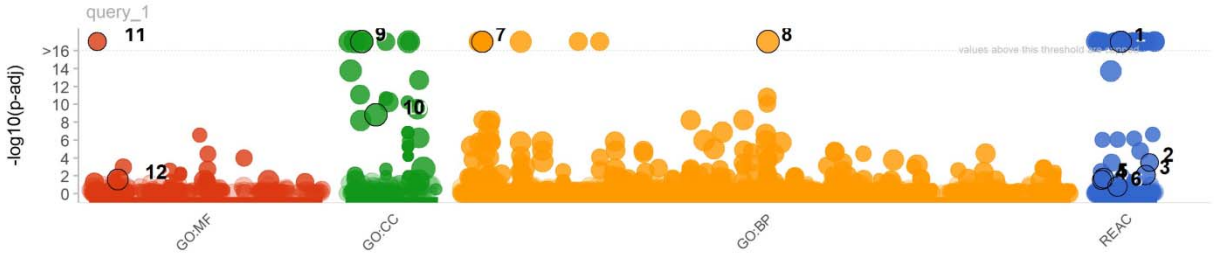


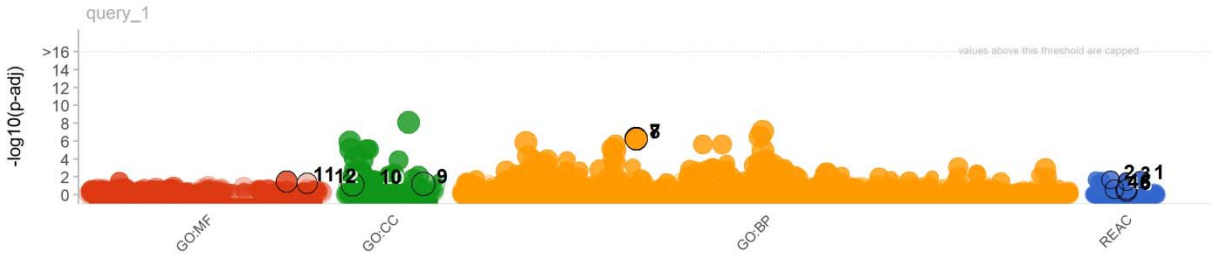
Fig. 3. Heat map of differentially expressed genes. Legend on the top left indicate log fold change of genes. (A1 – A25 = Normal control samples; B1 – B 73 = MS samples)



id	source	term_id	term_name	term_size		p_value
1	REAC	REAC:R-HSA-168256	Immune System	2079		2.5e-36
2	REAC	REAC:R-HSA-202403	TCR signaling	120		3.0e-04
3	REAC	REAC:R-HSA-449147	Signaling by Interleukins	472		7.6e-03
4	REAC	REAC:R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	328		2.8e-02
5	REAC	REAC:R-HSA-1280215	Cytokine Signaling in Immune system	777		1.9e-02
6	REAC	REAC:R-HSA-500792	GPCR ligand binding	460		1.5e-01
7	GO:BP	GO:0002376	immune system process	2796		5.1e-82
8	GO:BP	GO:0050896	response to stimulus	8993		2.5e-36
9	GO:CC	GO:0016020	membrane	9912		6.8e-19
10	GO:CC	GO:0032991	protein-containing complex	7861		1.4e-09
11	GO:MF	GO:0003823	antigen binding	175		3.8e-113
12	GO:MF	GO:0005102	signaling receptor binding	1499		2.5e-02

g:Profiler (biit.cs.ut.ee/gprofiler)

Fig. 4. GO and REACTOME pathway enrichment analysis for up regulated genes. $p < 0.05$. Abbreviations: BP, biological process; CC, cell component; MF, molecular function. GO, Gene Ontology; REAC, REACTOME. The size of the circle represents the number of genes involved, and the abscissa represents the frequency of the genes involved in the term total genes.



id	source	term_id	term_name	term_size	p_value
1	REAC	REAC:R-HSA-1655829	Regulation of cholesterol biosynthesis by SREBP (SREBF)	53	2.1e-02
2	REAC	REAC:R-HSA-1474228	Degradation of the extracellular matrix	140	2.1e-02
3	REAC	REAC:R-HSA-8957322	Metabolism of steroids	152	3.3e-02
4	REAC	REAC:R-HSA-1474244	Extracellular matrix organization	298	2.4e-01
5	REAC	REAC:R-HSA-556833	Metabolism of lipids	735	2.5e-01
6	REAC	REAC:R-HSA-1430728	Metabolism	2079	3.3e-01
7	GO:BP	GO:0032502	developmental process	6478	6.0e-07
8	GO:BP	GO:0032501	multicellular organismal process	7234	5.5e-07
9	GO:CC	GO:0110165	cellular anatomical structure	21571	6.0e-02
10	GO:CC	GO:0005737	cytoplasm	12394	6.7e-02
11	GO:MF	GO:0098772	molecular function regulator activity	2120	3.3e-02
12	GO:MF	GO:0140677	molecular function activator activity	1132	5.1e-02

g:Profiler (biit.cs.ut.ee/gprofiler)

Fig. 5. GO and REACTOME pathway enrichment analysis for down regulated genes. $p < 0.05$. Abbreviations: BP, biological process; CC, cell component; MF, molecular function. GO, Gene Ontology; REAC, REACTOME. The size of the circle represents the number of genes involved, and the abscissa represents the frequency of the genes involved in the term total genes.

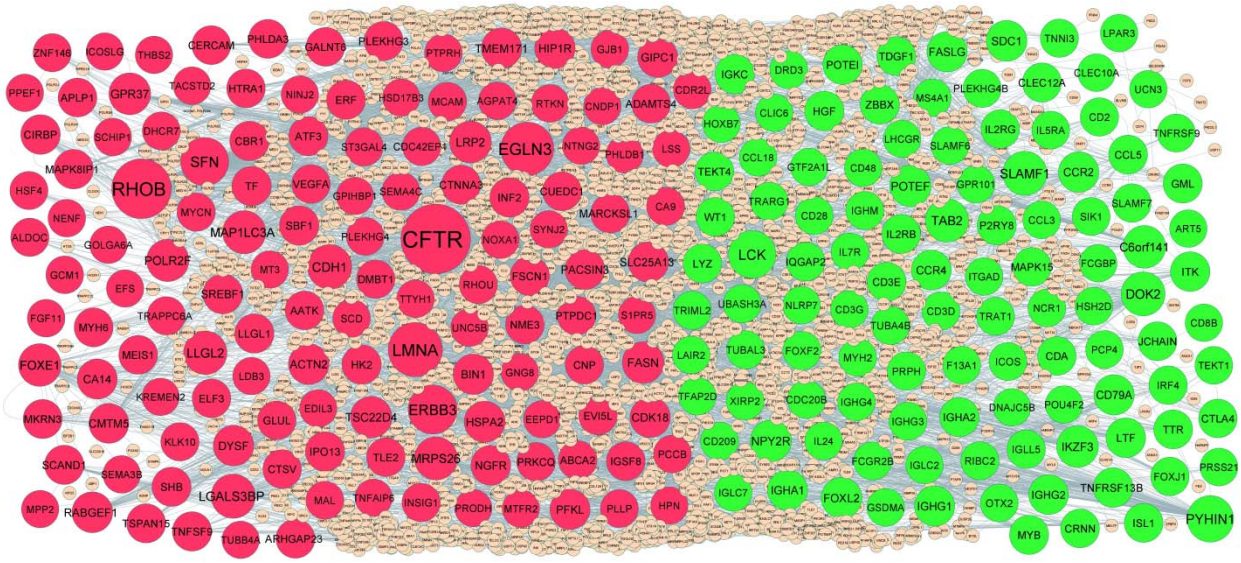


Fig. 6. PPI network of DEGs. Up regulated genes are marked in parrot green; down regulated genes are marked in red.

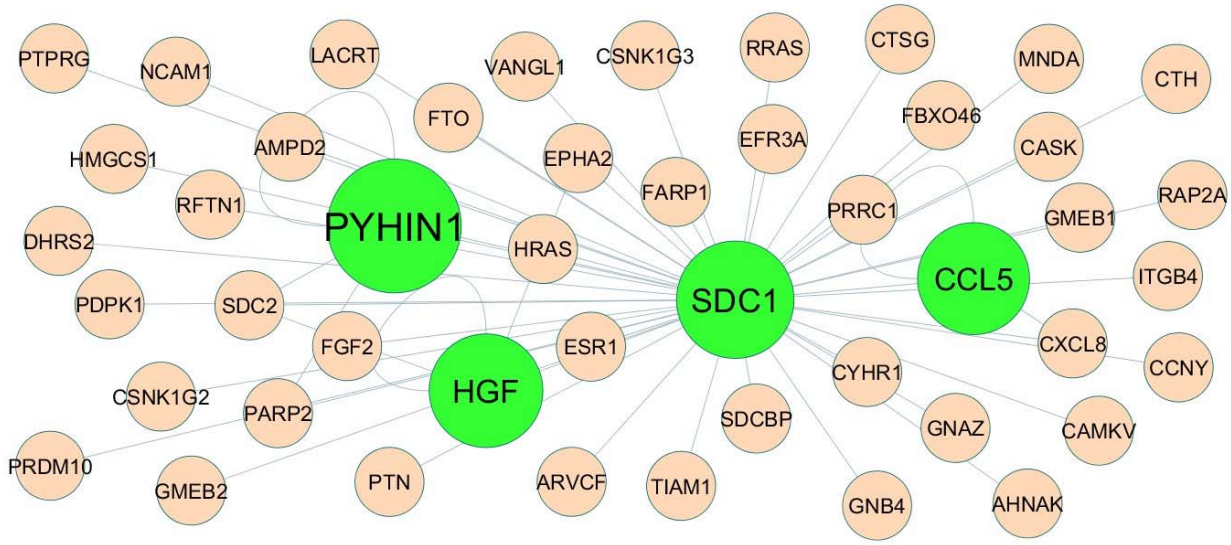
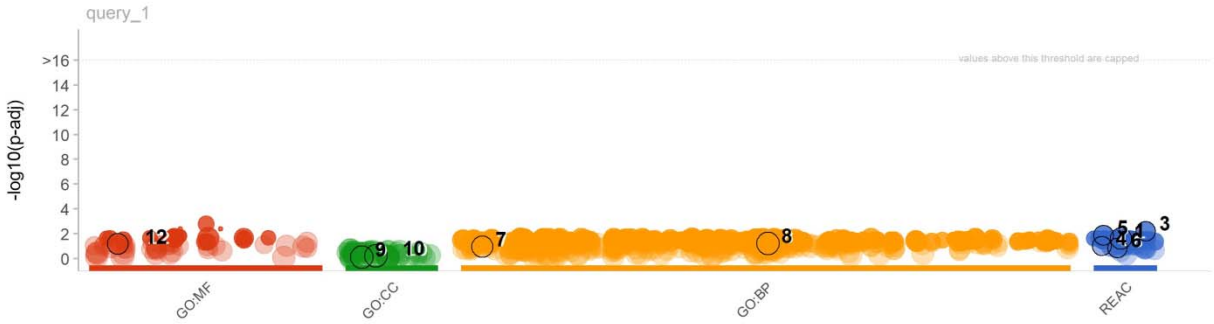


Fig. 7. Modules 1 was isolated form PPI of up regulated genes. Module 1 has 47 nodes and 54 edges for up regulated genes. Up regulated genes are marked in green



id	source	term_id	term_name	term_size	p_value
1	REAC	REAC:R-HSA-168256	Immune System	2079	2.4e-02
3	REAC	REAC:R-HSA-449147	Signaling by Interleukins	472	6.1e-03
4	REAC	REAC:R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	328	1.0e-01
5	REAC	REAC:R-HSA-1280215	Cytokine Signaling in Immune system	777	1.4e-02
6	REAC	REAC:R-HSA-500792	GPCR ligand binding	460	1.4e-01
7	GO:BP	GO:0002376	immune system process	2796	1.1e-01
8	GO:BP	GO:0050896	response to stimulus	8993	6.1e-02
9	GO:CC	GO:0016020	membrane	9912	7.9e-01
10	GO:CC	GO:0032991	protein-containing complex	7861	6.3e-01
12	GO:MF	GO:0005102	signaling receptor binding	1499	7.0e-02

g:Profiler (biit.cs.ut.ee/gprofiler)

Fig. 8. Enrichment analysis for module 1. The size of the circle represents the number of genes involved, and the abscissa represents the frequency of the genes involved in the term total genes.

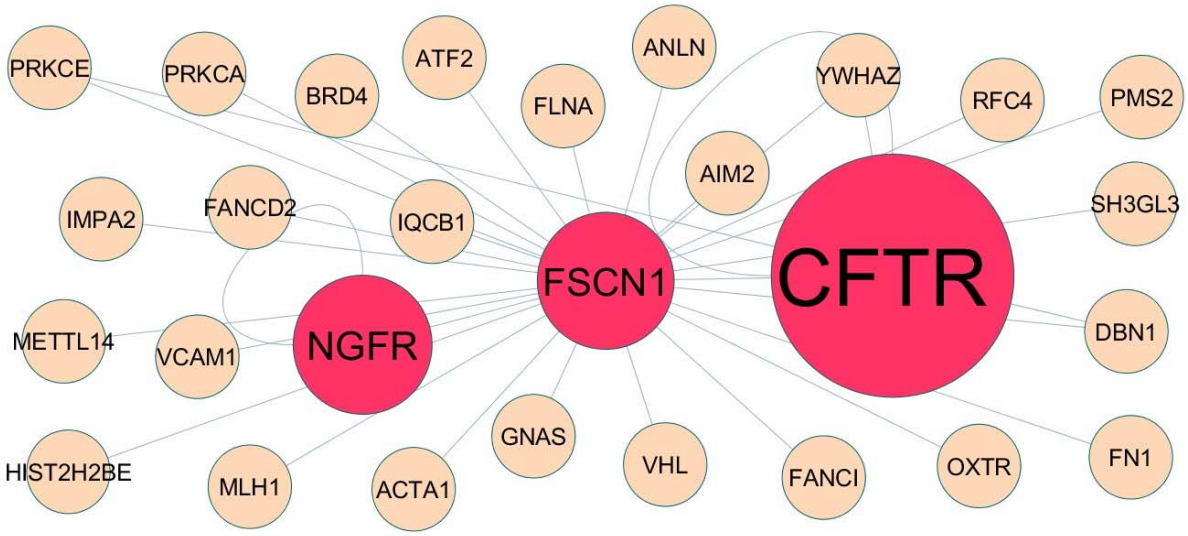
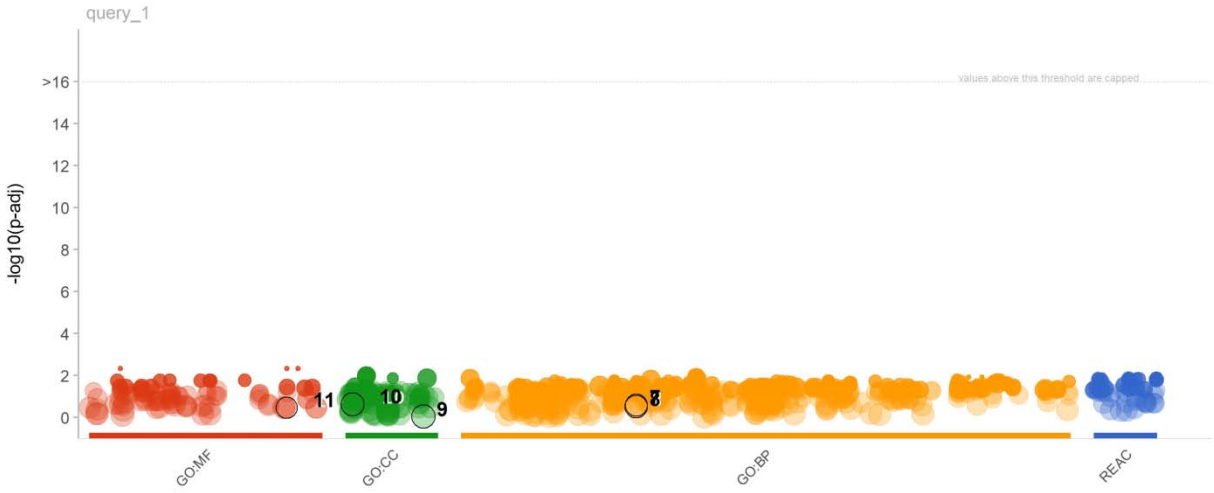


Fig. 9. Module 2 was isolated form PPI of up regulated genes. Module 2 has 28 nodes and 32 edges for down regulated genes. Down regulated genes are marked in red



id	source	term_id	term_name	term_size		p_value
7	GO:BP	GO:0032502	developmental process	6478		2.6e-01
8	GO:BP	GO:0032501	multicellular organismal process	7234		3.1e-01
9	GO:CC	GO:0110165	cellular anatomical structure	21571		9.4e-01
10	GO:CC	GO:0005737	cytoplasm	12394		2.3e-01
11	GO:MF	GO:0098772	molecular function regulator activity	2120		3.4e-01

g:Profiler (biit.cs.ut.ee/gprofiler)

Fig. 10. Enrichment analysis for module 2. The size of the circle represents the number of genes involved, and the abscissa represents the frequency of the genes involved in the term total genes.

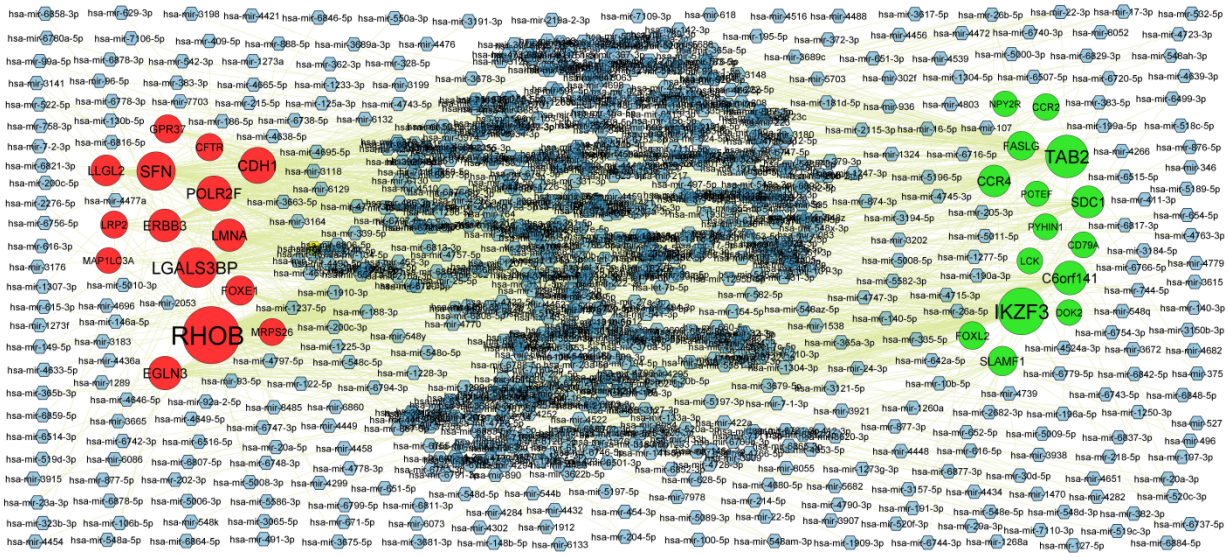


Fig. 11. Hub gene - miRNA regulatory network. The blue color diamond nodes represent the key miRNAs; up regulated genes are marked in green; down regulated genes are marked in red.

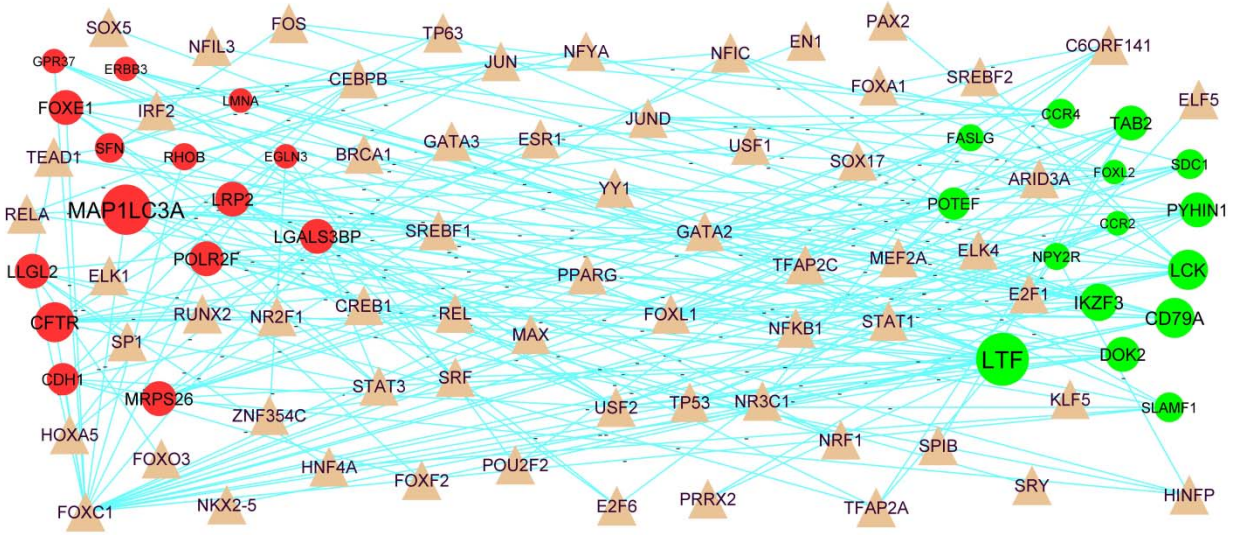


Fig. 12. Hub gene - TF regulatory network. The brown color triangle nodes represent the key TFs; up regulated genes are marked in green; down regulated genes are marked in red.

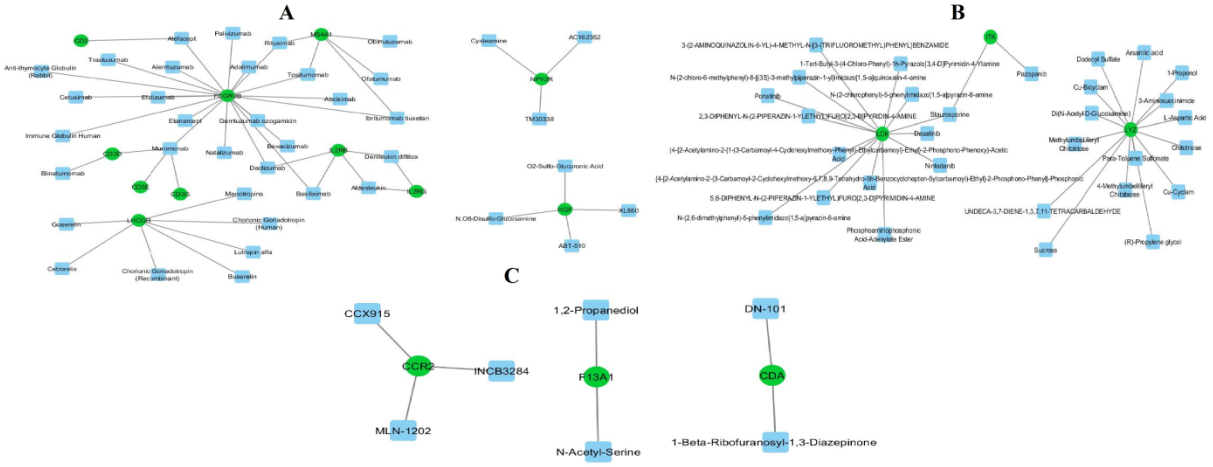


Fig. 13. Drug-hub gene interaction network. The blue color rectangle nodes represent the drug molecule; up regulated genes are marked in green

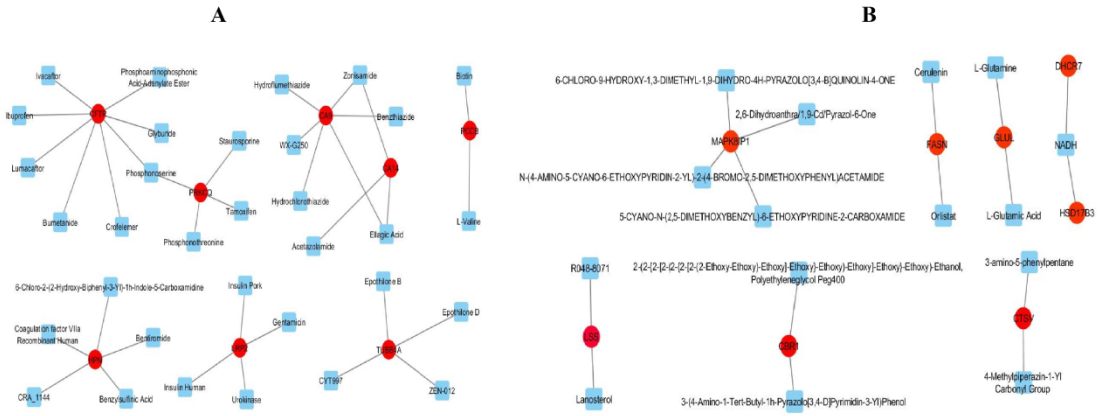


Fig. 14. Drug-hub gene interaction network. The blue color rectangle nodes represent the key drug molecules; down regulated genes are marked in red

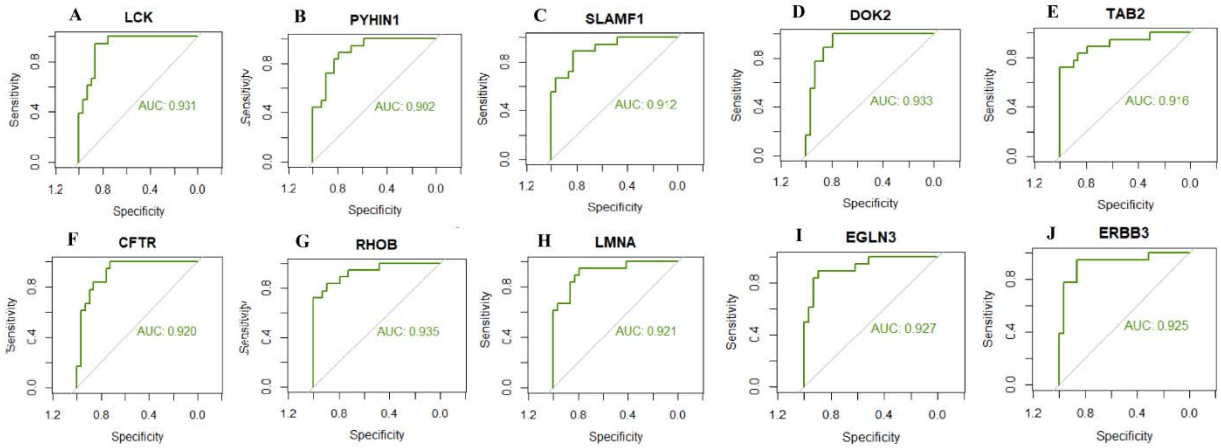
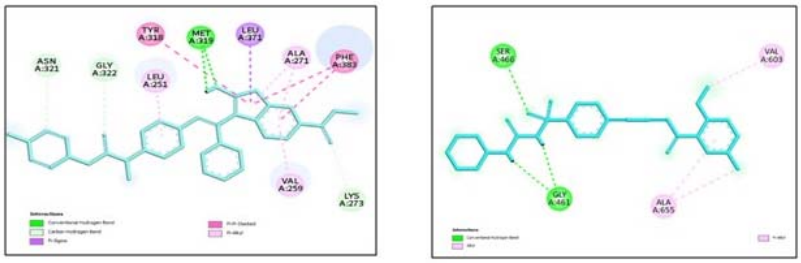
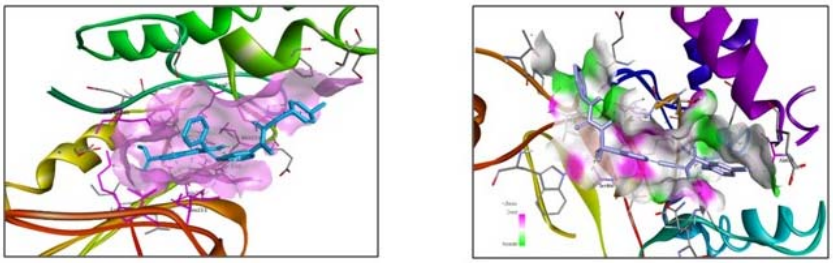


Fig. 15. ROC curve analyses of hub genes. A) LCK B) PYHIN1 C) SLAMF1 D) DOK2 E) TAB2 F) CFTR G) RHOB H) LMNA I) EGLN3 J) ERBB3



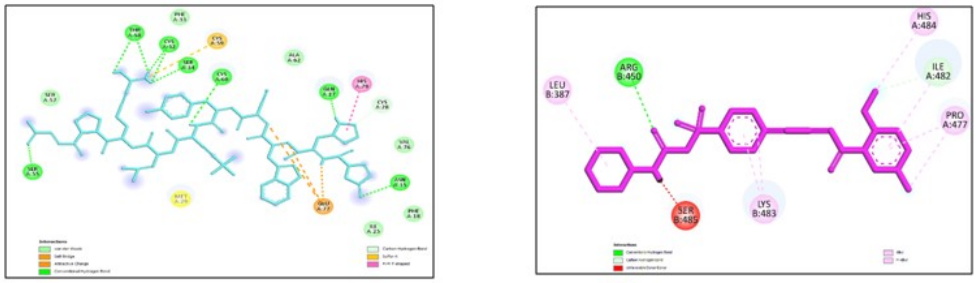
A Nintedanib2og8 LCK 2D **B Glyburide 2bbs CFTR 2D**

Fig .16. 2D binding image of A) Ninatanib with LCK (pdb: 2og8) gene B) Glyburide with CFTR (pdb: 2bbs) gene.



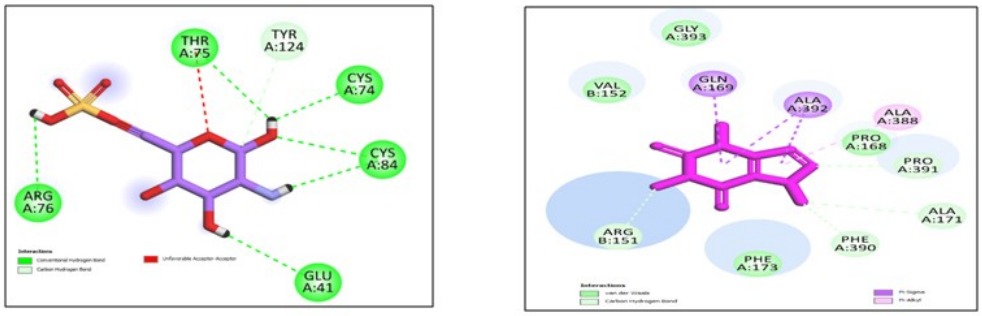
A Nintedanib2og8 LCK 3D **B Glyburide 2bbs CFTR 3D**

Fig .17. 3D binding image of A) Ninatanib with LCK (pdb: 2og8) gene B) Glyburide with CFTR (pdb: 2bbs) gene.



A Goserelin 1qfw LHCGR 2D **B Glyburide 2pzg CFTR 2D**

Fig .18. 2D binding image of A) Goserelin with LHCGR (pdb: 1qfw) gene B) Glyburide with CFTR (pdb: 2pzg) gene.



A Glucosamine 6 sulphate 3hms HGF 2D **B Caffeine 5dvx CA9 2D**

Fig .19. 2D binding image of A) Glucosamine 6 sulphate with HGF (pdb: 3hms) gene B) Caffeine with CA9 (pdb: 5dvx) gene.

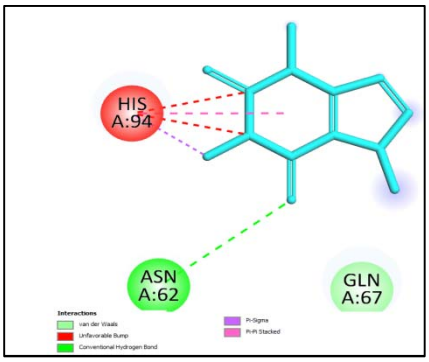
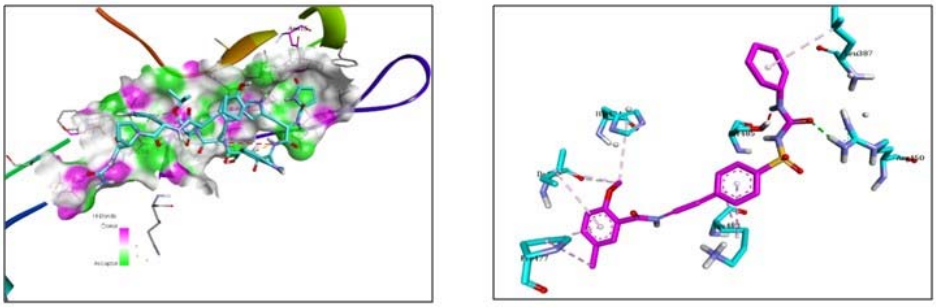
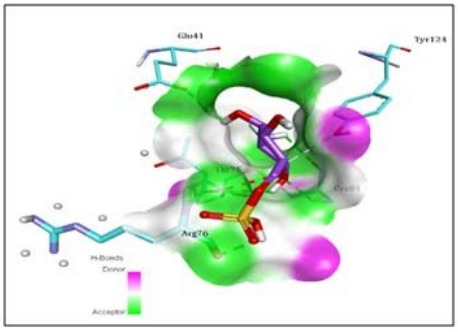


Fig .20. 2D binding image of Caffeine with CA14 (pdb: 4lu3) gene

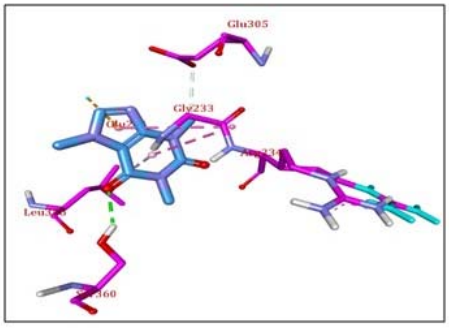


A Goserelin 1qfw LHCGR 3D **B Glyburide 2pzg CFTR 3D**

Fig .21. 3D binding image of A) Goserelin with LHCGR (pdb: 1qfw) gene B) Glyburide with CFTR (pdb: 2pzg) gene.



A Glucosamine 6 sulphate 3hms HGF 3D



B Caffeine 5dvx CA9 3D

Fig .22. 3D binding image of A) Glucosamine 6 sulphate with HGF (pdb: 3hms) gene B) Caffeine with CA9 (pdb: 5dvx) gene.

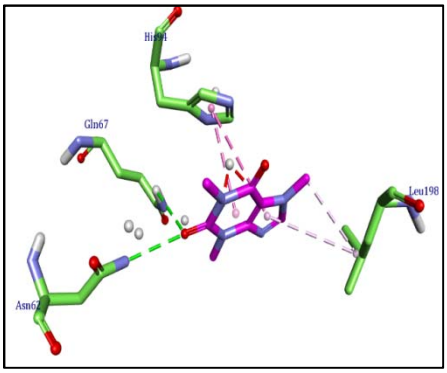


Fig .23. 3D binding image of Caffeine with CA14 (pdb: 4lu3) gene