Integrated bioinformatics analysis reveals novel key biomarkers and potential candidate small molecule drugs in gestational diabetes mellitus

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Abstract

Gestational diabetes mellitus (GDM) is one of the metabolic diseases during pregnancy. The identification of the central molecular mechanisms liable for the disease pathogenesis might lead to the advancement of new therapeutic options. The current investigation aimed to identify central differentially expressed genes (DEGs) in GDM. The transcription profiling by array data (E-MTAB-6418) was obtained from the ArrayExpress database. The DEGs between GDM samples and non GDM samples were analyzed with limma package. Gene ontology (GO) and REACTOME enrichment analysis were performed using ToppGene. Then we constructed the protein-protein interaction (PPI) network of DEGs by the Search Tool for the Retrieval of Interacting Genes database (STRING) and module analysis was performed. Subsequently, we constructed the miRNA-hub gene network and TF-hub gene regulatory network by the miRNet database and NetworkAnalyst database. The validation of hub genes was performed through receiver operating characteristic curve (ROC). Finally, the candidate small molecules as potential drugs to treat GDM were predicted by using molecular docking. Through transcription profiling by array data, a total of 869 DEGs were detected including 439 up regulated and 430 down regulated genes. Biological process analysis of GO enrichment analysis showed these DEGs were mainly enriched in reproduction, nuclear outer membrane-endoplasmic reticulum membrane network, identical protein binding, cell adhesion, supramolecular complex and signaling receptor binding. Signaling pathway enrichment analysis indicated that these DEGs played a vital in cell surface interactions at the vascular wall and extracellular matrix organization. Ten genes, HSP90AA1, EGFR, RPS13, RBX1, PAK1, FYN, ABL1, SMAD3, STAT3, and PRKCA in the center of the PPI network, modules, miRNA-hub gene regulatory network and TF-hub gene regulatory network were associated with GDM, according to ROC analysis. Finally, the most significant small molecules were predicted based on molecular docking. Our results indicated that HSP90AA1, EGFR, RPS13, RBX1, PAK1, FYN, ABL1, SMAD3, STAT3, and PRKCA could be the potential novel biomarkers for GDM diagnosis, prognosis and the promising therapeutic targets. The current might be essential to understanding the molecular mechanism of GDM initiation and development.
**Keywords:** bioinformatics analysis; small drug molecules; differentially expressed genes; gestational diabetes mellitus; novel biomarkers.

**Introduction**

Gestational diabetes mellitus (GDM) is the diabetes diagnosed during pregnancy, which affecting 2–5% of all pregnant women worldwide [1-2]. Risk factors associated with GDM includes obesity, previous occurrence of diabetes, family history of type 2 diabetes, preeclampsia, hypertension, cardiovascular diseases and genetic factors [3]. In GDM blood glucose levels are elevated during the third trimester of pregnancy [4]. Moreover, the elevated glucose level in pregnancy is closely linked with detrimental consequences in the newborn babe, such as fetal hyperglycemia and cardiovascular disease [5]. Therefore, investigating the molecular mechanisms of GDM and early screening of patients with GDM are essential to restrain the occurrence and progression of GDM.

It is therefore essential to find new genes and pathways that are associated with GDM and patient prognosis, which might not only help to explicate the underlying molecular mechanisms associated, but also to discover new diagnostic molecular markers and therapeutic targets. Transcription profiling by array can rapidly detect gene expression on a global basis and are particularly useful in screening for differentially expressed genes (DEGs) [6]. Gene chips allow the analysis of gene expression in a high throughput way with great sensitivity, specificity and repeatability. A symbolic amount of data has been produced via the use of gene chips and the majority of such gene expression data has been uploaded and stored in public databases. Previous investigation concerning GDM transcription profiling by array have found hundreds of DEGs [7-8]. The availability of bioinformatics analysis based on high-throughput technology enabled the investigation of the modification in gene expression and the interaction between differential genes in GDM, to provide novel insights for further in-depth investigations.
In the current investigation, public transcription profiling by array data of E-MTAB-6418 from ArrayExpress database was downloaded. A total of 38 GDM samples and 70 non GDM samples data in E-MTAB-6418 were available. DEGs between GDM and non GDM were filtered and obtained using bioconductor package limma in R software. Gene Ontology (GO) and REACTOME pathway enrichment analyses of the DEGs were performed. The functions of the DEGs were further assessed by PPI network and modular analyses to identify the hub genes in GDM. Subsequently, miRNA-hub gene regulatory network and TF-hub gene regulatory network were constructed to identify the target genes, miRNAs and TFs in GDM. Hub genes were validated by receiver operating characteristic curve (ROC). Finally, screening of small drug molecules carried out by using molecular docking. The investigation was designed to obtain deep insights during the pathogenesis of GDM.

Materials and methods

Transcription profiling by array data information

The mRNA expression profile E-MTAB-6418 [9] based on A-MEXP-2072 - Illumina HumanHT-12_V4_0_R2_15002873_B was downloaded from the ArrayExpress database (https://www.ebi.ac.uk/arrayexpress/) [10], which included 38 GDM samples and 70 non GDM samples.

Identification of DEGs

To obtain differentially expressed genes (DEGs) between GDM samples and non GDM samples. After limma package in R analysis [11], results including adjusted P values (adj. P. Val) and log FC were provided. Cut-off criterion was set as adj. P. Val <0.05, |log FC| > 1.158 for up regulated genes and |log FC| < -0.83 for down regulated genes. A list of candidate DEGs was obtained via the above methods.

Gene ontology and pathway enrichment of DEGs analysis

Gene ontology (GO) analysis (http://geneontology.org/) [12] and REACTOME (https://reactome.org/) [13] pathway enrichment analysis are both integrated in the ToppGene (ToppFun) (https://toppgene.cchmc.org/enrichment.jsp) [14] program. Therefore, ToppGene is capable of providing comprehensive annotations for functional and pathway interpretations. In this experiment, DEGs were uploaded
onto ToppGene in order to perform related GO and REACTOME pathway enrichment analyses. The cut-off criterion was set as P<0.05.

**PPI network establishment and modules selection**

Search Tool for the Retrieval of Interacting Genes StringDB interactome (https://string-db.org/) is a database of known and predicted protein-protein interactions [15]. All candidate DEGs were posted into the STRING website, with a confidence score of ≥0.4 set as the cut-off criterion for PPI network construction. Then, Cytoscape (version 3.8.2, http://www.cytoscape.org/) [16] software was utilized to construct protein interaction relationship network. The Network Analyzer plugin was performed to scale node degree [17], betweenness centrality [18], stress centrality [19] and closeness centrality [20] of the PPI network. Significant modules in the visible PPI network were screened using the PEWCC1 (http://apps.cytoscape.org/apps/PEWCC1) [21] plugin. Degree cut-off=2, node score cut-off=0.2, k-core=2, and max depth=100 were set as the cut-off criterion. Three highest-degree modules were extracted, and the potential mechanisms of each module were investigated with ToppGene. A degree of ≥10 was set as the filter criterion. Hub genes with high degree were selected as the potential key genes and biomarkers.

**miRNA-hub gene regulatory network construction** The miRNet database (https://www.mirnet.ca/) [22] is an open-source platform mainly focusing on miRNA-target interactions. miRNet utilizes fourteen established miRNA-target prediction databases, including TarBase, miRTarBase, miRecords, miRanda, miR2Disease, HMDD, PhenomiR, SM2miR, PharmacomiR, EpimiR, starBase, TransmiR, ADmiRE, and TAM 2.0. In this study, miRNAs were considered the targeted miRNAs of hub genes. Subsequently, the network of the hub genes and their targeted miRNAs was visualized by Cytoscape software.

**TF-hub gene regulatory network construction**

The NetworkAnalyst database (https://www.networkanalyst.ca/) [23] is an open-source platform mainly focusing on TF-target interactions. NetworkAnalyst utilizes three established TF-target prediction databases, including ENCODE, JASPAR, ChEA. In this study, TFs were considered the targeted TFs of hub genes based on ChEA database. In this study, TFs were considered the targeted TFs of
hub genes. Subsequently, the network of the hub genes and their targeted TFs was visualized by Cytoscape software.

**Receiver operating characteristic (ROC) curve analysis**

The receiver operating characteristic curve (ROC) was constructed by predicting the probability of a diagnosis being of high or low integrated score of significant hub gene expression in GDM. Area under curve (AUC) analysis was operated to calculate the diagnostic ability by using the statistical package pROC in R software [24].

**RT-PCR Analysis**

The HTR-8/SVneo (ATCC CRL3271) cell line procured from ATCC. For normal HTR-8/SVneo (ATCC CRL3271) cell line was grown in RPMI-1640 medium added with 10% fetal bovine serum, containing 5.5 mM glucose, and 1% penicillin/streptomycin. Incubate this cell line at 37°C in a 5% CO2 in humidified cell culture incubator. Similarly, for GDM HTR-8/SVneo (ATCC CRL3271) cell line was grown in RPMI-1640 medium added with 10% fetal bovine serum, containing 5.5 mM glucose, and 1% penicillin/streptomycin. Incubate this cell line at 37°C in a 5% CO2 in humidified cell culture incubator for 24 hrs, then stimulated with various concentrations 40 mM of D-glucose for 6 h. TRIzol (cat. no. 9109; Takara Bio, Inc.) was used to isolate total RNA from HTR-8/SVneo cell line and HTR-8/SVneo cell line treated with glucose according to the manufacturer's instructions. TRI Reagent (Sigma, USA).was used to isolate total RNA from each tissue sample according to the manufacturer's instructions. Then, total RNA was reverse transcribed into cDNAs using the FastQuant RT kit (with gDNase; Tiangen Biotech Co., Ltd.). RT-qPCR was performed to measure the levels of cDNAs using a QuantStudio 7 Flex real-time PCR system (Thermo Fisher Scientific, Waltham, MA, USA). RT-PCR procedure was performed as follows: Pre-denaturation at 95°C for 30 sec for 1 cycle followed by 40 cycles of 95°C for 5 sec and 60°C for 20 sec. The relative expression level of the hub genes was calculated following comparative CT method [25]. β-actin was used to normalize the mRNA expression level. The primer sequences are listed in Table 1.

**Molecular docking experiments**
Molecular docking was used to find biologically active hits among the designed ligands. Using perpetual software module BIOVIA Discovery Studio (Perpetual), Surflex-Docking docking studies were conducted on active constituents. The lowest binding energy conformation was presumed to form a stable complex within the active site of the over expressed proteins. The 2D structures were sketched using Chemdraw software, imported and saved into sdf format using Open Babel free software. The protein structure was processed after introduction of the protein, the co-crystallized ligand and all the water molecule were excluded from the crystal structure; more hydrogen was added and refined the side chain. This study employed CDOCKER, a grid-based molecular docking approach that utilizes the CHARMM force field. A higher number indicates a stronger bond. The CDOCKER score is expressed as a negative number (-CDOCKER ENERGY). The H-bonds, van der Waals, and electrostatic interactions between the target protein and the ligand were used to measure the CDOCKER energy. The modeled protein's binding site was determined using the template protein's crystal data and proteins in which do not Co-crystallized ligand generated binding site automatically. To make it easier for ligands to interact with amino acids, the binding site sphere center was set at 9 Å radius. Furthermore, using smart minimizer algorithm, CHARMM force field was applied followed by energy minimization to define local minima (lowest energy conformation) of the modeled over expressed proteins with an energy gradient of 0.1 kcal mol$^{-1}$ Å$^{-1}$ respectively. The energy minimized receptor protein and the set of 44 natural molecules which was reported as effective in diabetes mellitus and the well-known commonly used allopathic drug Metformin and Glyburide were used as standard and to compare the binding interactions with natural molecules on over expressed proteins in gestational diabetes. The binding site sphere radius set at $X = 29.50$, $Y = -31.38$ and $Z = -38.79$ were submitted to the CDOCKER parameter and also calculated binding energy. The X-ray co-crystallized structure and were extracted from Protein Data Bank of PDB code of 4UV7, 5NJX, 3Q4Z and 3FNI of over expressed genes of Epidermal growth factor receptor (EGFR), Heat shock protein 90 alpha family class A member 1 (HSP90AA1), P21 RAC1 activated kinase 1 (PAK1) and Ring-box 1 (RBX1) respectively in gestational diabetes were selected for docking studies [26-29]. The best position was inserted into the molecular area between the protein and the ligand. The 2D and 3D interaction of amino acid molecules was achieved using the free online Discovery Studio Visualizer.
Results

Identification of DEGs

Transcription profiling by array data sets was obtained from the ArrayExpress database containing GDM samples and non GDM samples; E-MTAB-6418. Then, the R package named “limma” was processed for analysis with adjusted P < 0.05, |log FC| > 1.158 for up regulated genes and |log FC| < -0.83 for down regulated genes. All DEGs were displayed in volcano maps (Fig. 1). A total of 869 genes were finally obtained including 439 up regulated genes and 430 down regulated genes in the GDM samples compared to the non GDM samples and are listed Table 1. Top 869 genes in this dataset were displayed in the heatmap (Fig. 2).

Gene ontology and pathway enrichment of DEGs analysis

To clarify the major functions of these DEGs, we first explored the associated biological processes and REACTOME pathways. The top highly enriched GO terms were divided into three categories: biological process (BP), cellular component (CC), and molecular function (MF) and are listed in Table 2. The most enriched GO terms in BP was reproduction, macromolecule catabolic process, cell adhesion and localization of cell, that in CC was nuclear outer membrane-endoplasmic reticulum membrane network, golgi apparatus, supramolecular complex and cell junction, and that in MF were identical protein binding, molecular function regulator, signaling receptor binding and molecular function regulator. In the REACTOME pathway enrichment analysis, the DEGs were mostly enriched in cell surface interactions at the vascular wall, epigenetic regulation of gene expression, extracellular matrix organization and axon guidance and are listed in Table 3.

PPI network establishment and modules selection

By using the STRING database, the PPI network of DEGs was established and consisted of 4687 nodes and 11236 edges (Fig.3). A total of 10 hub genes were selected for key biomarker identification and are listed in Table 3. They consisted of 5 up regulated genes (HSP90AA1, EGFR, RPS13, RBX1 and PAK1) and 5 down regulated genes (FYN, ABL1, SMAD3, STAT3 and PRKCA). Then PEWCC1 was used to find clusters in the network. Four modules were calculated
according to k-core $k = 2$. Among them, module 1 contained 16 nodes and 32 edges, with the highest score (Fig. 4A) and module 2 contained 16 nodes and 34 edges (Fig. 4B). We performed the functional analysis for the top 2 modules. In functional enrichment analysis, the DEGs of module 1 were mostly enriched in post-translational protein modification, developmental biology and macromolecule catabolic process; the DEGs of module 2 in supramolecular complex and localization of cell.

**miRNA-hub gene regulatory network construction**

miRNet database was applied to screen the targeted miRNAs of the hub genes. Cytoscape software was used to construct the miRNA-hub gene network. As illustrated in Fig. 5, the interaction network consists of 307 hub genes and 2280 miRNAs. According to the hub genes and miRNAs in the network ranked by their degree of connectivity using Network Analyzer and are listed in Table 4. Based on the expression trend of hub genes in GDM, we found that UBE2D3 was the predicted target of hsa-mir-6127, HSP90AA1 was the predicted target of hsa-let-7d-5p, PAK2 was the predicted target of hsa-mir-8063, DDB1 was the predicted target of hsa-mir-329-3p, DVL3 was the predicted target of hsa-mir-1207-5p, FYN was the predicted target of hsa-mir-4651, ABL1 was the predicted target of hsa-mir-8063, DDB1 was the predicted target of hsa-mir-329-3p, DVL3 was the predicted target of hsa-mir-1207-5p, FYN was the predicted target of hsa-mir-4651, ABL1 was the predicted target of hsa-mir-222-3p, SMAD3 was the predicted target of hsa-mir-410-5p, SMAD3 was the predicted target of hsa-mir-410-5p, SMAD3 was the predicted target of hsa-mir-29c-3p and PRKCA was the predicted target of hsa-mir-663a.

**TF-hub gene regulatory network construction**

NetworkAnalyst database was applied to screen the targeted TFs of the hub genes. Cytoscape software was used to construct the TF-hub gene network. As illustrated in Fig. 6, the interaction network consists of 306 hub genes and 195 TFs. According to the hub genes and TFs in the network ranked by their degree of connectivity using Network Analyzer and are listed in Table 4. Based on the expression trend of hub genes in GDM, we found that HSP90AA1 was the predicted target of E2F1, UBE2D3 was the predicted target of HCFC1, EGFR was the predicted target of SRY, PSMC4 was the predicted target of ZFX, DDB1 was the predicted target of RUNX1, STAT3 was the predicted target of SPI1, CCND1 was the predicted target of MYBL2, SMAD3 was the predicted target of SUZ12,
FOXO1 was the predicted target of TBX3 and PRKCA was the predicted target of YAP1.

**Receiver operating characteristic (ROC) curve analysis**

ROC curve analysis was implemented to evaluate the capacity of hub genes to distinguish GDM and non GDM in E-MTAB-6418, HSP90AA1, EGFR, RPS13, RBX1, PAK1, FYN, ABL1, SMAD3, STAT3 and PRKCA, exhibiting better diagnostic efficiency for GDM and non GDM, and the combined diagnosis of these ten hub genes was more effective. The AUC index for the 10 hub gene scores were 0.906, 0.838, 0.825, 0.897, 0.863, 0.876, 0.855, 0.880, 0.932 and 0.872, and are shown Fig.7.

**RT-PCR Analysis**

To further verify the expression level of hub genes in GDM, RT-PCR was performed to calculate the mRNA levels of the ten hub genes identified in the present study (HSP90AA1, EGFR, RPS13, RBX1, PAK1, FYN, ABL1, SMAD3, STAT3 and PRKCA) in GDM. As illustrated in Fig. 8, the expression of HSP90AA1, EGFR, RPS13, RBX1, PAK1 were significantly up regulated in GDM samples compared with normal, while FYN, ABL1, SMAD3, STAT3 and PRKCA were significantly down regulated in GDM samples compared with normal. The present RT-PCR results were in line with the aforementioned bioinformatics analysis, suggesting that these hub genes might be linked to the molecular mechanism underlying GDM.

**Molecular docking experiments**

In the recent findings, the docking study was performed using Biovia Discovery Studio perpetual software to analyse the binding pattern of the natural plants products such as herbs have the ability to lower blood glucose levels and ameliorate diabetes with decreased adverse side effects. The natural well known phytoconstituents which decreases the blood sugar level are Malvidin 3-laminaribioside (MLR), Ferulic acid (FRA), Inosporone (INO), Allicin (ALL), Liriodenin (LIR), Azadirachitin (AZA), Sulforaphane, Cajanin (CAJ), Carvone (CAR), Capsaicin (CAP), Terpineol (TER), Phellandrene (PHE), Terpene (TPN), Ellagic acid (ELA), Leucodelphinidin, O-methyltylophorinidine (OMT),
Gymnemic acid, beta-Carotene (BCR), Leucocyanidin (LEC), Syringin (SYR), Ginsenoside (GNS), Phyllanthin (PHY), Punicalagin (PUC), Punicalin (PUN), Arjunic acid (AJA), Arjunetin (ARJ), Arabic acid (ARA), Arjungenin (ARG), Gingerol (GIN), Shogaol, Aloe emodin (ALE), Arabic acid (ARA), Aloin (ALO), Charantin (CHR), Cinnamic acid (CIN), Curcumin (CUR), Eugenol (EUG), Gymnemagenin (GMG), Gymnestrojenin (GYM), Hydroxylucin (HYD), Methoxy hydroxyl chalcoli (MHC), Myricetin (MYR), Nimbine (NIM), Quercetin (QUE), Vicine (VIC) and Shagoal (SHA) are shown in Fig. 9. The molecules were constructed based on the natural plant products containing these chemical constituents which play vital role in reducing type 2 diabetes mellitus. The traditional plant products are used in conjunction with allopathic drug to reduce the dose of the allopathic drugs and or to increase the efficacy of allopathic drugs. Some common and most prominent antidiabetic plants and active principles were selected from their phytochemicals for docking studies in the present research to identify the active natural molecule to avoid the use of allopathic drugs in gestational diabetes and the blood sugar level is controlled by altering the diet. For docking experiments well known and most commonly used two allopathic drugs such as Glyburide (GLY), Metformin (MET) in gestational diabetes are used as standard and to compare the binding interaction of natural phyto constituents with allopathic drugs. A total of common 44 in that 42 natural active constituents few from each of flavonoids, saponins, tannins and glycosides etc., present in plant extracts responsible for antidiabetic function and 2 allopathic drugs were chosen for docking studies on over expressed proteins and the structures are depicted in figure 1 respectively. The one protein from each over expressed genes in gestational diabetes 2 diabetes mellitus such as EGFR (epidermal growth factor receptor), HSP90AA1 (heat shock protein 90 alpha family class A member 1), PAK1 (p21 (RAC1) activated kinase 1), and RBX1 (ring-box 1) and their X-RAY crystallographic structure and co-crystallized PDB code and their PDB code of 4UV7, 5NJX, 3Q4Z and 3FNI respectively were constructed for docking. The docking on natural active constituents was conducted to classify the potential molecule and their binding affinity to proteins. A higher number of negative number -CDOCKER energy and binding energy indicates a stronger binding interactions with proteins, few constituents obtained with a greater -CDOCKER energy and binding energy respectively with particular proteins. Docking experiments were carried out on a total of 42 constituents from plant products, few
constituents obtained excellent -CDOCKER energy and binding energy. Out of 44 molecules few of the molecules obtained -CDOCKER interaction energy of more than 40 and majority with more than 30 and less than 40, few molecules obtained optimum -CDOCKER interaction energy of less than 30 respectively. The molecules with -CDOCKER interaction energy of 40 and above are said to have good interaction with proteins and stable. The natural constituents of the molecules GLY, GNS, GYM, MLR, PUC and ALO, GLY, MLR and ALE, ALO, BCR, CAP, CHR, ELA, LUR, GIN, GLY, GMG, GNS, GYM, LEC, LIR, MLR, MYR, NIM, OMP, PHY, PUC, PUN, QUE, SHE, VI C obtained a -CDOCKER interaction energy of more than 40 with protein of PDB code 5NJX and 3FNI and 3Q4Z respectively. The natural constituents obtained -CDOCKER interaction energy of less than 40 and more than 30 are ALO, ARJ, BCR, CHR, CUR, PHY, PUN and BCR, CAJ, CAP, CUR, GIN, LEC, MYR, OMP, QUE, VIC and AJA, ARA, ARG, CAJ, FRA, HYD, MHC and GNS, PHY, PUC, PUN with 5NJX and 3FNI and 3Q4Z and 4UV7. The constituents obtained less than 30 and more than 20 are AJA, ALE, ARG, CAJ, CAP, GIN, GMG, GYM, HYD, LEC, MHC, MLR, MYR, NIM, OMP, QUE, VIC and AJA, ALE, ALL, ARG, AJA, CHR, CIN, EUG, FRA, GMG, GNS, GYM, LIR, MHC, NIM, PUC and ALL, CIN, EUG, MET, TEP and ALA, ALE, ALO, ARJ, BCR, CAJ, CHR, ELA, FRA, GIN, GMG, LEC, MLR, MYR, OMP, QUE, SHA with 5NJX and 3FNI and 3Q4Z and 4UV7. Following the molecules obtained less than 20 -CDOCKER interaction energy are ALL, ARA, CAR, CHR, CIN, EUG, FRA, LIR, MET, PHE, TEP and ARJ, ARA, CAR, HYD, MET, PHE, TPN and CAR, PHE, TPN and AJA, ALL, ARG, CAR, CIN, EUG, GYM, HYD, LIR, MET, MHC, NIM, PHE, TEP, TPN, VIC with protein 5NJX and 3FNI and 3Q4Z and 4UV7 respectively the biding energy, -CDOCKER energy and -CDOCKER interaction energy are depicted in Table 7. The two molecules such as ALO and MAL Fig. 10 and Fig. 11, their interaction with amino acids of proteins with 3D strictures for 3FN1 Fig. 12 and 3Q4Z Fig. 13, while 2D strictures for 3FN1 Fig. 14 and 3Q4Z Fig. 15.

**Discussion**

Although people have continuously investigated GDM, the early diagnosis and treatment of GDM is still a huge problem due to the inadequacy of understanding of the molecular mechanisms that drive the occurrence and progression of GDM.
Therefore, in-depth investigation into the factors and mechanisms of GDM advancement are necessary for GDM diagnosis and treatment. Due to well-developed transcription profiling by array technology, it is accessible to resolve the general genetic modification in the development of diseases, which can allow for the recognition of gene targets for diagnosis, therapy, and prognosis of GDM.

In our study, a total of 869 DEGs were screened, including 439 up regulated genes and 430 down regulated genes. Several studies have reported that expression of CGB5 was essential for pregnancy success [30]. Aberrations of CRH (corticotropin releasing hormone) [31] and PSG1 [32] contribute to preeclampsia occurrence. The expression of CYP19A1 was significantly up regulated in hypertensive disorders of pregnancy [33]. Based on previous studies, CD248 is generally associated with progression of hypertension [34], but this gene might be linked with development of GDM. Lin et al [35] reported that expression of COL1A1 was essential for type 2 diabetes mellitus progression, but this gene might be involved in the development of GDM. Delfín et al [36] found that ABI3BP was responsible for progression of cardiovascular diseases, but this gene might be linked with development of GDM. MFAP4 was reported to cause type 1 diabetes mellitus [37], but this gene might be responsible for progression of GDM.

DEGs were found to be enriched in reproduction, nuclear outer membrane-endoplasmic reticulum membrane network, identical protein binding, cell surface interactions at the vascular wall, cell adhesion, supramolecular complex, signaling receptor binding and extracellular matrix organization. CEBPB (CCAAT enhancer binding protein beta) [38], ACSL4 [39], MBD2 [40], ULK1 [41], UCB2 [42], TWIST1 [43], HOOK2 [44], CLDN7 [45], TBK1 [46], YIPF6 [47], TFRC (transferrin receptor) [48], ENPP2 [49], SLIT2 [50], MFGE8 [51], FAT1 [52], GPC4 [53], COL6A3 [54], EGFL6 [55], AOC3 [56], CCN2 [57], LYVE1 [58], RARA (retinoic acid receptor alpha) [59], COL18A1 [60], THY1 [61], CD36 [62], PEMT (phosphatidylethanolamine N-methyltransferase) [63], AIFIL [64], OXTR (oxytocin receptor) [65], LMNA (lamin A/C) [66], CXCL14 [67], DKK3 [68], ANGPTL2 [69] and CMTM7 [70] were reported to be associated with obesity, but these genes might be linked with progression of GDM. AHR (aryl hydrocarbon receptor) [71], STS (steroid sulfatase) [72], PLAC1 [73], CYP11A1 [74], PSG11 [75], STAT5B [76], TLR3 [77], FOLR1 [78], HSPB1 [79],
HSP90AA1 [80], ANXA4 [81], ATF3 [82], DAPK1 [83], ENTPD1 [84], ABL1 [85], VSIG4 [86], CD99 [87], VWF (von Willebrand factor) [88], PODXL (podocalyxin like) [89], PDPN (podoplanin) [90], RND3 [91], VCAN (versican) [92], AXL (AXL receptor tyrosine kinase) [93], PIEZO1 [94], GAS6 [93], LAMA4 [95], CAV1 [96], DLL1 [97], CD44 [98], CD81 [99], SMAD3 [100], NES (nestin) [101], DCN (decorin) [102], AGTR1 [103], SLIT3 [104], B2M [105], STAT3 [106], STC1 [107], and ADAMTS1 [108] were shown to participate in facilitating the preeclampsia. Majchrzak-Celińska et al [109] and Shimodaira et al [110] reported that HSD11B2 and HSD3B1 are responsible for hypertensive disorders of pregnancy. Altered expression of CSNK2A2 [111], NFE2 [112], CAMK2G [113], RASGRP1 [114], S100P [115], SRR (serine racemase) [116], DHPS (deoxyhypusine synthase) [117], DYRK1A [118], JAG1 [119], COL3A1 [120], VTN (vitronectin) [121], WNT3A [122], ACTA2 [123], SEMA3A [124], RARRES2 [125], CAV2 [126] and SPRED1 [127] were observed to be associated with the progression of type 2 diabetes mellitus, but these genes might be liable for advancement of GDM. In a previous report, Santiago et al [128], Auburger et al [129], Qu et al [130], Šnit et al [131] and Hjortebjerg et al [132] reported that SLC22A5, SH2B3, ITPR3, CALD1 and IGFBP4 expression might be regarded as an indicator of susceptibility to type 1 diabetes mellitus, but these genes might be associated with progression of GDM. Krishnan et al [133], Hu et al [134], Martins et al [135], Prieto-Sánchez et al [136], Sugulle et al [137], Zhao et al [138], Siddiqui et al [139], Han et al [140], Lappas et al [141], Wang et al [142], Artunc-Ulkumen et al [143], Blois et al [144], Vacínová et al [145] and Vilmi-Kerälä et al [146] demonstrated that the expression of CREBRF (CREB3 regulatory factor), STRA6, EGFR (epidermal growth factor receptor), MFSD2A, GDF15, PAK1, VCAM1, IGFBP2, IGFBP7, PRKCA (protein kinase C alpha), ADAMTS9, LGALS1, BIN1, TIMP1 and are associated with progression of GDM. Aquila et al [147], Chen et al [148], Xie et al [149], Zhang et al [150], Aspit et al [151], Akadam-Teker et al [152], Jiang et al [153], Cetinkaya et al [154], Grond-Ginsbach et al [155], Dong et al [156], Chardon et al [157], Chen et al [158], Yamada et al [159], Hu et al [160], Bobik and Kalinina [161], Schwanekamp et al [162], Liu et al [163], Schroer et al [164], Raza et al [165], Yang et al [166], Azuaje et al [167], Durbin et al [168], Chowdhury et al [169], Wang et al [170], Li et al [171], Lv et al [172], Bertoli-Avellà et al [173], Grossman et al [174], Andenæs et al [175] and Chen et al [176] demonstrated that HES1, SPIN1,
TBX3, EVA1A, CAP2, BMP1, HSPB8, RDX (radixin), COL5A1, LIMS2, PARVA (parvin alpha), EGFLAM (EGF like, fibronectin type III and laminin G domains), NEXN (nexilin F-actin binding protein), TNFRSF14, TGFBI (transforming growth factor beta induced), HAVCR2, CDH11, COL4A1, COL4A2, COL5A2, SHROOM3, HYAL2, PDLIM3, ETS2, PLSCR4, TGFBI, COL6A2 and LTBP2 could induce cardiovascular diseases, but these genes might be essential for progression of GDM. Flamant et al [177], Wan et al [178], Zhang et al [179], Vallvé et al [180], Heximer and Husain [181], Selvarajah et al [182], Jain et al [183], Sun et al [184], Satomi-Kobayashi et al [185], Jiang et al [186], Waghulde et al [187] and Dahal et al [188] reported that DDR1, CAST (calpastatin), KYNU (kynureninase), FBLN2, SPON1, VEGFC (vascular endothelial growth factor C), FLNA (filamin A), SNAI2, MYADM (myeloid associated differentiation marker), NECTIN2 and SMTN (smoothelin), GPER1, PDGFRB (platelet derived growth factor receptor beta) crucially contribute to the development of hypertension, but these genes might be linked with advancement of GDM.

From the PPI network and modules diagram, it can be observed that HSP90AA1, EGFR, RPS13, RBX1, PAK1, FYN (FYN proto-oncogene, Src family tyrosine kinase), ABL1, SMAD3, STAT3, PRKCA, UBE2A, UCHL3, TUBB2A, ACTA2 and TBCB (tubulin folding cofactor B) were the key nodes of the PPI network and modules, with the highest node degree, betweenness, stress and closeness value. RPS13, RBX1, FYN, UBE2A, TUBB2A and TBCB were the novel biomarkers for the progression of GDM.

From the miRNA-hub gene network construction and TF-hub gene network diagram, it can be observed that UBE2D3, HSP90AA1, PAK2, DDB1, DVL3, FYN, ABL1, SMAD3, STAT3, PRKCA, EGFR, PSMC4, CCND1, FOXO1, hsa-mir-6127, hsa-let-7d-5p, hsa-mir-8063, hsa-mir-329-3p, hsa-mir-1207-5p, hsa-mir-4651, hsa-mir-410-5p, hsa-mir-222-3p, hsa-mir-29c-3p, hsa-mir-663a, E2F1, HCFC1, SRY, ZFX, RUNX1, SPI1, MYBL2, SUZ12, TBX3 and YAP1 were the key nodes of the miRNA-hub gene network construction and TF-hub gene network, with the highest node degree value. Expression of the CCND1 gene plays a role in the development of obesity [189], but this gene might be associated with progression of GDM. FOXO1 [190], hsa-mir-1207-5p [191], hsa-mir-4651 [191], hsa-mir-222-3p [192] and E2F1 [193] are essential for the progression of GDM.
Hsa-let-7d-5p [194], hsa-mir-29c-3p [195] and SRY (Sex-determining Region Y) [196] have been shown to have an important role in type 2 diabetes mellitus, but these genes might be responsible for progression of GDM. Hsa-mir-663a [197] and TBX3 [198] have been shown as a promising biomarker in cardiovascular diseases, but this gene might be involved in progression of GDM. RUNX1 [199] and YAP1 [200] have been demonstrated to function in preeclampsia. UBE2D3, PAK2, DDB1, DVL3, PSMC4, hsa-mir-6127, hsa-mir-8063, hsa-mir-329-3p, hsa-mir-410-5p, HCFC1, ZFX (zinc finger protein, X-linked), SPI1, MYBL2 and SUZ12 were the novel biomarkers for the progression of GDM.

The molecule GLY, MLR obtained a good -CDOCKER interaction energy with 5NJX, 3FNI and 3Q4Z the -CDOCKER interaction energy of GLY is 41.37, 59.92, 41.44 and for MLR is 40.68, 87.65, 43.47 with 5NJX, 3FNI and 3Q4Z respectively. The two molecules such as ALO and MAL its interaction with amino acids are 2’ hydroxyl group formed hydrogen bond interaction with ASP-89 and 3’, 4’ hydroxyl groups formed hydrogen bond interaction with GLU-86. Following 6’ hydroxyl group formed hydrogen bond interaction with LYS-61. The C-13 hydroxyl formed hydrogen bond interaction with ASP-389 and ring C electrons formed pi-pi t-shaped interactions with HIS-63 and pi-alkyl interaction with LYS-388. Ring A electrons formed pi-carbon interaction with LYS-388 and LYS61 respectively. The ring C electrons and 4’ hydroxyl group of molecule MLR formed sulphur oxygen interaction with MET-344 and ring C electrons formed pi-alkyl interaction with LEU-396. The ring A 5 & 6 hydroxyl group formed hydrogen bond interaction with ASP-354 & LYS-538. Ring D 3’ & 6’ hydroxyl group formed hydrogen bond interaction with ASP-393 & GLY-277, 3’’ hydroxyl group formed pi-alkyl interaction with Mg ion. Ring D 5’’ hydroxyl group formed hydrogen bond interaction with ARG-299. Ring E 6’’ alkyl hydroxyl formed Carbon hydrogen interaction with LYS-391 and ring E oxygen, 3’’’ hydroxyl group and 6’’’ alkyl hydroxyl formed pi-alkyl interaction with Mg ions respectively.

In conclusion, the results from the current investigation not only identify a series of DEGs, but also analyze the significant modules, hub and target genes identification, and screening of small therapeutic molecules. In addition, in order to further verify the bioinformatics analysis data, the current investigation detected the expression levels of hub genes (HSP90AA1, EGFR, RPS13, RBX1, PAK1,
FYN, ABL1, SMAD3, STAT3 and PRKCA) in a GDM. These hub genes might serve as potential diagnostic and prognostic biomarkers, and novel therapeutic targets in GDM.

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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 ArrayExpress database (https://www.ebi.ac.uk/arrayexpress/) repository. [E-MTAB-6418] (https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-6418/?array=A-MEXP-2072]

Consent for publication

Not applicable.

Competing interests

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

C. V - Software and investigation

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Tables

Table 1 The sequences of primers for quantitative RT-PCR

| Genes   | Forward Primers          | Reverse Primers          |
|---------|--------------------------|--------------------------|
| HSP90AA1| AGGAGGTGAGACACGTTCGC     | AGAGTTGAGTCTTTGTGTCGG    |
| EGFR    | AGGCACGAGTAAACAGCTCAC    | ATGAGGACATAACGCAACGACC   |
| RPS13   | TCCCAGTCGGTTTACCCTAT     | CAGGATTACCCCATCTTGAAAG   |
| RBX1    | TTGTGTTGATAACTGTGCCAT    | GACGCCCTGTTAGGCTGACAT    |
| PAK1    | CGACCCCTCCGATGAAATAA     | CAAACGCGATGAAATTTGCTG    |
| FYN     | ATGGGCTGTGTCGAATGTAAG    | GAAGCTGGGAGTGCTGAG       |
| ABL1    | AAGCCCGCTCCTGTGAACCT     | AGACCCGAGCTTTTACCT       |
| SMAD3   | TGGACGCAGTTCTCCACAC      | CCGGCTCGACTGAGTAAC       |
| STAT3   | CAGCAGCTTGACACAGCTGA     | AACACCGAAAGTGCCATGTGA    |
| PRKCA   | GTCCACAAAGAGGTGCCATGAA   | AAGGTGGGCTTCCGTAAG       |

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

| IlluminaID | GeneSymbol | logFC | pValue | adj.P.Val | tvalue | Regulation | GeneName                                      |
|------------|------------|-------|--------|-----------|--------|------------|-----------------------------------------------|
| ILMN_324633| RNY5       | 1.462757 | 5.68E-06 | 0.002906 | 4.775349 | Up         | RNA, Ro60-associated Y5                       |
| ILMN_1691647| CGB5      | 1.297516 | 0.000781 | 0.021869 | 3.457767 | Up         | chorionic gonadotropin subunit beta 5          |
| ILMN_1668035| CRH       | 1.29002  | 0.001459 | 0.029715 | 3.266769 | Up         | corticotropin releasing hormone               |
| ILMN_1714238| PSG6      | 1.284052 | 0.00171  | 0.032189 | 3.217109 | Up         | pregnancy specific beta-1-glycoprotein 6     |
| ILMN_1772768| PSG7      | 1.257768 | 0.001767 | 0.032784 | 3.208816 | Up         | pregnancy specific beta-1-glycoprotein 7 (gene/pseudogene) |
| ILMN_2413473| GH2       | 1.248351 | 0.002276 | 0.037103 | 3.126124 | Up         | growth hormone 2                             |
| ILMN_1801776| PSG9      | 1.204077 | 0.002468 | 0.038662 | 3.100092 | Up         | pregnancy specific beta-1-glycoprotein 9     |
| ILMN_1798000| PSG1      | 1.147959 | 0.000469 | 0.017456 | 3.608336 | Up         | pregnancy specific beta-1-glycoprotein 1     |
| Gene Symbol | Description | Fold Change | P-value | q-value | Pathway | Function |
|-------------|-------------|-------------|---------|---------|---------|----------|
| PSG5        | pregnancy specific beta-1-glycoprotein 5 | 1.143624    | 0.000969| 0.024168| Up      |          |
| PSG9        | pregnancy specific beta-1-glycoprotein 11 | 1.130568    | 0.000132| 0.028092| Up      |          |
| CYP19A1     | cytochrome P450 family 19 subfamily A member 1 | 1.125321    | 0.002128| 0.044444| Up      |          |
| PSG1        | pregnancy specific beta-1-glycoprotein 2 | 1.115865    | 0.002624| 0.040078| Up      |          |
| LHB         | pregnancy specific beta-1-glycoprotein 11 | 1.086528    | 0.002237| 0.037529| Up      |          |
| PSG4        | pregnancy specific beta-1-glycoprotein 4 | 1.079921    | 0.002644| 0.040091| Up      |          |
| PSG2        | pregnancy specific beta-1-glycoprotein 2 | 1.079921    | 0.002644| 0.040091| Up      |          |
| PSG11       | pregnancy specific beta-1-glycoprotein 11 | 1.079921    | 0.002644| 0.040091| Up      |          |
| LHB         | luteinizing hormone subunit beta | 1.086528    | 0.002237| 0.037529| Up      |          |
| SEMA3B      | semaphorin 3B | 1.091814    | 0.001424| 0.029234| Up      |          |
| CSH2        | chorionic somatomamotropin hormone 2 | 0.93195     | 0.003208| 0.044568| Up      |          |
| CGB1        | chorionic gonadotropin subunit beta | 0.914238    | 0.003818| 0.048801| Up      |          |
| CGB7        | chorionic gonadotropin subunit beta | 0.914238    | 0.003818| 0.048801| Up      |          |
| PLAC1       | placenta enriched | 0.846799    | 0.003832| 0.048867| Up      |          |
| LGALS14     | galectin 14 | 0.831948    | 0.001715| 0.032189| Up      |          |
| TFP2        | tissue factor pathway inhibitor 2 | 0.817388    | 0.001424| 0.029234| Up      |          |
| HOX9        | HOP homeobox | 0.796216    | 0.00037 | 0.01533 | Up      |          |
| LOC10050635 | uncharacterized LOC10050635 | 0.792699    | 0.0007 | 0.025812| Up      |          |
| ERV3-1      | endogenous retrovirus group 3 member 1, envelope | 0.79098    | 0.001056| 0.025169| Up      |          |
| EXPH5       | exophilin 5 | 0.771167    | 0.000748| 0.021335| Up      |          |
| OLAH        | oleyl-ACP hydrolase | 0.774415    | 0.00023 | 0.012505| Up      |          |
| SPTLC3      | serine palmitoyltransferase long chain base subunit 3 | 0.771167    | 0.000748| 0.021335| Up      |          |
| P53          | keratin associated protein 26-1 | 0.796216    | 0.00037 | 0.01533 | Up      |          |
| NCB3        | uncharacterized LOC10050635 | 0.792699    | 0.0007 | 0.025812| Up      |          |
| TGF15       | growth differentiation factor 15 | 0.79098    | 0.001056| 0.025169| Up      |          |
| ADHFE1      | alcohol dehydrogenase iron containing | 0.79098    | 0.001056| 0.025169| Up      |          |
| EMX2        | empty spiracles homeobox 2 | 0.724034    | 0.002299| 0.036621| Up      |          |
| HSD3B1      | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 | 0.724034    | 0.002299| 0.036621| Up      |          |
| INSL4       | insulin like 4 | 0.724034    | 0.002299| 0.036621| Up      |          |
| TPPP3       | tubulin polymerization promoting protein family member 3 | 0.724034    | 0.002299| 0.036621| Up      |          |
| MAFF        | MAF bZIP transcription factor F | 0.724034    | 0.002299| 0.036621| Up      |          |
| Gene ID     | Description                                                | Log2 Fold Change | p-value  | q-value |
|------------|-------------------------------------------------------------|-----------------|----------|---------|
| ILMN_236818 | TRPV6 transient receptor potential cation channel subfamily V member 6 | 3.388062        | 0.001158 | 0.02618 |
| ILMN_1704066 | TENT5A terminal nucleotidyltransferase 5A                  | 3.62472         | 0.001305 | 0.03724 |
| ILMN_1800412 | BMP1 bone morphogenetic protein 1                         | 3.614562        | 0.001305 | 0.03724 |
| ILMN_1727633 | NECTIN3 nectin cell adhesion molecule 3                   | 3.11981         | 0.001305 | 0.03724 |
| ILMN_1668455 | PPP1R14C protein phosphatase 1 regulatory inhibitor subunit 14C | 3.235567        | 0.001305 | 0.03724 |
| ILMN_1695562 | ZNF471 zinc finger protein 471                            | 3.38509         | 0.001305 | 0.03724 |
| ILMN_1714586 | VGLL3 vestigial like family member 3                      | 3.191522        | 0.001305 | 0.03724 |
| ILMN_1744949 | RHBDB3 Rho related BTB domain containing 3                 | 3.235567        | 0.001305 | 0.03724 |
| ILMN_1703284 | SPIRE2 spire type actin nucleation factor 2                | 3.007246        | 0.001305 | 0.03724 |
| ILMN_174376 | GLDN gliomedin                                             | 3.118817        | 0.001305 | 0.03724 |
| ILMN_2415421 | SLC30A2 solute carrier family 30 member 2                  | 3.087159        | 0.001305 | 0.03724 |
| ILMN_1757406 | H1-2 linker histone, cluster member                        | 3.316284        | 0.001305 | 0.03724 |
| ILMN_1651496 | H2BC5 H2B clustered histone 5                              | 4.027633        | 0.001305 | 0.03724 |
| ILMN_1713125 | ENTPD1 ectonucleoside triphosphate diphosphohydrolase 1    | 3.290157        | 0.001305 | 0.03724 |
| ILMN_1790228 | FURIN furin, paired basic amino acid cleaving enzyme        | 3.292157        | 0.001305 | 0.03724 |
| ILMN_1741143 | TXK TXK tyrosine kinase                                    | 3.288903        | 0.001305 | 0.03724 |
| ILMN_1787750 | CD200 CD200 molecule                                       | 3.35461         | 0.001305 | 0.03724 |
| ILMN_1795106 | PSG8 pregnancy specific beta-1-glycoprotein 8              | 3.053083        | 0.001305 | 0.03724 |
| ILMN_1672908 | TWIST1 twist family bHLH transcription factor 1             | 3.138064        | 0.001305 | 0.03724 |
| ILMN_1787691 | CITED4 Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 4 | 3.616082        | 0.001305 | 0.03724 |
| ILMN_1740917 | SCNN1B sodium channel epithelial 1 beta subunit            | 3.155039        | 0.001305 | 0.03724 |
| ILMN_1681248 | TCHH trichohyalin                                         | 3.42568         | 0.001305 | 0.03724 |
| ILMN_1713397 | NCCRPI F-box associated domain containing                  | 3.236641        | 0.001305 | 0.03724 |
| ILMN_1771019 | MTMR4 myotubularin related protein 4                       | 3.383725        | 0.001305 | 0.03724 |
| ILMN_1792689 | H2AC6 H2A clustered histone 6                              | 3.853384        | 0.001305 | 0.03724 |
| ILMN_1732071 | H2BC21 H2B clustered histone 21                            | 3.660351        | 0.001305 | 0.03724 |
| ILMN_1777934 | MORN3 MORN repeat containing 3                            | 3.060351        | 0.001305 | 0.03724 |
| ILMN_1754126 | SH2D5 SH2 domain containing 5 cytochrome P450 family 11 subfamily A member 1 | 3.562897        | 0.001305 | 0.03724 |
| ILMN_1768820 | CYP11A1 CD200 molecule                                    | 3.125417        | 0.001305 | 0.03724 |
| ILMN_1721842 | RYBP RING1 and YY1 binding protein                        | 3.344898        | 0.001305 | 0.03724 |
| ILMN_2323172 | CSF3R colony stimulating factor 3 receptor                | 3.140995        | 0.001305 | 0.03724 |
| ILMN_1693789 | ALPP alkaline phosphatase, placental                      | 3.002056        | 0.001305 | 0.03724 |
| ILMN_2129015 | AFF1 AF4/FMR2 family member 1                             | 3.026214        | 0.001305 | 0.03724 |
| ILMN_1807652 | STRA6 stimulated by retinoic acid 6                       | 3.285192        | 0.001305 | 0.03724 |
| ILMN_1746517 | KYNU kynurenin                                             | 3.164234        | 0.001305 | 0.03724 |
| ILMN_1793695 | ITHS inter-alpha-trypsin inhibitor heavy chain 5           | 3.065788        | 0.001305 | 0.03724 |
| ILMN_1814600 | DEPCDC1B DEP domain containing 1B                         | 3.305687        | 0.001305 | 0.03724 |
| ILMN_1708340 | DAPK1 death associated protein kinase 1                   | 3.018827        | 0.001305 | 0.03724 |
| ILMN_2204545 | ST3GAL4 ST3 beta-galactoside alpha-2,3-sialyltransferase 4 | 3.212881        | 0.001305 | 0.03724 |
| ILMN_1794239 | ODAPH odontogenesis associated phosphoprotein transforming acidic coiled-coil containing protein 2 | 3.590399        | 0.001305 | 0.03724 |
| ILMN_2315780 | TACC2 RB binding protein 6 ubiquitin ligase               | 3.783862        | 0.001305 | 0.03724 |
| Gene ID     | Gene Symbol | Gene Name                                                                 | FDR   | q-value | Log2 Fold Change | Expression Level |
|------------|-------------|---------------------------------------------------------------------------|-------|---------|------------------|------------------|
| ILMN_1791545 | KRT23       | keratin 23                                                                | 0.527971 | 0.00209 | 0.011919         | 3.838417         |
| ILMN_1798458 | KAZN        | kazrin, periplakin interacting protein                                     | 0.51384  | 0.00125 | 0.027297         | 3.113396         |
| ILMN_1776883 | ADAMTSL4    | ADAMTS like 4                                                             | 0.513545 | 0.00031 | 0.014326         | 3.727088         |
| ILMN_1811593 | NIPAL1      | NIPA like domain containing 1                                             | 0.509377 | 0.00057 | 0.018927         | 3.549631         |
| ILMN_3236821 | HSPB1       | heat shock protein family B (small) member 1                              | 0.507177 | 0.00083 | 0.022284         | 3.438549         |
| ILMN_1795838 | C4orf19     | chromosome 4 open reading frame 19                                        | 0.504867 | 0.00304 | 0.043409         | 3.031496         |
| ILMN_1690004 | TNFRSF12A   | TNF receptor superfamily member 12A                                       | 0.49831  | 1.22E-05| 0.003404         | 4.586051         |
| ILMN_1702105 | EFS         | embryonal Fyn-associated substrate                                        | 0.49728 | 0.00237 | 0.037920         | 3.11261          |
| ILMN_1725831 | TINCR       | TINCR ubiquitin domain containing Rho family interacting cell polarization regulator 2 | 0.495004 | 0.00054 | 0.018404         | 3.565008         |
| ILMN_1813139 | ANKDD1A     | ankyrin repeat and death domain containing 1A                            | 0.490504 | 0.00054 | 0.018404         | 3.565008         |
| ILMN_2194448 | STT3B       | STT3 oligosaccharyltransferase complex catalytic subunit B endogenous retrovirus group W member 1, envelope | 0.477337 | 0.00221 | 0.047380         | 3.069508         |
| ILMN_1684034 | FKBP2       | FKBP prolylisomerase 2                                                   | 0.466134 | 0.00495 | 0.017880         | 3.59265          |
| ILMN_1796423 | CRYBG2      | crystallin beta-gamma domain containing 2                                 | 0.465597 | 0.00216 | 0.027400         | 3.31097          |
| ILMN_1813625 | TRIM25      | tripartite motif containing 25                                            | 0.458975 | 0.00214 | 0.058920         | 3.144568         |
| ILMN_1652690 | GRAMD2B     | GRAM domain containing 2B                                                | 0.455737 | 0.00274 | 0.020970         | 3.480237         |
| ILMN_1752510 | FAM13A      | family with sequence similarity 13 member A                              | 0.453466 | 0.00335 | 0.014080         | 3.705566         |
| ILMN_2384857 | DHR52       | dehydrogenase/reductase 2                                                | 0.450744 | 0.01634 | 0.031747         | 3.23133          |
| ILMN_1720771 | STX11       | syntaxin 11                                                               | 0.449749 | 0.00214 | 0.058920         | 3.144568         |
| ILMN_1807563 | FKBP2       | FKBP prolylisomerase 2                                                   | 0.446443 | 0.00182 | 0.011037         | 3.877815         |
| ILMN_1740170 | CHCHD10     | coiled-coil-helix-coiled-coil-helix domain containing 10                 | 0.445493 | 0.00011 | 0.008930         | 4.005574         |
| ILMN_1806149 | C16orf74    | CHCHD10                                                                  | 0.444802 | 0.00216 | 0.027400         | 3.31097          |
| ILMN_1751120 | H4C8        | chromosome 16 open reading frame 74                                       | 0.444802 | 0.00216 | 0.027400         | 3.31097          |
| ILMN_1740604 | RAB11FIP5   | RAB11 family interacting protein 5                                        | 0.440815 | 0.00214 | 0.058920         | 3.144568         |
| ILMN_1753515 | SRR         | serine racemase                                                           | 0.435466 | 0.00325 | 0.048840         | 3.010168         |
| ILMN_1772627 | NSG1        | neuronal vesicle trafficking associated 1                                 | 0.434463 | 0.00127 | 0.029273         | 3.273602         |
| ILMN_2364700 | ENSA        | endolysosome alpha                                                        | 0.434463 | 0.00127 | 0.029273         | 3.273602         |
| ILMN_1674243 | TFRC        | transferrin receptor                                                     | 0.434463 | 0.00127 | 0.029273         | 3.273602         |
| Gene ID      | Gene Name       | E-Value 1  | FDR 1     | Log2FoldChange  | State |
|-------------|-----------------|------------|-----------|----------------|-------|
| ILMN_1779448 | EFHD1           | 0.435614   | 0.003381  | 0.045635       | Up    |
| ILMN_1798975 | EGFR            | 0.434921   | 0.002718  | 0.040787       | Up    |
| ILMN_1802053 | ZNF91           | 0.433844   | 0.000914  | 0.023507       | Up    |
| ILMN_1797557 | PLEKH6          | 0.43335    | 0.003538  | 0.046906       | Up    |
| ILMN_1814333 | SERPINI1        | 0.43318    | 0.00055   | 0.049898       | Up    |
| ILMN_1683211 | NCAN            | 0.430909   | 0.002311  | 0.037392       | Up    |
| ILMN_2142353 | GRTP1           | 0.430742   | 8.27E-05  | 0.023877       | Up    |
| ILMN_1809477 | CARHS1P         | 0.428795   | 0.001041  | 0.024977       | Up    |
| ILMN_1763765 | PAK1            | 0.427899   | 0.000645  | 0.023617       | Up    |
| ILMN_1795972 | CLIP4           | 0.427572   | 0.000845  | 0.024977       | Up    |
| ILMN_2143685 | CLDN7           | 0.426872   | 0.000634  | 0.019679       | Up    |
| ILMN_2074860 | RNTSK           | 0.425278   | 0.000506  | 0.017919       | Up    |
| ILMN_1742538 | PCDHGC4         | 0.422624   | 0.00088   | 0.023184       | Up    |
| ILMN_1698917 | LCOR            | 0.419011   | 0.001391  | 0.028854       | Up    |
| ILMN_1667994 | AMD1            | 0.418735   | 0.001391  | 0.028854       | Up    |
| ILMN_183598  | ACSL4           | 0.416616   | 0.000954  | 0.029451       | Up    |
| ILMN_1796206 | KMT2C           | 0.415266   | 8.27E-05  | 0.007525       | Up    |
| ILMN_1729417 | GNE             | 0.413507   | 0.001169  | 0.02622        | Up    |
| ILMN_1778956 | STS             | 0.411932   | 0.000347  | 0.014977       | Up    |
| ILMN_2405254 | GRB7            | 0.408773   | 0.000261  | 0.013186       | Up    |
| ILMN_1813314 | H2BC12          | 0.408761   | 0.002651  | 0.04015        | Up    |
| ILMN_2346339 | FOLR1           | 0.407865   | 0.000266  | 0.01333        | Up    |
| ILMN_1747112 | GPAAI           | 0.407772   | 1.5E-05   | 0.003692       | Up    |
| ILMN_1738683 | TMEM140         | 0.40612    | 0.000597  | 0.019237       | Up    |
| ILMN_3226388 | PSG10P          | 0.399644   | 0.00336   | 0.045553       | Up    |
| ILMN_1769092 | EVAIB           | 0.398688   | 0.002925  | 0.042546       | Up    |
| ILMN_1654322 | ATP1B3          | 0.398471   | 0.00148   | 0.029861       | Up    |
| ILMN_1699674 | ZNF703          | 0.397878   | 0.003462  | 0.046339       | Up    |
| ILMN_2159730 | GABRB1          | 0.396679   | 0.000663  | 0.020103       | Up    |
| ILMN_2542357 | KLHL5           | 0.395369   | 0.003031  | 0.043318       | Up    |
| ILMN_1700472 | EID2            | 0.394584   | 8.47E-06  | 0.00295        | Up    |
| ILMN_2374865 | ATF3            | 0.394537   | 0.001939  | 0.034245       | Up    |
| ILMN_1652540 | RELL2           | 0.39244    | 0.00081   | 0.022284       | Up    |
| ILMN_1697642 | BCAP29          | 0.391558   | 0.00201   | 0.011654       | Up    |
| ILMN_2382974 | CCDC7           | 0.391544   | 0.000891  | 0.023304       | Up    |
| ILMN_1742260 | ITPRD2          | 0.39091    | 0.001076  | 0.023734       | Up    |
| ILMN_2060145 | GRHL2           | 0.389706   | 0.000397  | 0.015954       | Up    |
| ILMN_2195821 | CREBAP2         | 0.389024   | 0.000261  | 0.013186       | Up    |
| ILMN_1746676 | CLDN8           | 0.388757   | 0.002765  | 0.041192       | Up    |
| ILMN_1700583 | ZNF750          | 0.388452   | 0.000505  | 0.017918       | Up    |
| ILMN_1659113 | NUCB2           | 0.386679   | 0.002616  | 0.039837       | Up    |
| ILMN_1701393 | TBX3            | 0.381209   | 1.9E-05   | 0.004198       | Up    |
| Gene ID     | Description                          | Log2 Fold Change | p-value  | Adjusted p-value | Significance | Status  |
|------------|---------------------------------------|------------------|----------|------------------|-------------|---------|
| ILMN_1769201 | ELF3                                 | 0.38088          | 0.02808  | 0.041529         | Up          | E74 like ETS transcription factor 3 |
| ILMN_1791280 | HSPB8                                | 0.380526         | 0.02023  | 0.03504          | Up          | heat shock protein family B (small) member 8 |
| ILMN_2149292 | TMEM40                               | 0.37849          | 0.00676  | 0.020287         | Up          | transmembrane protein 40 |
| ILMN_1707088 | DENND2D                              | 0.37794          | 7.09E-05 | 0.007061         | Up          | DENN domain containing 2D pleckstrin homology like domain family B member 2 |
| ILMN_2179778 | PHLD8                                | 0.377513         | 0.00242  | 0.012762         | Up          |  |
| ILMN_1801216 | S100P                                | 0.375994         | 7.09E-05 | 0.007061         | Up          | S100 calcium binding protein P pleckstrin homology, MyTH4 and FERM domain containing 1 |
| ILMN_1699254 | PLEKHH1                              | 0.37328          | 0.000271 | 0.013483         | Up          | pleckstrin homology like domain family B member 2 |
| ILMN_1710954 | FBXL19-AS1                           | 0.37328          | 0.000271 | 0.013483         | Up          | FBXL19 antisense RNA 1 |
| ILMN_2376502 | RHOBTB1                              | 0.372696         | 0.01027  | 0.024813         | Up          | Rho related BTB domain containing 1 |
| ILMN_1673455 | RASAL2                               | 0.372204         | 6.16E-05 | 0.006575         | Up          | RAS protein activator like 2 |
| ILMN_3194638 | EVA1A                                | 0.371837         | 0.00021  | 0.013517         | Up          | eva-1 homolog A, regulator of programmed cell death |
| ILMN_1710284 | HES1                                 | 0.370834         | 7.09E-05 | 0.007061         | Up          | hes family bHLH transcription factor 1 |
| ILMN_2064655 | CXorf40A                             | 0.369875         | 3.68E-05 | 0.005267         | Up          | chromosome X open reading frame 40A |
| ILMN_2373566 | PJA1                                 | 0.365283         | 0.00767  | 0.032784         | Up          | praja ring finger ubiquitin ligase 1 |
| ILMN_1779648 | H2AW                                 | 0.365117         | 0.000271 | 0.013483         | Up          | H2A.W histone |
| ILMN_2333107 | TLE5                                 | 0.363987         | 0.003856 | 0.014545         | Up          | TLE family member 5, transcriptional modulator |
| ILMN_1722025 | CPEB4                                | 0.363264         | 0.000601 | 0.019237         | Up          | cytoplasmic polyadenylation element binding protein 4 |
| ILMN_1670263 | CNST                                 | 0.362857         | 0.01654  | 0.031635         | Up          | consortin, connexin sorting protein |
| ILMN_2214678 | MXD1                                 | 0.36052          | 0.003377 | 0.04562          | Up          | MAX dimerization protein 1 gamma-aminobutyric acid type A receptor subunit |
| ILMN_2324202 | GABRE                                | 0.359786         | 0.01796  | 0.032966         | Up          | chromosome X open reading frame 40A |
| ILMN_2049727 | OSER1                                | 0.358697         | 0.00322  | 0.014545         | Up          | oxidative stress responsive serine rich 1 |
| ILMN_1704377 | USP27X                               | 0.35826          | 0.00113  | 0.025976         | Up          | ubiquitin specific peptidase 27 X-linked |
| ILMN_3233388 | RELL1                                | 0.357964         | 0.002177 | 0.036172         | Up          | RELT like 1 |
| ILMN_1670878 | YTHDC1                               | 0.357534         | 1.29E-06 | 0.001955         | Up          | YTH domain containing 1 |
| ILMN_1815445 | IDS                                  | 0.356888         | 0.002505 | 0.038937         | Up          | idurionate 2-sulfatase |
| ILMN_1775448 | PFN2                                 | 0.353131         | 0.000871 | 0.023045         | Up          | profilin 2 |
| ILMN_1657423 | SPG21                                | 0.353073         | 0.000213 | 0.011986         | Up          | SPG21 abhydrolase domain containing, maspardin |
| ILMN_2162799 | AHR                                  | 0.353025         | 0.002516 | 0.039016         | Up          | aryl hydrocarbon receptor |
| ILMN_1698323 | PLEKHB2                              | 0.352741         | 0.00209  | 0.035562         | Up          | pleckstrin homology domain containing B2 |
| ILMN_1725718 | ZSCAN4                               | 0.352414         | 0.000589 | 0.019114         | Up          | zinc finger and SCAN domain containing 4 |
| ILMN_2414325 | TFNAP8                               | 0.351941         | 4.64E-05 | 0.005784         | Up          | TGF alpha induced protein 8 |
| ILMN_1656291 | TSKS                                 | 0.350101         | 3.27E-05 | 0.005189         | Up          | testis specific serine kinase substrate |
| ILMN_3245236 | FBRS                                 | 0.349549         | 0.002921 | 0.042546         | Up          | fibrosin |
| ILMN_3243972 | SNORA70B                            | 0.349376         | 0.00036  | 0.015127         | Up          | small nucleolar RNA, H/ACA box 70B |
| ILMN_1687519 | SNAP23                               | 0.349045         | 0.000691 | 0.020442         | Up          | synaptosome associated protein 23 |
| ILMN_3307729 | CXXC5                                | 0.347435         | 0.003855 | 0.04893          | Up          | CXXC finger protein 5 calcium/calmodulin dependent protein kinase II gamma |
| ILMN_2359601 | CAMK2G                               | 0.346831         | 1.67E-06 | 0.001955         | Up          | RNA binding motif single stranded interacting protein 1 |
| ILMN_2358541 | RBMS1                                | 0.346578         | 0.001495 | 0.030009         | Up          | discoidin domain receptor tyrosine kinase 1 |
| ILMN_1655702 | ABHD5                                | 0.345520         | 0.000199 | 0.011583         | Up          | abhydrolase domain containing 5 |
| ILMN_1730294 | INO80C                               | 0.345306         | 0.000584 | 0.01904          | Up          | INO80 complex subunit C |
| ILMN_1729095 | PDZD2                                | 0.34383          | 0.000816 | 0.022314         | Up          | PDZ domain containing 2 |
| Gene ID     | Description                                      | Log2 Fold Change | P Value   | q Value   | Expression  |
|------------|--------------------------------------------------|------------------|-----------|-----------|-------------|
| ILMN_1775405 | ARL4A                                           | 0.3433           | 0.000509  | 0.017937  | Up          |
| ILMN_1680937 | H2BC4                                           | 0.342683         | 0.003032  | 0.045124  | Up          |
| ILMN_1689578 | TRL3                                            | 0.342449         | 0.002261  | 0.036968  | Up          |
| ILMN_2278335 | AKR1B15                                         | 0.342114         | 0.001891  | 0.033769  | Up          |
| ILMN_1721922 | NAB2                                            | 0.340891         | 0.000509  | 0.017937  | Up          |
| ILMN_1691237 | CAP2                                            | 0.339551         | 0.002261  | 0.036968  | Up          |
| ILMN_2395389 | PSMC4                                           | 0.336399         | 0.002261  | 0.036968  | Up          |
| ILMN_2173919 | MYO9A                                           | 0.33636          | 0.002261  | 0.036968  | Up          |
| ILMN_1690826 | TNKS1BP1                                        | 0.335255         | 0.002261  | 0.036968  | Up          |
| ILMN_1742824 | SPATA13                                         | 0.331477         | 0.002261  | 0.036968  | Up          |
| ILMN_1688755 | AAK1                                            | 0.329844         | 0.002261  | 0.036968  | Up          |
| ILMN_1781374 | TUFT1                                           | 0.328884         | 0.002261  | 0.036968  | Up          |
| ILMN_2124386 | RGL2                                            | 0.327869         | 0.002261  | 0.036968  | Up          |
| ILMN_1803939 | YIPF6                                           | 0.327011         | 0.002261  | 0.036968  | Up          |
| ILMN_2170949 | SNX10                                           | 0.326699         | 0.002261  | 0.036968  | Up          |
| ILMN_1775304 | DNAJB1                                          | 0.326714         | 0.002261  | 0.036968  | Up          |
| ILMN_1657515 | RPS6KA5                                         | 0.32621           | 0.002261  | 0.036968  | Up          |
| ILMN_1690826 | TNKS1BP1                                        | 0.321786         | 0.002261  | 0.036968  | Up          |
| ILMN_1814002 | TEAD3                                           | 0.320268         | 0.002261  | 0.036968  | Up          |
| ILMN_1768958 | RASGRP1                                         | 0.31925           | 0.002261  | 0.036968  | Up          |
| ILMN_2077623 | RRAS2                                           | 0.319214         | 0.002261  | 0.036968  | Up          |
| ILMN_1693014 | CEBPB                                           | 0.318883         | 0.002261  | 0.036968  | Up          |
| ILMN_3235340 | ACER2                                           | 0.318499         | 0.002261  | 0.036968  | Up          |
| ILMN_2403458 | SMARCB1                                         | 0.318053         | 0.002261  | 0.036968  | Up          |
| ILMN_1805395 | LTB3                                            | 0.317611         | 0.002261  | 0.036968  | Up          |
| ILMN_1804148 | TMED4                                           | 0.317228         | 0.002261  | 0.036968  | Up          |
| ILMN_1702447 | IGF2BP2                                         | 0.316952         | 0.002261  | 0.036968  | Up          |
| ILMN_1717195 | MB2D                                            | 0.316258         | 0.002261  | 0.036968  | Up          |
| ILMN_1747451 | PLCXD1                                          | 0.316197         | 0.002261  | 0.036968  | Up          |
| ILMN_1777439 | TCL6                                            | 0.313824         | 0.002261  | 0.036968  | Up          |
| ILMN_2358457 | ATF4                                            | 0.312963         | 0.002261  | 0.036968  | Up          |
| ILMN_1694233 | ACYP1                                           | 0.312484         | 0.002261  | 0.036968  | Up          |
| ILMN_1675937 | ANKRD9                                          | 0.312142         | 0.002261  | 0.036968  | Up          |
| ILMN_1670304 | FAM156A                                         | 0.311579         | 0.002261  | 0.036968  | Up          |
| ILMN_1717234 | CAST                                            | 0.310235         | 0.002261  | 0.036968  | Up          |
| ILMN_1710136 | PUDP                                            | 0.309696         | 0.002261  | 0.036968  | Up          |
| ILMN_1750969 | FAM120AOS                                       | 0.309171         | 0.002261  | 0.036968  | Up          |
| ILMN_1717046 | MOB3B                                           | 0.309072         | 0.002261  | 0.036968  | Up          |
| ILMN_1684042 | BET1                                            | 0.307537         | 0.002261  | 0.036968  | Up          |
| Gene Name          | Accession | Fold Change | p-value | Adj. p-value | Description                                      |
|--------------------|-----------|-------------|---------|--------------|--------------------------------------------------|
| HIV-1 Tat interactive protein | ILMN_1664303 | 0.306236    | 0.0063  | 0.019629     | Up                                                |
| CRIM1 divergent transcript  | ILMN_3263225 | 0.305254    | 0.00552 | 0.018347     | Up                                                |
| atypical chemokine receptor 2 | ILMN_1763127 | 0.305224    | 0.01928 | 0.03416      | Up                                                |
| radixin            | ILMN_1708611 | 0.30478     | 0.01592 | 0.031099     | Up                                                |
| zinc finger protein 83 | ILMN_2190414 | 0.304639    | 0.00691 | 0.020442     | Up                                                |
| ST8SIA6 antisense RNA 1 | ILMN_3184978 | 0.304228    | 3.46E-05| 0.005189     | Up                                                |
| farnesyltransferase, CAAX box, alpha | ILMN_1746494 | 0.303227    | 2.43E-05| 0.00477      | Up                                                |
| RANBP2 like and GRIP domain containing 8 | ILMN_3238854 | 0.302737    | 0.000139 | 0.00984     | Up                                                |
| RAR related orphan receptor A | ILMN_1741371 | 0.301932    | 0.00691 | 0.020442     | Up                                                |
| opsin 3            | ILMN_1716988 | 0.300318    | 0.02185 | 0.036205     | Up                                                |
| ST8SIA6 antisense RNA 4 | ILMN_1780382 | 0.299459    | 3.46E-05| 0.005189     | Up                                                |
| damage specific DNA binding protein 1 | ILMN_1782685 | 0.298269    | 0.003743| 0.04825      | Up                                                |
| adenosine kinase    | ILMN_1801020 | 0.298209    | 0.00201 | 0.011664     | Up                                                |
| 3-phosphoinositide dependent protein kinase 1 | ILMN_1653793 | 0.297954    | 0.002793| 0.041395     | Up                                                |
| lysophosphatidylcholineacyltransferase 3 | ILMN_1805225 | 0.296395    | 6.38E-06| 0.00295      | Up                                                |
| cytochrome c oxidase copper chaperone COX17 | ILMN_1741371 | 0.296064    | 0.003279| 0.045007     | Up                                                |
| H2B clustered histone 6 | ILMN_1687947 | 0.295728    | 0.000669| 0.020173     | Up                                                |
| casein kinase 2 alpha 2 | ILMN_1734478 | 0.295428    | 0.002683| 0.040473     | Up                                                |
| insulin like growth factor 2 mRNA binding protein 3 | ILMN_1662578 | 0.294084    | 0.00014 | 0.00984     | Up                                                |
| STAG3L5P-PVGRG2P-PLRB readthrough | ILMN_1807423 | 0.293802    | 0.00826 | 0.02247      | Up                                                |
| ST8SIA6-AS1 antisense RNA 1 | ILMN_3204734 | 0.293124    | 0.003136| 0.044111     | Up                                                |
| cell cycle associated protein 1 | ILMN_1754145 | 0.293108    | 0.00032 | 0.014545     | Up                                                |
| SERTA domain containing 4 | ILMN_1730794 | 0.292851    | 9.6E-05 | 0.008175     | Up                                                |
| pleckstrin homology domain containing A1 | ILMN_1719344 | 0.291747    | 0.002354| 0.03774      | Up                                                |
| solute carrier family 4 member 2 | ILMN_1723843 | 0.291428    | 0.002683| 0.040473     | Up                                                |
| glycoprotein integral membrane 1 | ILMN_1710027 | 0.290602    | 0.0003  | 0.014133     | Up                                                |
| phenylethanolamine N-methyltransferase phosphatidylinositol-4-phosphate 5-kinase type 1 beta | ILMN_1733478 | 0.289858    | 5.33E-06| 0.002879     | Up                                                |
| electron transfer flavoprotein dehydrogenase | ILMN_1758034 | 0.288994    | 0.00644 | 0.019798     | Up                                                |
| lyso phospholysolephosphate 1 ADP ribosylation factor like GTPase 6 interacting protein 6 | ILMN_1666713 | 0.288789    | 0.00059 | 0.019114     | Up                                                |
| heat shock protein 90 alpha family class A member 1 | ILMN_1797964 | 0.286061    | 0.00378 | 0.015488     | Up                                                |
| mammalian receptor binding factor 2 | ILMN_1719344 | 0.286739    | 0.00285 | 0.041916     | Up                                                |
| mammalian receptor binding factor 6 | ILMN_1734655 | 0.286517    | 0.000583| 0.01904      | Up                                                |
| mammalian receptor binding 9B | ILMN_1711408 | 0.286403    | 0.002191| 0.036239     | Up                                                |
| S-phase cyclin A associated protein in the ER | ILMN_1811178 | 0.286258    | 0.002028| 0.035067     | Up                                                |
| Gene ID      | Gene ID      | Symbol   | Log2FoldChange | FoldChange | Status | Description                                                                 |
|-------------|-------------|----------|---------------|------------|--------|-----------------------------------------------------------------------------|
| ILMN_1669895 | MTM1        | CLN3     | 0.284755      | 3.264326   | Up     | lysosomal/endosomal transmembrane protein, battenin                        |
| ILMN_1781560 | ST3GAL6     | ST3      | 0.284681      | 3.440705   | Up     | beta-galactoside alpha-2,3-sialyltransferase 6                             |
| ILMN_1734229 | SPPL2A      | SPPL2    | 0.283933      | 3.352613   | Up     | signal peptide peptidase like 2A                                          |
| ILMN_2094166 | CHMP5       | CHMP5    | 0.282317      | 3.324924   | Up     | charged multivesicular body protein 5                                      |
| ILMN_1773849 | ATP6V0C     | ATPase   | 0.282222      | 3.419682   | Up     | H+ transporting V0 subunit c                                              |
| ILMN_1739876 | RAB3GAP1    | RAB3     | 0.281181      | 3.324924   | Up     | GTPase activating protein catalytic subunit 1                              |
| ILMN_1797594 | NFAT5       | NFAT     | 0.28094       | 3.072332   | Up     | nuclear factor of activated T cells 5                                     |
| ILMN_1734542 | OVGP1       | OVGP1    | 0.280116      | 3.161242   | Up     | oviductal glycoprotein 1                                                  |
| ILMN_1665982 | AKTIP       | AKT      | 0.277649      | 3.190258   | Up     | interacting protein                                                       |
| ILMN_1679268 | PELI1       | PELI1    | 0.277477      | 3.204955   | Up     | E3 ubiquitin protein ligase 1                                              |
| ILMN_3249846 | LIMS3-LOC440895 | LIMS3-LOC 440895 | 0.276865  | 3.330332   | Up | WW domain containing adaptor with coiled-coil                             |
| ILMN_2323526 | WAC         | WAC      | 0.276545      | 3.769114   | Up     | WW domain containing adaptor with coiled-coil                             |
| ILMN_1748077 | DDX59       | DDX      | 0.275827      | 3.149590   | Up     | DEAD-box helicase 59                                                       |
| ILMN_1782444 | YIPF4       | YIPF4    | 0.275515      | 3.300882   | Up     | Yip1 domain family member 4                                                |
| ILMN_2339284 | CHD2        | CHD2     | 0.27514       | 3.862717   | Up     | chromodomain helicase DNA binding protein 2                                |
| ILMN_1706342 | ZNF746      | ZNF      | 0.274977      | 3.250211   | Up     | zinc finger protein 746                                                    |
| ILMN_3215367 | PPP4R2      | PPP4     | 0.274625      | 3.472213   | Up     | protein phosphatase 4 regulatory subunit 2                                 |
| ILMN_1687279 | DHPS        | DHPS     | 0.274317      | 3.445971   | Up     | deoxyhypusine synthase                                                     |
| ILMN_1685678 | EEF1B2      | EEF      | 0.273865      | 3.366614   | Up     | eukaryotic translation elongation factor 1 beta 2                          |
| ILMN_1690066 | TGD2        | TGD2     | 0.273626      | 3.720901   | Up     | tigger transposable element derived 2catechol-O-methyltransferase domain containing 1 |
| ILMN_1736752 | COMTD1      | COMTD1   | 0.273513      | 3.216644   | Up     | CCGG triplet repeat binding protein 1                                      |
| ILMN_2387090 | CGGBP1      | CGGBP1   | 0.273351      | 3.699974   | Up     | germ cell-less 1, spermatogenesis associated                               |
| ILMN_2194627 | GMCL1       | GMCL1    | 0.273232      | 3.759819   | Up     | S100 calcium binding protein A1                                              |
| ILMN_3241234 | S100A11     | S100A11  | 0.273188      | 3.431703   | Up     | S-protein phosphatase 4 regulatory subunit 2                                |
| ILMN_1678454 | CASP4       | CASP4    | 0.27189       | 3.25192    | Up     | caspase 4                                                                  |
| ILMN_1705907 | NUP153      | NUP153   | 0.271384      | 3.782266   | Up     | nucleoporin 153                                                           |
| ILMN_2106265 | GDPD1       | GDPD1    | 0.271243      | 2.992682   | Up     | glycophosphodiesterphosphodiesterase domain containing 1                   |
| ILMN_1699357 | SLC22A5     | SLC22A5  | 0.270646      | 3.019938   | Up     | solute carrier family 22 member 5 protein phosphatase 1 regulatory inhibitor subunit 14B |
| ILMN_3282768 | PPP1R114B   | PPP1R1   | 0.27002       | 3.331779   | Up     | TIA1 cytotoxic granule associated RNA binding protein like 1               |
| ILMN_1784655 | TLCRD1      | TLCRD1   | 0.269664      | 3.219351   | Up     | TIA1 cytotoxic granule associated RNA binding protein like 1               |
| ILMN_1809344 | BTBD10      | BTBD10   | 0.269367      | 2.945897   | Up     | TIA1 cytotoxic granule associated RNA binding protein like 1               |
| ILMN_1651268 | BORCS5      | BORCS5   | 0.268841      | 3.576152   | Up     | related complex subunit 5                                                  |
| ILMN_1676385 | PAK2        | PAK2     | 0.268282      | 3.920545   | Up     | p21 (RAC1) activated kinase 2                                               |
| ILMN_1658337 | AKIRIN1     | AKIRIN1  | 0.268214      | 3.020957   | Up     | akirin 1                                                                   |
| ILMN_2137464 | DVL3        | DVL3     | 0.267864      | 3.327306   | Up     | dishevelled segment polarity protein 3                                     |
| ILMN_1721833 | IER5        | IER5     | 0.26766       | 3.026706   | Up     | immediate early response 5                                                 |
| ILMN_1781431 | GLCCI1      | GLCCI1   | 0.267281      | 4.099378   | Up     | glucocorticoid induced 1                                                   |
| ILMN_1808824 | NEBL        | NEBL     | 0.266945      | 3.238616   | Up     | nebulite                                                                    |
| ILMN_1813028 | CBX5        | CBX5     | 0.266965      | 4.259566   | Up     | chromobox 5                                                                |
| ILMN_1717745 | TIAL1       | TIAL1    | 0.266333      | 4.747368   | Up     | TIA1 cytotoxic granule associated RNA binding protein like 1               |
| ILMN_1695110 | BCAT2       | BCAT2    | 0.266237      | 3.051398   | Up     | branched chain amino acid transaminase 2                                  |
| Gene ID   | Symbol | Fold Change | p-value | q-value | Description                                                                 |
|----------|--------|-------------|---------|---------|----------------------------------------------------------------------------|
| ILMN_1735052 | ULK1   | 3.042442    | 0.266063 | 0.003262 | unc-51 like autophagy activating kinase 1                                   |
| ILMN_1666670 | RBX1   | 4.659225    | 0.265833 | 0.003026 | ring-box 1                                                                 |
| ILMN_1801476 | CDS1   | 3.140131    | 0.265788 | 0.003026 | CDP-diacylglycerol synthase 1                                              |
| ILMN_1707350 | TUSC1  | 3.139179    | 0.265484 | 0.003026 | tumor suppressor candidate 1                                               |
| ILMN_1671265 | ING2   | 3.937352    | 0.264936 | 0.003026 | inhibitor of growth family member 2                                        |
| ILMN_1776297 | GOLGA4 | 3.380238    | 0.262744 | 0.003026 | golgin A4                                                                  |
| ILMN_1717063 | FBXO9  | 4.803593    | 0.262633 | 0.003026 | F-box protein 9                                                             |
| ILMN_1671265 | ING2   | 3.937352    | 0.264936 | 0.003026 | inhibitor of growth family member 2                                        |
| ILMN_1704550 | AZIN1  | 3.112496    | 0.262282 | 0.003026 | antizyme inhibitor 1                                                        |
| ILMN_1695961 | UCHL3  | 4.250481    | 0.262244 | 0.003026 | ubiquitin C-terminal hydrolase L3                                          |
| ILMN_1709043 | RAB25  | 3.021403    | 0.262537 | 0.003026 | RAB25, member RAS oncogene family                                          |
| ILMN_1792497 | CLK1   | 4.142743    | 0.261157 | 0.003026 | CDC like kinase 3                                                           |
| ILMN_3197097 | TSTD1  | 3.909022    | 0.261943 | 0.003026 | thiosulfate sulfurtransferase like domain containing 1                     |
| ILMN_1736154 | LZTS3  | 3.74905    | 0.257357 | 0.003026 | leucine zipper tumor suppressor family member 3                             |
| ILMN_2328776 | STK26  | 3.01189    | 0.257337 | 0.003026 | serine/threonine kinase 2                                                  |
| ILMN_3246900 | LINC01278 | 3.09914 | 0.255848 | 0.003026 | long intergenic non-protein coding RNA 1278                                |
| ILMN_1702407 | AGFG1  | 3.442009    | 0.255601 | 0.003026 | ArtGAP with FG repeats 1                                                    |
| ILMN_1684346 | TNFAIP8L1 | 3.229929 | 0.255953 | 0.003026 | TNF alpha induced protein 8 like 1                                         |
| ILMN_1737475 | ABHD11 | 3.149412    | 0.255933 | 0.003026 | abhydrolase domain containing 1                                             |
| ILMN_1682147 | HOOK2  | 3.00611    | 0.255831 | 0.003026 | hook microtubule tethering protein 2                                       |
| ILMN_1736154 | LZTS3  | 3.74905    | 0.255831 | 0.003026 | leucine zipper tumor suppressor family member 3                             |
| ILMN_2399264 | SEPTIN6 | 3.01189    | 0.255523 | 0.003026 | sepin 6                                                                    |
| ILMN_2055523 | CSN16  | 3.65339    | 0.255523 | 0.003026 | chondroitin sulfate sulfotransferase 1                                     |
| ILMN_3279712 | SMS    | 3.216153    | 0.255523 | 0.003026 | acetyl-CoA synthase                                                         |
| ILMN_1701514 | TRAF3P2 | 3.018317    | 0.252377 | 0.003026 | TRAF3 interacting protein 2                                                |
| ILMN_3227529 | RPS13  | 3.65339    | 0.252377 | 0.003026 | ribosomal protein S13                                                       |
| ILMN_1680397 | CXCR2  | 3.439126    | 0.251961 | 0.003026 | C-X-C motif chemokine receptor 2                                           |
| ILMN_1661142 | TMF1   | 3.439126    | 0.251961 | 0.003026 | TATA element modulatory factor 1                                           |
| ILMN_2228044 | TBC1D23 | 4.797583    | 0.251655 | 0.003026 | TBC1 domain family member 2                                                |
| ILMN_2352326 | COASY  | 3.014949    | 0.251485 | 0.003026 | Coenzyme A synthase                                                         |
| ILMN_1753457 | PKP3   | 3.449557    | 0.251362 | 0.003026 | plakophilin 3                                                               |
| ILMN_2081673 | INSL6  | 4.732468    | 0.250409 | 0.003026 | insulin like 6                                                             |
| ILMN_1743396 | ACOX3  | 3.340671    | 0.250377 | 0.003026 | acyl-CoA oxidase 3, pristanoyl                                              |
| ILMN_1711786 | NFE2   | 3.32609    | 0.250104 | 0.003026 | nuclear factor, erythroid 2 capping actin protein of muscle Z-line subunit  |
| ILMN_3289099 | CAPZA1 | 3.263922    | 0.249888 | 0.003026 | alpha 1                                                                    |
| ILMN_2151056 | BORCS7 | 3.776529    | 0.249315 | 0.003026 | BLOC-1 related complex subunit 7                                           |
| ILMN_1716195 | H2BC8  | 3.481999    | 0.248678 | 0.003026 | H2B clustered histone 8                                                     |
| ILMN_2368684 | JUP    | 3.001191    | 0.248584 | 0.003026 | junction plakoglobin                                                        |
| ILMN_1700026 | PXDC1  | 3.19572    | 0.248166 | 0.003026 | PX domain containing 1                                                     |
| ILMN_1690894 | HSP90IB3P | 3.2861     | 0.248104 | 0.003026 | heat shock protein 90 beta family member 3                                 |

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| Gene ID     | Description                                                   | Log2FC | p-value  | FDR      | Status  |
|------------|---------------------------------------------------------------|--------|----------|----------|---------|
| ILMN_1662880 | LINC01554 long intergenic non-protein coding RNA 1554          | 3.908142 | 0.000163 | 0.010418 | Up      |
| ILMN_1664560 | DYT1A SERTAD4-AS1 SERTAD4 antisense RNA 1                     | 4.406676 | 0.004816 | 0.000163 | Up      |
| ILMN_2347541 | NIN long intergenic non-protein coding RNA 3                  | 3.056875 | 0.001015 | 0.000163 | Up      |
| ILMN_3185198 | ACTR3C actin related protein 3C                               | 3.392602 | 0.001286 | 0.000163 | Up      |
| ILMN_2274420 | SPTLC1 serine palmitoyltransferase long chain base subunit 1  | 3.255789 | 0.000994 | 0.000163 | Up      |
| ILMN_1711792 | GPBP1 GC-rich promoter binding protein 1                      | 3.939077 | 0.001094 | 0.000163 | Up      |
| ILMN_1785765 | TM9SF2 transmembrane 9 superfamily member 2                   | 2.980358 | 0.004712 | 0.000163 | Up      |
| ILMN_1739967 | TBK1 TANK binding kinase 1                                    | 3.72025  | 0.001452 | 0.000163 | Up      |
| ILMN_3243514 | PP12613 uncharacterized LOC100192379                         | 4.213967 | 0.000607 | 0.000163 | Up      |
| ILMN_2113938 | TOR1AIP2 torsin 1A interacting protein 2                      | 3.061016 | 0.002770 | 0.000163 | Up      |
| ILMN_1697864 | CXorf38 chromosome X open reading frame 38                     | 4.647172 | 0.003088 | 0.000163 | Up      |
| ILMN_1737005 | SMG9 nonsense mediated mRNA decay factor                      | 4.647172 | 0.003088 | 0.000163 | Up      |
| ILMN_2275248 | ECE2 endothelin converting enzyme 2                           | 3.919402 | 0.000607 | 0.000163 | Up      |
| ILMN_1669090 | CXorf56 chromosome X open reading frame 38                     | 4.130027 | 0.001015 | 0.000163 | Up      |
| ILMN_1804064 | ESRRG estrogen related receptor gamma                          | 3.176409 | 0.003406 | 0.000163 | Up      |
| ILMN_1682919 | PAFAH2 platelet activating factor related protein factor 1     | 3.027658 | 0.002078 | 0.000163 | Up      |
| ILMN_1676763 | PIPS1 PIPS5K1A and PSMD4 like (pseudogene)                    | 3.715885 | 0.001452 | 0.000163 | Up      |
| ILMN_1810782 | SH3KBP1 SH3 domain containing kinase binding protein 1         | 3.003739 | 0.001452 | 0.000163 | Up      |
| ILMN_1666258 | AMFR autocrine motility factor receptor                        | 3.157186 | 0.003418 | 0.000163 | Up      |
| ILMN_1776154 | COG3 component of oligomeric golgi complex 3                  | 3.234779 | 0.001310 | 0.000163 | Up      |
| ILMN_2387553 | PSMA3 proteasome 20S subunit alpha 3                          | 3.973908 | 0.009505 | 0.000163 | Up      |
| ILMN_1730630 | CXorf56 chromosome X open reading frame 38                     | 3.1615   | 0.003103 | 0.000163 | Up      |
| ILMN_1673380 | GNG12 G protein subunit gamma 12                               | 3.033043 | 0.004332 | 0.000163 | Up      |
| ILMN_3247111 | LRRG9 leucine rich containing 6                               | 3.489939 | 0.002087 | 0.000163 | Up      |
| ILMN_1757956 | PCCG1 polycomb group ring finger 1                             | 3.478289 | 0.002012 | 0.000163 | Up      |
| ILMN_1759460 | TAF7 TATA-box binding protein associated factor 7              | 5.027658 | 0.002078 | 0.000163 | Up      |
| ILMN_1747241 | IWS1 interacts with Supt6h, CTD assembly factor 1              | 2.996419 | 0.004572 | 0.000163 | Up      |
| ILMN_1676763 | PIPS1 PIPS5K1A and PSMD4 like (pseudogene)                    | 3.715885 | 0.001452 | 0.000163 | Up      |
| ILMN_1813148 | TM1G1 target of myb1 membrane trafficking protein              | 3.04312  | 0.004284 | 0.000163 | Up      |
| ILMN_1760256 | RBM22 RNA binding motif protein 22                             | 3.198833 | 0.003308 | 0.000163 | Up      |
| Gene Symbol | Log2 Fold Change | p Value | q Value | Benjamini-Hochberg FDR | Status |
|-------------|-----------------|---------|---------|------------------------|--------|
| ILMN_1658743 | CCNDP1          | 0.229972 | 9.97E-05 | 0.008353 | 4.04187 | Up |
| ILMN_1717294 | PTPN3           | 0.229265 | 0.002347 | 0.037683 | 3.11632 | Up |
| ILMN_2101920 | HNRNPH1         | 0.228516 | 0.000147 | 0.026058 | 3.34185 | Up |
| ILMN_1736234 | CHTOP            | 0.228516 | 0.001144 | 0.019296 | 3.39222 | Up |
| ILMN_1700384 | KIAA1522        | 0.228516 | 0.000577 | 0.018974 | 3.54766 | Up |
| ILMN_1719237 | SPDYE8P         | 0.228465 | 0.00384 | 0.048887 | 2.95495 | Up |
| ILMN_1701724 | GET4            | 0.228197 | 0.000247 | 0.012906 | 3.79222 | Up |
| ILMN_1785852 | NABP1           | 0.227819 | 0.002071 | 0.035437 | 3.15632 | Up |
| ILMN_1755649 | SLC16A5         | 0.227432 | 0.001462 | 0.020716 | 3.46055 | Up |
| ILMN_1701308 | COL1A1          | -0.77213 | 5.05E-07 | 0.001127 | -5.34677 | Down |
| ILMN_1723522 | APOLD1          | -0.75887 | 0.000051 | 0.017953 | -3.58362 | Down |
| ILMN_1779875 | THY1            | -0.75181 | 3.89E-05 | 0.005414 | -4.29148 | Down |
| ILMN_1696347 | CTSC            | -0.73439 | 0.000014 | 0.015151 | -3.68044 | Down |
| ILMN_1706505 | COL5A1          | -0.68289 | 8.23E-08 | 0.00792 | -5.75462 | Down |
| ILMN_3237946 | PXDN            | -0.68073 | 4.96E-06 | 0.002879 | -4.80838 | Down |
| ILMN_1673639 | AB1BP2          | -0.67199 | 0.000361 | 0.023743 | -3.40373 | Down |
| ILMN_1766914 | MFAP4           | -0.66612 | 4.35E-06 | 0.002722 | -4.84032 | Down |
| ILMN_1795325 | ACTG2           | -0.65224 | 0.000984 | 0.024307 | -3.38785 | Down |
| ILMN_1757604 | TPM2            | -0.65 | 0.000014 | 0.00984 | -3.59645 | Down |
| ILMN_1700643 | COL6A3          | -0.64553 | 2.54E-05 | 0.004833 | -4.21049 | Down |
| ILMN_1725193 | IGFBP2          | -0.63091 | 0.000135 | 0.024881 | -3.37242 | Down |
| ILMN_1720231 | TNNT3           | -0.61686 | 0.000039 | 0.020442 | -3.49345 | Down |
| ILMN_2104356 | COL1A2          | -0.60473 | 8.52E-06 | 0.00295 | -4.67573 | Down |
| ILMN_1773079 | COL3A1          | -0.60333 | 5.14E-06 | 0.002879 | -4.96929 | Down |
| ILMN_1707070 | PCOLCE          | -0.59908 | 1.55E-06 | 0.001955 | -5.8687 | Down |
| ILMN_1797776 | PRSS23          | -0.59791 | 3.60E-05 | 0.001955 | -5.11653 | Down |
| ILMN_2390919 | FBLN2           | -0.59331 | 6.9E-06 | 0.00295 | -4.12775 | Down |
| ILMN_1712046 | CPXM1           | -0.59179 | 0.000142 | 0.00989 | -3.94586 | Down |
| ILMN_1670379 | ANTXR1          | -0.59159 | 3.06E-05 | 0.005173 | -4.35299 | Down |
| ILMN_1743445 | FAM107A         | -0.58708 | 0.001007 | 0.02461 | -3.38091 | Down |
| ILMN_1697268 | EMLIN2          | -0.58178 | 2.61E-05 | 0.004833 | -4.39456 | Down |
| ILMN_1756071 | MFGE8           | -0.58136 | 0.00023 | 0.012505 | -3.81152 | Down |
| ILMN_2115125 | CCN2            | -0.56274 | 0.00135 | 0.028444 | -3.29078 | Down |
| ILMN_1700690 | VAT1            | -0.55561 | 1.38E-05 | 0.003478 | -4.55664 | Down |
| ILMN_1761968 | PPP1R14A        | -0.55328 | 6.36E-05 | 0.00295 | -4.74771 | Down |
| ILMN_1783909 | COL6A2          | -0.55352 | 3.46E-05 | 0.005189 | -4.32174 | Down |
| Gene | Gene Expression | Gene ID | Function or Protein | Expression Value | Enrichment Value | Fold Change | Status |
|------|-----------------|---------|---------------------|------------------|-----------------|-------------|--------|
| GPER1 | Down | ILMN_2384056 | G protein-coupled estrogen receptor 1 | -0.55173 | 0.001275 | 0.027557 | -3.30852 |
| LAMC3 | Down | ILMN_1688642 | laminin subunit gamma 3 | -0.54794 | 0.000167 | 0.010606 | -3.90071 |
| GAS6 | Down | ILMN_1779558 | growth arrest specific 6 | -0.54545 | 0.001127 | 0.027557 | -3.56823 |
| RFTN1 | Down | ILMN_1800787 | raftlin, lipid raft linker 1 | -0.54246 | 0.003091 | 0.027557 | -4.6434 |
| LASP1 | Down | ILMN_1665909 | LIM and SH3 protein 1 | -0.53543 | 0.001955 | 0.027557 | -5.10383 |
| SLIT3 | Down | ILMN_1811313 | slit guidance ligand 3 | -0.53304 | 0.007511 | 0.027557 | -5.83956 |
| CAVIN3 | Down | ILMN_1793476 | caveolae associated protein 3 | -0.5317 | 0.007511 | 0.027557 | -4.43772 |
| VCAM1 | Down | ILMN_2307903 | vascular cell adhesion molecule 1 | -0.53139 | 0.007511 | 0.027557 | -4.09693 |
| PARM1 | Down | ILMN_1656560 | prostate androgen-regulated mucin-like protein 1 | -0.53103 | 0.007511 | 0.027557 | -3.91255 |
| CDH11 | Down | ILMN_1672611 | cadherin 11 | -0.52302 | 0.007511 | 0.027557 | -3.83169 |
| OLFML2B | Down | ILMN_1765557 | olfactomedin like 2B | -0.52097 | 0.007511 | 0.027557 | -4.6686 |
| PDGFRB | Down | ILMN_1815057 | platelet derived growth factor receptor beta | -0.52016 | 0.007511 | 0.027557 | -4.48559 |
| TSC22D3 | Down | ILMN_1736178 | TSC22 domain family member 3 | -0.5199 | 0.007511 | 0.027557 | -4.33169 |
| LGALS1 | Down | ILMN_1723978 | galectin 1 | -0.51718 | 0.007511 | 0.027557 | -3.68144 |
| NES | Down | ILMN_1738147 | nestin | -0.51576 | 0.007511 | 0.027557 | -4.6686 |
| PDE8B | Down | ILMN_1687301 | phosphodiesterase 8B | -0.51488 | 0.007511 | 0.027557 | -4.38289 |
| VCAN | Down | ILMN_1687652 | versican | -0.51483 | 0.007511 | 0.027557 | -4.21926 |
| IGFBP7 | Down | ILMN_1748124 | insulin like growth factor binding protein 7 | -0.51439 | 0.007511 | 0.027557 | -4.21926 |
| LGALS1 | Down | ILMN_1738147 | galectin 1 | -0.51576 | 0.007511 | 0.027557 | -4.6686 |
| VASP | Down | ILMN_1665219 | vasorin | -0.50184 | 0.007511 | 0.027557 | -3.3994 |
| IGFBP4 | Down | ILMN_1665865 | insulin like growth factor binding protein 4 | -0.49057 | 0.007511 | 0.027557 | -3.05613 |
| ENPP2 | Down | ILMN_1653424 | ectonucleotidepyrophosphatase/phosphodiesterase 2 | -0.49776 | 0.007511 | 0.027557 | -4.13908 |
| LAMB2 | Down | ILMN_1752968 | laminin subunit beta 2 | -0.49708 | 0.007511 | 0.027557 | -3.73636 |
| HEYL | Down | ILMN_1667295 | ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3 | -0.49611 | 0.007511 | 0.027557 | -4.03652 |
| VASA | Down | ILMN_1812618 | vasorin | -0.49482 | 0.007511 | 0.027557 | -3.59477 |
| APAP | Down | ILMN_1661599 | ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3 | -0.49404 | 0.007511 | 0.027557 | -3.0217 |
| DDI4 | Down | ILMN_1713496 | DNA damage inducible transcript 4 | -0.49301 | 0.007511 | 0.027557 | -3.09422 |
| ST3GAL5 | Down | ILMN_1665865 | ST3 beta-galactoside alpha-2,3-sialyltransferase 5 | -0.492 | 0.007511 | 0.027557 | -4.08534 |
| TGFBR3 | Down | ILMN_1687652 | transforming growth factor beta 3 | -0.48958 | 0.007511 | 0.027557 | -3.15638 |
| EMP1 | Down | ILMN_1801616 | epithelial membrane protein 1 | -0.48942 | 0.007511 | 0.027557 | -3.87097 |
| TNC | Down | ILMN_1733259 | laminin subunit gamma 3 | -0.48909 | 0.007511 | 0.027557 | -3.79958 |
| PDSPN | Down | ILMN_1607490 | podoplanin | -0.48881 | 0.007511 | 0.027557 | -3.95297 |
| LTBP4 | Down | ILMN_1665219 | latent transforming growth factor beta binding protein 4 | -0.4882 | 0.007511 | 0.027557 | -3.70174 |
| FILIP1L | Down | ILMN_1738578 | filamin A interacting protein 1 like | -0.48742 | 0.007511 | 0.027557 | -3.88315 |
| IGFLAM | Down | ILMN_1654109 | EGF like, fibronectin type III and laminin G domains | -0.48718 | 0.007511 | 0.027557 | -3.80108 |
| SPARC | Down | ILMN_1796734 | secreted protein acidic and cysteine rich | -0.48641 | 0.007511 | 0.027557 | -4.49427 |
| EPDR1 | Down | ILMN_1675977 | epidermin related 1 | -0.48638 | 0.007511 | 0.027557 | -3.04891 |
| VWF | Down | ILMN_1752755 | von Willebrand factor | -0.48403 | 0.007511 | 0.027557 | -3.491 |
| MXRA7 | Down | ILMN_1743836 | matrix remodeling associated 7 | -0.48256 | 0.007511 | 0.027557 | -3.9585 |
| COL6A1 | Down | ILMN_1732151 | collagen type VI alpha 1 chain | -0.48252 | 0.007511 | 0.027557 | -3.56848 |
| Gene ID       | Symbol | Log2 Fold Change | FDR   | P Value  | Regulation | Description                                      |
|--------------|--------|-----------------|-------|----------|------------|--------------------------------------------------|
| ILMN_1696965 | TNFRSF21 | -0.48252       | 3.82E-07 | 0.001058 | Down       | TNF receptor superfamily member 21               |
| ILMN_1671703 | ACTA2  | -0.48127       | 0.001006 | 0.024602 | Down       | actin alpha 2, smooth muscle                      |
| ILMN_1777190 | CFD    | -0.48004       | 0.001794 | 0.032947 | Down       | complement factor D                               |
| ILMN_1785646 | PMP22  | -0.47862       | 1.24E-05 | 0.003412 | Down       | peripheral myelin protein 22                      |
| ILMN_1795166 | PTH1R  | -0.47706       | 1.22E-05 | 0.003404 | Down       | parathyroid hormone 1 receptor                    |
| ILMN_1779182 | TEMEM98 | -0.47485       | 3.81E-06 | 0.002678 | Down       | transmembrane protein 98 latent transforming growth factor beta binding protein 2 |
| ILMN_3248591 | LTBP2  | -0.47272       | 3.28E-05 | 0.005189 | Down       | latent transforming growth factor beta binding protein 2 |
| ILMN_1672503 | DPYSL2 | -0.47143       | 5.37E-05 | 0.002879 | Down       | dihydroxymethylase like 2                         |
| ILMN_2223941 | FBLN5  | -0.47095       | 1.94E-06 | 0.002072 | Down       | fibulin 5                                         |
| ILMN_1688480 | CCND1  | -0.46977       | 0.000483 | 0.017744 | Down       | fascin actin-bundling protein 1                   |
| ILMN_1808114 | LYVE1  | -0.46936       | 0.003925 | 0.049436 | Down       | lymphatic vessel endothelial hyaluronan receptor 1 |
| ILMN_2087692 | CYBRD1 | -0.46894       | 2.69E-05 | 0.004861 | Down       | cytochrome b reductase 1                          |
| ILMN_1808707 | FSCN1  | -0.46767       | 3.69E-05 | 0.005267 | Down       | fascin actin-bundling protein 1                   |
| ILMN_1660808 | WPDC1  | -0.46665       | 0.000163 | 0.010418 | Down       | WAP four-disulfide core domain 1                  |
| ILMN_2337655 | WARS1  | -0.4653        | 4.87E-05 | 0.005873 | Down       | tryptophanyl-tRNA synthetase 1                    |
| ILMN_1795166 | PTH1R  | -0.47706       | 1.22E-05 | 0.003404 | Down       | parathyroid hormone 1 receptor                    |
| ILMN_2057479 | EGFRL6 | -0.44039       | 0.002923 | 0.042546 | Down       | EGF like domain multiple 6                        |
| Gene ID    | Description                  | Pearson Correlation | p-value | Fold Change | Status   |
|------------|------------------------------|---------------------|---------|-------------|----------|
| ILMN_1784863 | CD36                         | -0.43914            | 0.001443 | 0.029457    | -3.27014 | Down     |
| ILMN_1789492 | ZDHHC8                       | -0.43853            | 1.97E-05 | 0.004301    | -4.4659  | Down     |
| ILMN_1790689 | CRISPLD2                     | -0.43782            | 0.00578  | 0.018974    | -3.54695 | Down     |
| ILMN_1795442 | LAMA4                        | -0.43711            | 0.00763  | -4.08249    | Down     |
| ILMN_1702501 | RPS6KA2                      | -0.43678            | 2.81E-06 | 0.002369    | -4.94542 | Down     |
| ILMN_1671016 | GJA4                         | -0.43464            | 0.000331 | 0.014708    | -3.70883 | Down     |
| ILMN_1695442 | LAMA4                        | -0.43355            | 0.000768 | 0.021647    | -3.46258 | Down     |
| ILMN_1676449 | SLIT2                        | -0.43033            | 0.009961 | 0.024096    | -3.9507  | Down     |
| ILMN_1715999 | CAVIN2                       | -0.41726            | 1.48E-06 | 0.001955    | -5.1066  | Down     |
| ILMN_1709486 | SRPX                         | -0.4129             | 0.002926 | 0.045246    | -3.08744 | Down     |
| ILMN_1675936 | HIGD1B                       | -0.41058            | 0.000123 | 0.025959    | -3.66386 | Down     |
| ILMN_1800697 | LDR2                         | -0.41769            | 0.000812 | 0.022284    | -3.44608 | Down     |
| ILMN_1689595 | SORL            | -0.41276            | 1.8E-06  | 0.001955    | -5.09704 | Down     |
| ILMN_1681679 | TSPO                         | -0.40818            | 0.000143 | 0.009968    | -3.9429  | Down     |
| ILMN_1727532 | OLFML3                       | -0.40554            | 1.42E-06 | 0.001955    | -5.1066  | Down     |
| ILMN_1722532 | CMTM3                        | -0.40145            | 3.33E-05 | 0.005189    | -4.31961 | Down     |
| ILMN_1683535 | FARP1                        | -0.40137            | 3.99E-06 | 0.002688    | -4.86121 | Down     |
| ILMN_1756573 | NDUF4A4L2                    | -0.40777            | 0.00111  | 0.008868    | -4.013   | Down     |
| ILMN_2368735 | IGFBP3                       | -0.40708            | 0.001143 | 0.026058    | -3.34212 | Down     |

**Down** indicates a decrease in expression.
| Gene ID   | Symbol | log2FoldChange | Adj. P-value | Benjamini-Hochberg FDR | Expression | Description |
|-----------|--------|----------------|--------------|-------------------------|------------|-------------|
| ILMN_2038775 | TUBB2A | -0.40565       | 0.001946    | 0.03431                 | Down       | tubulin beta 2A class IIa |
| ILMN_1812031 | PALM   | -0.4051       | 1.37E-05    | 0.003478                | Down       | paralemmin   |
| ILMN_1709307 | GPSM1  | -0.4053       | 3.66E-05    | 0.005267                | Down       | G protein signaling modulator 1 |
| ILMN_3246214 | B4GAT1 | -0.40496      | 5.01058     | -5.4081                | Down       | beta-1,4-glucuronyltransferase 1 |
| ILMN_1802411 | ITGA1  | -0.4038       | 3.16E-05    | 0.005189                | Down       | integrin subunit alpha 1 |
| ILMN_1714861 | CD68   | -0.40235      | 0.001299    | 0.037871                | Down       | CD68 molecule pleckstrin homology like domain family B member 1 |
| ILMN_1666819 | PHLD1B | -0.40156      | 5.39E-06    | 0.005073                | Down       | carbohydrate sulfotransferase 3 |
| ILMN_1802968 | SOX18  | -0.40033      | 0.000526    | 0.018141                | Down       | SRY-box transcription factor 18 |
| ILMN_2173611 | MT1E   | -0.39986      | 0.000353    | 0.015039                | Down       | metallothionein 1E |
| ILMN_1668283 | HYAL2  | -0.39864      | 0.000846    | 0.019821                | Down       | hyaluridase 2 |
| ILMN_1757440 | DIPK1B | -0.39796      | 0.00033     | 0.014704                | Down       | divergent protein kinase domain 1B |
| ILMN_1773059 | ADGRA2 | -0.39739      | 0.000911    | 0.023503                | Down       | adhesion G protein-coupled receptor A2 |
| ILMN_1795429 | VCL    | -0.39693      | 0.000348    | 0.014991                | Down       | vinculin |
| ILMN_1789733 | CLIP3  | -0.39665      | 1.53E-05    | 0.00373                 | Down       | CAP-Gly domain containing linker protein 3 |
| ILMN_1675062 | MYL9   | -0.39519      | 0.001559    | 0.030619                | Down       | myosin light chain 9 |
| ILMN_1711566 | TIMP1  | -0.39465      | 0.001568    | 0.030761                | Down       | TIMP metalloepitidase inhibitor 1 |
| ILMN_1682781 | TEAD2  | -0.39462      | 2.27E-05    | 0.004675                | Down       | TEA domain transcription factor 2 |
| ILMN_1806733 | COL18A1| -0.39225      | 0.000595    | 0.019227                | Down       | collagen type XVIII alpha 1 chain |
| ILMN_1760901 | PRCP   | -0.39168      | 0.000281    | 0.013751                | Down       | prolylcarboxypeptidase |
| ILMN_1691376 | JAG1   | -0.39137      | 0.000108    | 0.008727                | Down       | jagged canonical Notch ligand 1 |
| ILMN_1808238 | RBMPS2 | -0.39047      | 2.27E-05    | 0.004675                | Down       | RNA binding protein, mRNA processing factor 2 |
| ILMN_1684391 | PLOD1  | -0.38987      | 5.67E-06    | 0.002906                | Down       | procollagen-lysine,2-oxoglutarate 5-dioxygenase 1 |
| ILMN_1755657 | RASIP1 | -0.38985      | 0.00111     | 0.025736                | Down       | Ras interacting protein 1 |
| ILMN_1754795 | FAT1   | -0.38928      | 0.000803    | 0.02216                 | Down       | FAT atypical cadherin 1 atypical chemokine receptor 1 (Duffy blood group) |
| ILMN_1723884 | ACKR1  | -0.38904      | 0.000258    | 0.013173                | Down       | NCK associated protein 5 like |
| ILMN_1763640 | NCKAP5L| -0.38828      | 4.47E-05    | 0.005755                | Down       | NCK associated protein 5 like |
| ILMN_2066151 | TEK    | -0.38809      | 0.001131    | 0.025976                | Down       | TEK receptor tyrosine kinase |
| ILMN_1730995 | AFAP1L2| -0.38806      | 6.29E-05    | 0.006657                | Down       | actin filament associated protein 1 like 2 |
| ILMN_1676846 | ABCE1  | -0.38772      | 0.002141    | 0.035854                | Down       | ATP binding cassette subfamily E member 1 |
| ILMN_2306540 | PDE9A  | -0.38716      | 0.000255    | 0.013135                | Down       | phosphodiesterase 9A |
| ILMN_1756920 | ADAM15 | -0.38698      | 2.31E-05    | 0.004723                | Down       | ADAM metalloepitidase domain 15 |
| ILMN_1667460 | SULF1  | -0.38575      | 0.000356    | 0.015084                | Down       | sulfatase 2 |
| ILMN_1778881 | EBF1   | -0.38542      | 0.000387    | 0.015721                | Down       | EBF transcription factor 1 |
| ILMN_1810852 | LAMC1  | -0.38297      | 0.000107    | 0.006889                | Down       | laminin subunit gamma 1 |
| ILMN_1723123 | FGFR3  | -0.38138      | 0.000151    | 0.010247                | Down       | fibroblast growth factor receptor 3 |
| ILMN_1741632 | RAB3L1 | -0.3811       | 1.3E-05     | 0.003464                | Down       | RAB3A interacting protein like 1 |
| ILMN_2230025 | PDLIM3 | -0.381       | 0.000642    | 0.019792                | Down       | PDLIM domain 3 |
| ILMN_1772612 | ANGPTL2| -0.37902      | 2.69E-05    | 0.004861                | Down       | angiopoietin like 2 |
| Accessory ID     | Gene Symbol | Expression Value | Log Fold Change | Genes and Functions |
|------------------|-------------|------------------|----------------|-------------------|
| ILMN_1810844     | RARRES2     | -0.37881         | -3.42025       | Down retinoic acid receptor responder 2 |
| ILMN_1738816     | FOXO1       | -0.37837         | -3.57509       | Down forkhead box O1 |
| ILMN_1689953     | CD8I        | -0.37702         | -5.58795       | Down CD81 molecule |
| ILMN_1651950     | TPST1       | -0.37597         | -4.30272       | Down tyrosylprotein sulfotransferase 1 |
| ILMN_1692731     | TTYH3       | -0.37535         | -4.32847       | Down tweety family member 3 |
| ILMN_1658835     | CAV2        | -0.37448         | -3.39392       | Down caveolin 2 |
| ILMN_1680453     | ITM2C       | -0.37416         | -3.54215       | Down integral membrane protein 2C |
| ILMN_1702835     | SH3BGR1     | -0.37249         | -3.69952       | Down SH3 domain binding glutamate rich protein like |
| ILMN_1732923     | SIPA1L2     | -0.37207         | -3.46637       | Down signal induced proliferation associated 1 like 2 |
| ILMN_1797009     | F3          | -0.37136         | -3.71818       | Down coxigulation factor III, tissue factor phosphatidylinositol glycan anchor biosynthesis clat U |
| ILMN_1738263     | PIGU        | -0.37121         | -3.86457       | Down phosphatidylinositol glycan anchor biosynthesis class U |
| ILMN_1739946     | VKORC1      | -0.36840         | -3.95412       | Down vitamin K epoxide reductase complex subunit 1 |
| ILMN_1803312     | DMT1        | -0.36765         | -4.44661       | Down DIMT1 rRNAmethyltransferase and ribosome maturation factor |
| ILMN_2089752     | ALKAL2      | -0.36753         | -3.95119       | Down ALK and LTK ligand 2 |
| ILMN_1729563     | UGDH        | -0.36578         | -3.1755        | Down UDP-glucose 6-dehydrogenase |
| ILMN_1695290     | FERMT2      | -0.36562         | -4.68113       | Down fermitin family member 2 |
| ILMN_1748473     | GIMAP4      | -0.3634          | -3.88275       | Down GTPase, IMAP family member 4 |
| ILMN_3242038     | GPX8        | -0.36483         | -3.73508       | Down glutathione peroxidase 8 (putative) |
| ILMN_1781256     | LEFTY2      | -0.36409         | -3.2258        | Down left-right determination factor 2 |
| ILMN_1718607     | TSPAN4      | -0.36243         | -3.98826       | Down tetraspanin 4 |
| ILMN_1653028     | COL4A1      | -0.36243         | -3.78705       | Down collagen type IV alpha 1 chain |
| ILMN_1806403     | RASL12      | -0.3617          | -3.87729       | Down RAS like family 12 |
| ILMN_1770338     | TM4SF1      | -0.36154         | -3.16202       | Down transmembrane 4 L six family member 1 |
| ILMN_1757552     | CAVIN1      | -0.36036         | -4.47961       | Down caveolae associated protein 1 |
| ILMN_2148944     | ADCY4       | -0.36032         | -3.16139       | Down adenylatecyclase 4 |
| ILMN_2346997     | RAB23       | -0.36006         | -4.241          | Down RAB23, member RAS oncogene family |
| ILMN_1803429     | CD44        | -0.35802         | -3.268          | Down CD44 molecule (Indian blood group) |
| ILMN_1757845     | SPIRE2      | -0.35788         | -3.9577        | Down spire type actin nucleation factor 1 |
| ILMN_2063168     | MALL        | -0.35738         | -3.69453       | Down mal, T cell differentiation protein like |
| ILMN_1794942     | HOXC6       | -0.35691         | -4.45271       | Down homeobox C6 |
| ILMN_2089073     | ATP9A       | -0.35669         | -3.71549       | Down ATPase phospholipid transporting 9A (putative) |
| ILMN_1676897     | HSPA12B     | -0.35655         | -3.31351       | Down heat shock protein family A (Hsp70) member 12B |
| ILMN_1720158     | ETS2        | -0.35607         | -4.47844       | Down ETS proto-oncogene 2, transcription factor |
| ILMN_1767448     | LHFP6       | -0.35579         | -3.44843       | Down LHFP6 tetraspan subfamily member 6 |
| ILMN_338560      | IF27L2      | -0.35573         | -4.38599       | Down interferon alpha inducible protein 27 like 2 |
| ILMN_1784871     | FASN        | -0.35492         | -5.14833       | Down fatty acid synthase |
| ILMN_1680874     | TUBB2B      | -0.35438         | -4.42951       | Down tubulin beta 2B class Iib |
| ILMN_2081682     | SMAP2       | -0.35276         | -4.16954       | Down small ArfGAP2 |
| ILMN_1774982     | CDC42EP5    | -0.35271         | -4.24433       | Down CDC42 effector protein 5 |
| ILMN_1788019     | LAMA2       | -0.35245         | -3.0638        | Down laminin subunit alpha 2 |
| ILMN_1783276     | NEXN        | -0.35153         | -3.88438       | Down nixin F-actin binding protein |
| ILMN_1676088     | MSRB3       | -0.35012         | -3.68065       | Down methionine sulfoxidereductase B3 |

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| Gene      | FC     | P-value  | Log2 Fold Change | Description                                                                 |
|-----------|--------|----------|------------------|-----------------------------------------------------------------------------|
| RNASE1    | -0.34959 | 0.003183 | 0.044326        | Down ribonuclease A family member 1, pancreatic                              |
| PHGDH     | -0.34957 | 0.007633 | -3.08329        | Down phosphoglycerate dehydrogenase ADAM metallopeptidase with thrombospondin type 1 motif 9 |
| ADAMTS9   | -0.34922 | 0.026853 | -3.32252        | Down discoidin domain receptor tyrosine kinase 2 transforming growth factor beta 1 induced transcript 1 |
| LRP3      | -0.3484  | 0.001775 | -5.19866        | Down LDL receptor related protein 3                                          |
| DDR2      | -0.34789 | 0.008756 | -4.019          | Down ADAM metallopeptidase with thrombospondin type 1 motif 9               |
| TGFBI1    | -0.34786 | 0.012343 | -3.18789        | Down ADAM metallopeptidase with thrombospondin type 1 motif 9               |
| POTEF     | -0.34742 | 0.018229 | -3.57218        | Down POTE ankyrin domain family member F                                     |
| AGRN      | -0.34641 | 0.022991 | -3.45127        | Down agrin                                                                  |
| PIEZO1    | -0.3461  | 0.00798  | -3.45127        | Down piezo type mechanosensitive ion channel component 1                    |
| LFNG      | -0.34636 | 0.006073 | -4.21211        | Down LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase           |
| CRYZ      | -0.3461  | 0.018298 | -3.56835        | Down crystallin zeta                                                         |
| LYPD6     | -0.34584 | 0.00347  | -3.33892        | Down C-C motif chemokine ligand 13                                          |
| POTEF     | -0.34528 | 0.045851 | -2.99986        | Down dickkopf WNT signaling pathway inhibitor 3                             |
| FZD4      | -0.34522 | 0.016957 | -3.62449        | Down frizzled class receptor 4                                               |
| PFKFB3    | -0.34512 | 0.018294 | -3.56884        | Down 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3                  |
| ZNF358    | -0.34471 | 0.002517 | -4.9227         | Down zinc finger protein 35B                                                 |
| NFIB      | -0.34285 | 0.031722 | -3.23532        | Down nuclear factor 1 B                                                     |
| ANTXR2    | -0.3415  | 0.006347 | -4.19218        | Down ANTXR cell adhesion molecule 2                                          |
| TME35B    | -0.33999 | 0.007511 | -4.09378        | Down transmembrane protein 35B                                               |
| EXTL3     | -0.33995 | 0.03162  | -3.22796        | Down exostosin like glycosyltransferase 3                                   |
| SLC16A10  | -0.33976 | 0.043262 | -3.04796        | Down solute carrier family 16 member 10                                    |
| MMP23B    | -0.33959 | 0.020805 | -3.48474        | Down matrix metallopeptidase 23B                                            |
| PRRX1     | -0.33948 | 0.010103 | -3.93722        | Down paired related homeobox 1                                              |
| ZMAT3     | -0.33777 | 0.001926 | -5.14964        | Down zinc finger matrin-type 3                                               |
| CAMK2N1   | -0.33759 | 0.025566 | -3.35581        | Down calcium/calmodulin dependent protein kinase II inhibitor 1             |
| EFEMP1    | -0.33701 | 0.043103 | -3.03665        | Down EGF containing fibulin extracellular matrix protein 1                  |
| SLC2A10   | -0.33689 | 0.02466  | -3.37924        | Down solute carrier family 2 member 10                                      |
| ARHGEF6   | -0.33673 | 0.034749 | -3.16805        | Down Rac/Cdc42 guanine nucleotide exchange factor 6                         |
| TME153B   | -0.3363 | 0.008273 | -4.04548        | Down transmembrane protein 256                                              |
| CMTM7     | -0.33562 | 0.006927 | -4.14452        | Down CKLF like MARVEL transmembrane domain containing 7                     |
| TFNRSF14  | -0.33559 | 0.013333 | -3.77075        | Down TNF receptor superfamily member 14                                     |
| GFOD1     | -0.33518 | 0.019425 | -3.52642        | Down glucose-fructose oxidoreductase domain containing 1                    |
| DLL1      | -0.3346 | 0.010936 | -3.88539        | Down delta like canonical Notch ligand 1                                    |
| LYL1      | -0.3343 | 0.017744 | -3.59922        | Down LYL1 basic helix-loop-helix family member                               |
| SEMA3A    | -0.33427 | 0.017744 | -3.59859        | Down semaphorin 3A                                                          |
| INKA2     | -0.33389 | 0.00295  | -4.71805        | Down inka box actin regulator 2                                              |
| SPTAN1    | -0.33345 | 0.007229 | -4.11685        | Down spectrin alpha, non-erythrocytic 1                                     |
| MRPL34    | -0.33294 | 0.030319 | -3.25087        | Down mitochondrial ribosomal protein L3                                     |
| FCGRT     | -0.33153 | 0.028444 | -3.29084        | Down Fc fragment of IgG receptor and transporter                             |
| SMAD3     | -0.33045 | 0.006811 | -4.15297        | Down SMAD family member 3                                                   |
| Gene ID       | Gene Name      | log2 fc | p-value | FDR       | E-value | log2 Fold Change | Function                                                                 |
|--------------|----------------|---------|---------|-----------|---------|-----------------|--------------------------------------------------------------------------|
| ILMN_205953  | PPM1F          | -0.3304 | 0.001065| 0.02524   | -3.36391| Down            | protein phosphatase, Mg2+/Mn2+ dependent 1F                             |
| ILMN_1790953 | TBCB           | -0.3301 | 0.004673| 0.044269  | -4.43726| Down            | tubulin folding cofactor B                                             |
| ILMN_1764788 | TNFRSF1B       | -0.32976| 0.001169| 0.044269  | -4.36391| Down            | TNF receptor superfamily member 1B                                    |
| ILMN_1754660 | ZCCHC24        | -0.32898| 0.000101| 0.038837  | -4.03815| Down            | zinc finger CCHC-type containing 24                                    |
| ILMN_2252309 | DP7            | -0.32892| 0.001126| 0.025921  | -3.34674| Down            | dipeptidyl peptidease 7                                                |
| ILMN_1674160 | BIN1           | -0.32855| 0.002014| 0.012004  | -3.83144| Down            | bridging integrator 1                                                   |
| ILMN_1675656 | PPP1BP2        | -0.32771| 0.00043 | 0.016889  | -3.63326| Down            | PPIA binding protein 2                                                  |
| ILMN_1728512 | YWHAH          | -0.32748| 6.04E-05| 0.006541  | -4.17595| Down            | tyrosine 3-monooxygenase/tryptophan 5-monoxygenase activation protein eta |
| ILMN_1789171 | EEF2K          | -0.32709| 1.05E-05| 0.03154   | -4.62387| Down            | eukaryotic elongation factor 2 kinase                                   |
| ILMN_1680973 | FOXF1          | -0.3269 | 0.000214| 0.012004  | -3.83144| Down            | forkhead box F1                                                        |
| ILMN_1769520 | UBE2L6         | -0.32541| 0.001765| 0.032784  | -3.20703| Down            | ubiquitin conjugating enzyme E2 L6                                     |
| ILMN_1770290 | CNN2           | -0.3232 | 0.000584| 0.01904   | -3.54398| Down            | smoothelin                                                              |
| ILMN_2064725 | METTL7B        | -0.32189| 0.000739| 0.021238  | -3.4793 | Down            | methyltransferase-like 7                                               |
| ILMN_1685540 | SHROOM3        | -0.32144| 9.41E-05| 0.000852  | -4.5735 | Down            | shroom family member 3                                                 |
| ILMN_1839019 | LPP            | -0.32071| 0.002215| 0.036485  | -3.13485| Down            | caldesmon 1                                                            |
| ILMN_1779735 | LAMTOR4        | -0.32003| 0.001384| 0.028811  | -3.28515| Down            | LN domain containing preferred translocation partner in lipoma          |
| ILMN_2316838 | GPBAR1         | -0.31949| 0.000134| 0.007956  | -3.69066| Down            | G protein-coupled bile acid receptor 1                                 |
| ILMN_1810559 | RHOQ           | -0.31922| 9.79E-05| 0.008252  | -4.04665| Down            | ras homolog family member Q                                            |
| ILMN_1804498 | BRAT1          | -0.31861| 0.000157| 0.010362  | -3.91859| Down            | BRCA1 associated ATM activator 1                                       |
| ILMN_1778444 | FKBP5          | -0.31765| 0.000284| 0.045007  | -3.00692| Down            | FKBP prolyl isomerase 5                                                |
| ILMN_1704154 | TNFRSF19       | -0.31706| 0.000322| 0.014545  | -3.71667| Down            | TNF receptor superfamily member 19                                     |
| ILMN_2104141 | FGDS           | -0.31637| 0.000237| 0.012746  | -3.80302| Down            | FYVE, RhoGEF and PH domain containing 5                                |
| ILMN_2149226 | CAV1           | -0.31687| 0.002907| 0.042449  | -3.04697| Down            | caveolin 1                                                              |
| ILMN_1654398 | RGL1           | -0.31678| 0.000409| 0.016197  | -3.64795| Down            | ral guanine nucleotide dissociation stimulator like 1                  |
| ILMN_3307982 | PARVA          | -0.31677| 1.15E-05| 0.003353  | -4.60138| Down            | parvin alpha                                                            |
| ILMN_3241262 | PABPC4L        | -0.3167 | 0.001528| 0.030233  | -3.2524 | Down            | poly(A) binding protein cytoplasmic 4 like                             |
| ILMN_1730229 | CGNL1          | -0.31553| 0.000937| 0.02378   | -3.40267| Down            | cingulin like 1                                                         |
| ILMN_1779071 | FEZI           | -0.31546| 3.78E-05| 0.005357  | -4.29902| Down            | fasciculation and elongation protein zeta 1                             |
| ILMN_1775330 | CCDC9B         | -0.31511| 8.78E-05| 0.007748  | -4.07615| Down            | coiled-coil domain containing 9B                                      |
| Gene ID       | Gene Symbol | Log2 Fold Change | P-Value  | Adjusted P-Value | Downstream | Function                                           |
|--------------|-------------|------------------|----------|------------------|------------|----------------------------------------------------|
| ILMN_1701204 | VEGFC       | -0.31459         | 0.000186 | 0.011194         | Down       | vascular endothelial growth factor C               |
| ILMN_1777881 | TSPAN17     | -0.31456         | 4.57E-05 | 0.005773         | Down       | tetraspanin 1                                    |
| ILMN_1677200 | CYFIP2      | -0.31396         | 0.0005   | 0.017901         | Down       | cytoplasmic FMR1 interacting protein 2            |
| ILMN_2056032 | CD99        | -0.3134          | 0.001609 | 0.013215         | Down       | CD99 molecule (Xg blood group)                    |
| ILMN_1752591 | LEPROT1     | -0.3128          | 0.001734 | 0.033282         | Down       | leptin receptor overlapping transcript like 1     |
| ILMN_1757338 | PLSRC4      | -0.31123         | 0.000327 | 0.014624         | Down       | phospholipid scramblase 4                        |
| ILMN_3245564 | ARHGAP44    | -0.3111          | 4.92E-05 | 0.005917         | Down       | Rho GTPase activating protein 44                   |
| ILMN_1699980 | TSPAN18     | -0.31001         | 0.000286 | 0.013944         | Down       | tetraspanin 18                                   |
| ILMN_3232894 | CNRIP1      | -0.30921         | 0.00187  | 0.033574         | Down       | cannabinoid receptor interacting protein 1        |
| ILMN_1771800 | PRKCA       | -0.30913         | 3.17E-05 | 0.005189         | Down       | protein kinase C alpha                            |
| ILMN_2397954 | PPP1R3C     | -0.30647         | 0.001626 | 0.031392         | Down       | protein phosphatase 1 regulatory subunit 3C        |
| ILMN_3236344 | BMS1P4      | -0.3057          | 0.000323 | 0.014545         | Down       | phosphatidylinositol-4-phosphate 5-kinase type 1 gamma |
| ILMN_1658847 | GFRA2       | -0.30559         | 0.000112 | 0.008882         | Down       | collagen type VIII alpha 2 chain                  |
| ILMN_1780057 | RENBP       | -0.3052          | 0.000155 | 0.010361         | Down       | renin binding protein                             |
| ILMN_1658847 | NARP        | -0.30411         | 0.000766 | 0.021608         | Down       | NOTCH regulated ankyrin repeat protein            |
| ILMN_1718303 | NECTIN2     | -0.30407         | 0.000344 | 0.014909         | Down       | nectin cell adhesion molecule 2                   |
| ILMN_1764410 | GUCD1       | -0.30401         | 0.001226 | 0.026935         | Down       | guanylylcyclase domain containing 1               |
| ILMN_1691717 | RHBDF2      | -0.30355         | 0.000467 | 0.017456         | Down       | rhomboid 5 homolog 2                             |
| ILMN_1766675 | CDH6        | -0.30348         | 5.65E-05 | 0.006347         | Down       | cadherin 6                                        |
| ILMN_1752046 | SHB3        | -0.30284         | 0.003129 | 0.044068         | Down       | SH2B adaptor protein 3                            |
| ILMN_1656300 | GFRA2       | -0.30283         | 0.000222 | 0.012233         | Down       | GDNF family receptor alpha 2                      |
| ILMN_2148459 | B2M         | -0.30266         | 0.003487 | 0.046567         | Down       | beta-2-microglobulin                             |
| ILMN_1795639 | MGMT        | -0.30229         | 0.000215 | 0.012004         | Down       | O-6-methylguanine-DNA methyltransferase           |
| ILMN_1687335 | FLNA        | -0.30213         | 0.00045  | 0.017125         | Down       | filamin A                                         |
| ILMN_2049536 | TRPV2       | -0.30191         | 5E-05    | 0.005957         | Down       | transient receptor potential cation channel subfamily V member 2 |
| ILMN_1668721 | CCND3       | -0.30153         | 0.003431 | 0.046061         | Down       | cyclin D3                                        |
| ILMN_1801226 | DOCK6       | -0.30138         | 0.000109 | 0.008759         | Down       | dedicator of cytokinesis 6                        |
| ILMN_3238196 | CYTH4       | -0.30118         | 0.001775 | 0.0328           | Down       | cytohesin 4                                       |
| ILMN_1760667 | POLR3G1L    | -0.30114         | 0.000115 | 0.009           | Down       | RNA polymerase III subunit G like                 |
| ILMN_2367707 | PKN1        | -0.30078         | 1.76E-05 | 0.004057         | Down       | protein kinase N1                                 |
| ILMN_1756539 | SCRN1       | -0.30064         | 2.03E-05 | 0.004408         | Down       | secrin 1                                          |
| ILMN_1746704 | TRIM8       | -0.30043         | 1.71E-06 | 0.001955         | Down       | tripartite motif containing 8                     |
| ILMN_1727043 | COLGALT1    | -0.30041         | 1.61E-06 | 0.001955         | Down       | collagen beta(1-O)galactosyltransferase 1         |
| ILMN_1789639 | FMOD        | -0.29998         | 0.000703 | 0.020621         | Down       | fibromodulin                                      |
| Gene ID   | Gene Name | Fold Change | p-value | q-value | -log10(p-value) |
|----------|-----------|-------------|---------|---------|-----------------|
| ILMN_1759513 | RND3     | -0.2987     | 0.00056 | 0.018724 | -3.5563         |
| ILMN_2339294 | LILRB5   | -0.29854    | 0.000286 | 0.013933 | -3.75099        |
| ILMN_2205896 | MEIS3P1  | -0.29849    | 0.005215 | 0.018724 | -3.51774        |
| ILMN_1677404 | RAP2A    | -0.29848    | 0.000259 | 0.013173 | -3.77819        |
| ILMN_1853824 | MGAT3    | -0.29749    | 0.00891  | 0.023034 | -3.4178         |
| ILMN_1712480 | AXIN2    | -0.29689    | 0.001111 | 0.008868 | -4.01392        |
| ILMN_1776157 | NPC2     | -0.29721    | 0.001023 | 0.007368 | -3.70339        |
| ILMN_2381697 | P4HA2    | -0.29305    | 0.00173  | 0.008253 | -3.89106        |
| ILMN_1803348 | EPHB1    | -0.29305    | 0.00173  | 0.008253 | -3.89106        |
| ILMN_1769118 | SHMT2    | -0.29282    | 0.00024  | 0.012746 | -3.79968        |
| ILMN_1770824 | ARHGAP4  | -0.29218    | 0.000231 | 0.01255  | -3.81002        |
| ILMN_1713732 | ABL1     | -0.29499    | 1.21E-05 | 0.003404 | -4.58941        |
| ILMN_1687440 | HIPK2    | -0.2942     | 0.001881 | 0.037334 | -3.1869         |
| ILMN_1694539 | MAP3K6   | -0.29418    | 7.48E-05 | 0.007229 | -4.11899        |
| ILMN_1801348 | EBP4     | -0.29305    | 0.00173  | 0.008253 | -3.89106        |
| ILMN_1779464 | PARP4    | -0.29295    | 4.71E-05 | 0.005816 | -4.24138        |
| ILMN_1671404 | SVIL     | -0.29228    | 0.00024  | 0.012746 | -3.79968        |
| ILMN_1769118 | SEPTIN9  | -0.29218    | 0.000231 | 0.01255  | -3.81002        |
| ILMN_2082585 | SNAI2    | -0.29197    | 2.58E-06 | 0.002346 | -4.96523        |
| ILMN_1785424 | ABLM1    | -0.29182    | 0.002923 | 0.042546 | -3.04516        |
| ILMN_2082585 | SNAI2    | -0.29137    | 0.009937 | 0.02378  | -3.40282        |
| ILMN_1809850 | RCN3     | -0.2896     | 0.001133 | 0.009736 | -3.96254        |
| ILMN_3246065 | CCDC151  | -0.28935    | 0.00122  | 0.009241 | -3.98798        |
| ILMN_1745806 | PEMT     | -0.28934    | 0.00161  | 0.010372 | -3.91073        |
| ILMN_1791226 | NXXN     | -0.28912    | 6.77E-05 | 0.006914 | -4.14567        |
| ILMN_1758315 | SLC9A9   | -0.28902    | 0.000259 | 0.013173 | -3.77817        |
| ILMN_1661194 | CLDN14   | -0.28826    | 0.00626  | 0.017456 | -3.61005        |
| ILMN_3225591 | RPL14    | -0.28806    | 0.000665 | 0.020117 | -3.50459        |
| ILMN_2237212 | MYO10    | -0.28774    | 0.001061 | 0.02524  | -3.36484        |
| ILMN_1913060 | CMKL1    | -0.28763    | 0.00032  | 0.014545 | -3.71847        |
| ILMN_1789502 | GPC4     | -0.28702    | 0.001807 | 0.033091 | -3.19966        |
| ILMN_2047599 | TMEM50B  | -0.28576    | 0.001003 | 0.024564 | -3.38214        |
| ILMN_1719543 | MAF      | -0.28566    | 0.000438 | 0.016832 | -3.62816        |
| ILMN_17148625 | TCEAL4   | -0.2856    | 0.000494 | 0.01788  | -3.59303        |
| ILMN_1670134 | FADS1    | -0.28515    | 0.00296  | 0.01409  | -3.74097        |
| ILMN_1660871 | NEK6     | -0.28507    | 0.00893  | 0.023304 | -3.41739        |
| ILMN_1674385 | YWHAQ    | -0.28455    | 2.86E-05 | 0.004971 | -4.37044        |
| GO ID   | CATEGORY | GO Name             | P Value calc1 | FDR B&H | FDR B&Y | Bonferroni Gene Count | Gene                                                                 |
|---------|----------|---------------------|---------------|---------|---------|-----------------------|----------------------------------------------------------------------|
| GO:0000003 | BP       | reproduction        | 1.54E-05      | 1.92E-02 | 1.75E-01 | 7.69E-02              | CEBPB, GRHL2, ACSL4, S100A11, KMT2C, UBE2A, TESK2, AGFG1, AHR, HEI1, MAFF, HSD11B2, PAQR7, RHOBTB3, NECTIN3, CRH, SLC4A2, STS, CSNK2A2, SLC2A5, GABRB1, PLAC1, SPICE2, PSN1, NHE4, THDC1, SEPTIN6, SPIN1, STRA6, MBD2, DDR1, TBX3, CAST, CGB7, TEAD3, LHB, GMCL1, OVG1P1, TL1A1, EGFR, INS1, LNP, TL3, TMF1, PLEKHA1 |
| GO:0000057 | BP       | macromolecular catabolic | 5.89E-04      | 1.28E-01 | 1.00E+00 | 1.00E+00              | CARHS2P1, RPS13, WA1, UBE2A, UBE2D3, C, UBE2A, UBE2D3, C |
process

GO:0042175 CC nuclear outer membrane-endoplasmic reticulum membrane network 1.06E-03 1.69E-01 1.00E+00 6.75E-01 38 SPTLC3, CDS1, BET1, ACSL4, SPCS1, PIGH, EVA1A, CLN3, HSD3B1, ULK1, HSD11B2, FKBP2, AMFR, FOLR1, SPTLC1, RABGAP1, T5, NSG1, GDF15, GPAA1, CYP19A1, STX5, BCA29, NUP153, TOR1AIP2, CAMK2G, NCNT, BAP1, TMED4, STT3B, RASGRP1, MFSD2A, SPPL2A, EGFR, LPCAT3, FURIN, TLR3, APAF1, TMF1

GO:0005794 CC Golgi apparatus 1.36E-02 3.09E-01 1.00E+00 1.00E+00 46 SGSM1, CNST, BET1, SPG21, ST3GAL6, CLN3, AMFR, ANK3, GDF15, YIPF4, RHOB, ST3GAL4, RA, BARGAP1, STS, NCAN, NSG1, PDE4DIP, RAB11FIP5, FHC1, TBC1D23, STX11, CSGALN, ACT1, ECE2, USP33, AGER2, ATP6V0C, ING2, STK26, C1GALT1, C4G3, BMP1, STX5, AP1G2, TAF7, GOLGA4, YIPF6, NUCB2, TMED4, LHB, RASGRP1, EGFR, FURIN, TLR3, TMF1, EFL1, APAF1, TMF1

GO:0042802 MF identical protein binding 4.89E-03 2.96E-01 1.00E+00 1.00E+00 59 CEBPB, IER5, TWIST1, S100A1, S100P, H2B, H2BC6, H2BC4, TLE5, CLK3, AHR, UCK2, TRPV6, HES1, HOOK2, ULK1, HSPB1, CAP2, HSP90AA1, AMFR, GDF15, ANXA4, SRR, C, LDN7, NECTIN3, CGG, BP1, TBK1, GRAMD2, B, ATF3, RIPOR2, STK26, NAB2, DAPK1, IBM1, JUP, DHPS, SMG9, KNYU, HSP8, NUP153, YIPF6, CAMK2G, D, YRK1A, GRB7, RDX, UBA3, TDG, CLDN8, TFRC, GMCL1, RASGR1, SPPL2A, EGFR, CBX5, ENTPD1, TLR3, PAK1, PAK2, SPATA13
| GO:0008772 | MF | molecular function regulator | 1.03E-02 | 2.96E-01 | 1.00E+00 | 1.00E+00 | 55 | SGSM1, NET1, PDPK1, DENND2D, SERPIN1, AGFG1, TNFAIP8, HSPB1, RASAL2, HSP90, AA1, DNAJB1, FNTA, GDF15, ANXA4, CRH, AZIN1, RAB3GAP1, CSH2, PPP4R2, ATP1B3, DEPDC1B, RIPOR2, INHA, MYO9A, INSLA, G2H2, BMP1, PTNP3, CG1, SEMA3B, RGL2, T0R1AIP2, RGDPS8, PPP1R14C, TFFP2, FBRS, C, AST, CGB7, COX17, PP1R14B, ITIH5, HBB, RASGRP1, EEF1B2, GR, TPL1, FAM13A, EGFRI, INS6, TIMP2, FURIN, TL3R3, PAK2, MARK2, ENSA, SPATA13 |
| --- | --- | --- | --- | --- | --- | --- | --- |

**Down regulated genes**

| GO:0007155 | BP | cell adhesion | 4.46E-28 | 8.58E-25 | 7.92E-24 | 2.57E-24 | 104 | CLDN14, ABL1, ENPP2, VSIG4, EMILIN2, LA, MC3, PGM5, NRARP, F, ZD4, SLIT2, MFAP4, M, FGE8, FAT1, FBLN2, MYL9, CD99, SPON1, J, AG1, GPC4, ANTXR1, SRP5, VCAM1, VCL, F, OXF1, COL1A1, MMP2, VEGFC, COL3A1, C, OL5A1, COL6A1, COL6A2, FLNA, COL6A3, COL8A2, FBLN5, VTN, VWF, COL16A1, ABI3, BP, PODXL, FOLR2, E, GF6L, CYFIP2, LIMS2, PDPR, RND3, JGBF1, P, CC2L2, IGBPBP7, PEZ1, PPM1F, VCAN, PARV, A, SNAI2, AOC3, PRK, CA, CCN2, EGFLAM, E, PDR1, FYN, NEXN, M, YADM, MYO10, AXL, ADAM15, PIEZO1, TNFRSF14, GAS6, ITGA1, TNFRSF21, LYVE1, P, TPRD, ADAMTS9, AC, KR3, WNT3A, NECTT1, N2, FERMT2, RARA, S, H2B3, DDR2, LAMA2, LAMA4, LAMB2, LA, MC1, CAV1, TEK, DLL1, P, PIP5K1C, LGALS1, T, GF1B11, TGFBI, LVAV, CR2, COL18A1, THY1, FAM107A, CD36, LPP, CD44, CD81, CLDN5, C, DH6, CDH11, SMAD3, B, HPA3 |

| GO:0051674 | BP | localization of cell | 2.02E-23 | 1.67E-20 | 1.54E-19 | 1.17E-19 | 111 | ABL1, ABR, MAP1B, A, PCDD1, PDGFRB, ENP, P2, MATN2, ACTA2, C, YGB, TMIGD3, SOX18, LAMC3, F3, ADCY3, S, EMA3A, SLIT2, FAT1, MGAT3, EFEMP1, C, D99, JAG1, AGTR1, GPC4, C, CCL13, CMKLR1, C |
| GO:0099080  | CC  | supramolecular complex | 3.08E-13 | 1.81E-11 | 1.24E-10 | 1.63E-10 | 77 |
|-------------|-----|------------------------|----------|----------|----------|----------|----|
| GO:0030054  | CC  | cell junction           | 3.95E-13 | 2.09E-11 | 1.43E-10 | 2.09E-10 | 71 |
| GO:0005102 | MF | signaling receptor binding | 6.59E-08 | 6.11E-06 | 4.59E-05 | 6.72E-05 | 75 |
|-----------|----|-----------------------------|----------|----------|----------|----------|----|
| PRKCA, EGFLAM, FS CN1, NEXN, RAB23, M YADM, LYPD6, ADA M15, SPTAN1, B2M, C CND1, AIF1, ITGA1, RASIP1, GJA4, PDLIM 3, SYT11, ARHGEF44, SVIL, NECTIN2, YWH AQ, FERM2, GPER1, SYNM, DDR2, LASP1, CAV1, CAV2, TEK, DL1, PIP5K1C, TGFBI11, HAVCR2, OXTR, THY1, FAM107A, FARP1, LPP, CD44, TSPAN4, C D81, CLDN5, CGNL1, ARHGEF2, AGRN, CDH6, CAVH11 |
| CMTM3, ABL1, CRLF1, PDGFRB, ETS2, SE MA3A, SLIT2, MFGF8, EEFMP1, JAG1, AGT R1, CCL13, LTBP4, VCA M1, VEGFC, COL3A 1, COL5A1, FLNA, FBL N5, VTN, VWF, COL16 A1, CNRIP1, CXCL14, ALK1, WYHAIHE, GFL6, PDPN, IGFBP2, I GFBP4, SLIT3, NCOA1, PRKCA, PKN1, CCN2, FYN, DKK3, HYAL2, N ES, ADAM15, B2M, G AS6, ITGA1, STAT3, S TCI, PXDN, PTPRD, W NT3A, PLSCR4, RARA , RARRES2, SH2B3, SH2D3C, LAMA2, LAMA4, LAMB2, CAV1, CAV2, DLL1, TGFBI11, TGFB3, LEFTY2, TGFBI1, RSP03, ANGPTL2, THY1, TIMP1, CD36, CD4, TSPAN4, PALM, SPRED1, CD81, CMTM7, SMD3 |
| GO:0098772 | MF | molecular function regulator | 2.41E-05 | 1.12E-03 | 8.38E-03 | 2.46E-02 | 69 |
| PRKCA, EGFLAM, FS CN1, NEXN, RAB23, M YADM, LYPD6, ADA M15, SPTAN1, B2M, C CND1, AIF1, ITGA1, RASIP1, GJA4, PDLIM 3, SYT11, ARHGEF44, SVIL, NECTIN2, YWH AQ, FERM2, GPER1, SYNM, DDR2, LASP1, CAV1, CAV2, TEK, DL1, PIP5K1C, TGFBI11, HAVCR2, OXTR, THY1, FAM107A, FARP1, LPP, CD44, TSPAN4, C D81, CLDN5, CGNL1, ARHGEF2, AGRN, CDH6, CAVH11 |
| CMTM3, ABL1, CRLF1, PDGFRB, ETS2, SE MA3A, SLIT2, MFGF8, EEFMP1, JAG1, AGT R1, CCL13, LTBP4, VCA M1, VEGFC, COL3A 1, COL5A1, FLNA, FBL N5, VTN, VWF, COL16 A1, CNRIP1, CXCL14, ALK1, WYHAIHE, GFL6, PDPN, IGFBP2, I GFBP4, SLIT3, NCOA1, PRKCA, PKN1, CCN2, FYN, DKK3, HYAL2, N ES, ADAM15, B2M, G AS6, ITGA1, STAT3, S TCI, PXDN, PTPRD, W NT3A, PLSCR4, RARA , RARRES2, SH2B3, SH2D3C, LAMA2, LAMA4, LAMB2, CAV1, CAV2, DLL1, TGFBI11, TGFB3, LEFTY2, TGFBI1, RSP03, ANGPTL2, THY1, TIMP1, CD36, CD4, TSPAN4, PALM, SPRED1, CD81, CMTM7, SMD3 |
### Table 4: The enriched pathway terms of the up and down regulated differentially expressed genes

| Pathway ID | Pathway Name                                                                 | P-value | FDR B&H | FDR B&Y | Bonferroni | Gene Count | Gene                                                                 |
|------------|-------------------------------------------------------------------------------|---------|---------|---------|------------|------------|----------------------------------------------------------------------|
| 1269373    | Cell surface interactions at the vascular wall                                | 2.86E-05| 4.73E-03| 3.47E-02| 2.46E-02   | 13         | PSG8,SLC3A2,ATP1B,3,PSG1,PSG2,PSG3,P,SG4,PSG5,PSG6,PSG7,PSG9,PSG11,GRB7 |
| 1269734    | Epigenetic regulation of gene expression                                      | 8.47E-04| 2.18E-02| 1.60E-01| 7.28E-01   | 11         | H2AC6,H2BC8,H2BC6,H2BC4,H2BC21,H4C8,H2BC21,MBD2,TAF1B,TDG,H2BC3   |
| 1270001    | Metabolism of lipids and lipoproteins                                         | 1.33E-03| 2.87E-02| 2.10E-01| 1.00E-00   | 33         | OLAH,SPTLC3,CDS1,ACADVL,ACOXL3A,CSL4,AHR,PIP5K1B,HSD3B1,TNFAIP8,HS |
| 1268701    | Post-translational protein modification                                       | 3.57E-03| 6.02E-02| 4.41E-01| 1.00E+00   | 38         | BET1,WAC,H2AC6,H2BC8,UBE2A,H2BC6,H2BC4,UBE2D3,H2B21,ST3GAL6,PIGH,   |
| 1268677    | Metabolism of proteins                                                        | 1.06E-02| 1.30E-01| 9.49E-01| 1.00E+00   | 52         | ACADVL,ACOXL3A,CSL4,AHR,PIP5K1B,HSD3B1,TNFAIP8,HS                   |
| 1270302    | Development                                                                   | 1.79E-02| 1.92E-01| 1.00E+00| 1.00E+00   | 36         | CEBPB,RPS6KA5,FCTR1,PSMA3,PSMC4,C1GALT1,COG3,H2AW,STX5,DHPS,NUP1    |
| Down regulated genes | | | | | |
|---------------------|-------|----------|----------|-------|
| **1270244** Extracellular matrix organization | 1.93E-23 | 1.40E-20 | 1.00E-19 | 1.40E-20 |
| **1270303** Axon guidance | 3.15E-05 | 1.35E-03 | 9.67E-03 | 2.29E-02 |
| **1269478** Signaling by PDGF | 2.76E-04 | 7.15E-03 | 5.13E-02 | 2.00E-01 |
| **1269340** Hemostasis | 1.83E-03 | 3.51E-02 | 2.51E-01 | 1.00E+00 |
| **1270302** Developmental Biology | 6.14E-03 | 8.76E-02 | 6.28E-01 | 1.00E+00 |
### Table 5 Topology table for up and down regulated genes.

| Regulation | Node       | Degree | Betweenness | Stress     | Closeness |
|------------|------------|--------|-------------|------------|-----------|
| Up         | HSP90AA1   | 655    | 0.22721     | 81351654   | 0.412863  |
| Up         | EGFR       | 324    | 0.081831    | 21358048   | 0.396882  |
| Up         | RPS13      | 176    | 0.040553    | 21024400   | 0.322742  |
| Up         | RBX1       | 132    | 0.02978     | 9542636    | 0.3408    |
| Up         | PAK1       | 115    | 0.016755    | 4561194    | 0.37158   |
| Up         | CSNK2A2    | 112    | 0.026157    | 6172590    | 0.354758  |
| Up         | PAK2       | 107    | 0.012051    | 4334042    | 0.349858  |
| Up         | DDB1       | 105    | 0.029417    | 6420978    | 0.340602  |
| Up         | PSMC4      | 101    | 0.019368    | 3810802    | 0.348739  |
| Up         | DVL3       | 99     | 0.017256    | 5360158    | 0.344762  |
| Up         | UBE2D3     | 96     | 0.018158    | 6872298    | 0.333975  |
| Up         | SMARCB1    | 90     | 0.021042    | 7085456    | 0.33215   |
| Up         | STAT5B     | 89     | 0.005633    | 1782886    | 0.349937  |
| Up         | STX5       | 86     | 0.021729    | 5783250    | 0.327692  |
| Up         | UBE2A      | 86     | 0.01665     | 6800442    | 0.330652  |
| Up         | NUP153     | 81     | 0.019493    | 3839268    | 0.33388   |
| Up         | JUP        | 79     | 0.012614    | 3875882    | 0.320148  |
| Up         | PSMA3      | 78     | 0.009276    | 2735940    | 0.330535  |
| Up         | SH3KBP1    | 76     | 0.011315    | 2648130    | 0.345321  |
| Up         | HSPB1      | 69     | 0.012593    | 3676246    | 0.34167   |
| Up         | BET1       | 67     | 0.013941    | 4543480    | 0.325711  |
| Up         | AMFR       | 66     | 0.018899    | 2411936    | 0.345907  |
| Up         | RRAS2      | 64     | 0.00438     | 2169028    | 0.301914  |
| Up         | MARK2      | 63     | 0.012107    | 3287224    | 0.338315  |
| Up         | CBX5       | 62     | 0.015481    | 3171408    | 0.327807  |
| Up         | CEBPB      | 62     | 0.007601    | 2245984    | 0.350172  |
| Up         | PDPK1      | 62     | 0.00919     | 1612918    | 0.342169  |
| Up         | HNRNPH1    | 59     | 0.013608    | 2423406    | 0.335625  |
| Up         | DNAJB1     | 58     | 0.00611     | 1362926    | 0.344205  |
| Up         | ATF3       | 57     | 0.005226    | 1555506    | 0.352755  |
| Up         | SPATA13    | 56     | 0.00717     | 2217896    | 0.295759  |
| Up         | FURIN      | 55     | 0.017306    | 2333572    | 0.332317  |
| Up         | RHOBTB1    | 54     | 0.005265    | 891404     | 0.309798  |
| Up         | SNAP23     | 52     | 0.010301    | 2133980    | 0.326551  |
| Up   | Gene       | TSS  | Log2FC | FDR  | Z.score | p.value | Enrichment | LogFC  | p.value | NetPath          |
|------|------------|------|--------|------|---------|---------|------------|--------|---------|------------------|
| Up   | STXI1      | 49   | 0.006356 | 0.276999 |
| Up   | TBK1       | 48   | 0.00946 | 0.346521 |
| Up   | RAB25      | 48   | 0.00796 | 0.282579 |
| Up   | ING2       | 42   | 0.006848 | 0.325236 |
| Up   | ULK1       | 42   | 0.007643 | 0.274292 |
| Up   | UCHL3      | 42   | 0.007629 | 0.325779 |
| Up   | PEN2       | 41   | 0.004889 | 0.329235 |
| Up   | CAP2       | 40   | 0.002011 | 0.288156 |
| Up   | UBA3       | 40   | 0.005749 | 0.326187 |
| Up   | DYRK1A     | 40   | 0.004394 | 0.309634 |
| Up   | RBM22      | 39   | 0.01146 | 0.322616 |
| Up   | TKX        | 38   | 0.001513 | 0.28752 |
| Up   | TAF7       | 38   | 0.010147 | 0.324044 |
| Up   | CAMK2G     | 38   | 0.007152 | 0.341969 |
| Up   | ATF4       | 37   | 0.006742 | 0.328036 |
| Up   | TLR3       | 36   | 0.004686 | 0.305217 |
| Up   | MYO9A      | 36   | 8.05E-04 | 0.28752 |
| Up   | BABAM1     | 36   | 0.008431 | 0.324044 |
| Up   | STK26      | 36   | 0.008804 | 0.323842 |
| Up   | ACTR3C     | 35   | 0.002617 | 0.282732 |
| Up   | CREB5      | 35   | 0.001154 | 0.298035 |
| Up   | NET1       | 33   | 0.003076 | 0.327189 |
| Up   | EEF1B2     | 32   | 0.00465 | 0.32501 |
| Up   | AHR        | 32   | 0.003156 | 0.347858 |
| Up   | PIP5K1B    | 31   | 0.00183 | 0.326391 |
| Up   | CLN3       | 31   | 0.007159 | 0.323485 |
| Up   | HES1       | 30   | 0.0035 | 0.300115 |
| Up   | RBPP6      | 29   | 0.008094 | 0.324089 |
| Up   | AP1G2      | 29   | 0.008892 | 0.321377 |
| Up   | RDX        | 29   | 0.003378 | 0.325146 |
| Up   | RGPDS1     | 28   | 0.002967 | 0.322995 |
| Up   | HSD3B1     | 28   | 0.009418 | 0.320497 |
| Up   | COG3       | 27   | 0.00261 | 0.24988 |
| Up   | ATP6V0C     | 27   | 0.008472 | 0.320959 |
| Up   | TFRC       | 27   | 0.004398 | 0.329004 |
| Up   | TIAL1      | 27   | 0.005954 | 0.324858 |
| Up   | DCP2       | 27   | 0.007451 | 0.243872 |
| Up   | CAPZA1     | 26   | 0.00269 | 0.325191 |
| Up   | FKBP2      | 25   | 0.03414 | 0.282255 |
| Up   | TWIST1     | 24   | 0.001372 | 0.298643 |
| Up   | TIMP2      | 24   | 0.001662 | 0.250924 |
| Up   | SPTLC1     | 24   | 0.008272 | 0.320827 |
| Up   | DAPK1      | 24   | 0.003354 | 0.3437 |
| Up   | STT3B       | 23   | 0.005888 | 0.320805 |
| Up   | RBMS1      | 23   | 0.005223 | 0.322772 |
| Up   | ANK3       | 21   | 0.004965 | 0.321819 |
| Up   | TGD        | 21   | 0.00124 | 0.326346 |
| Up   | CHMP5      | 20   | 0.00503 | 0.320915 |
| Up   | MB2D2      | 20   | 0.003168 | 0.265195 |
| Up   | TRIM25     | 20   | 0.002013 | 0.326073 |
| Up   | TEAD3      | 20   | 0.001225 | 0.323954 |
| Up   | SLCA32     | 20   | 0.005187 | 0.323435 |
| Up   | BMP1       | 19   | 0.00311 | 0.290095 |
| Up   | RHOBTB3    | 19   | 0.002152 | 0.322439 |
| Up   | CHD2       | 19   | 0.00121 | 0.256894 |
| Up   | RYBP       | 19   | 0.002415 | 0.322572 |
| Up   | GLRX       | 18   | 0.00459 | 0.320959 |
| Up   | KMT2C       | 18   | 0.003676 | 0.285019 |
| Up   | YTHDC1     | 18   | 0.003349 | 0.33407 |
| Up   | GRIK7       | 18   | 5.17E-04 | 0.294598 |
| Up   | JWSI       | 17   | 0.004258 | 0.236798 |
| Up   | TRAF3IP2    | 17   | 0.001901 | 0.324246 |
| Up   | CSF3R       | 17   | 0.001832 | 0.329027 |
| Up   | AFF1       | 17   | 0.003482 | 0.247805 |
| Up   | INO80C      | 17   | 0.003498 | 0.321245 |
| Up   | CASP4      | 17   | 0.002253 | 0.263822 |
| Up   | YIPF6       | 17   | 0.003441 | 0.320827 |
| Up   | PCDG1      | 16   | 0.003259 | 0.253558 |
| Up   | CXCRC2      | 16   | 0.003899 | 0.33452 |
| Up   | ELF3       | 16   | 6.72E-04 | 0.203260 |
| Gene Symbol | Fold Change | p-value | Log2FoldChange | Adjusted p-value |
|-------------|-------------|---------|----------------|-----------------|
| USP33       | 16          | 0.002932| 430028         | 0.322927        |
| AGFG1       | 15          | 0.003227| 435804         | 0.321443        |
| LNPEP       | 14          | 7.10E-04| 211470         | 0.322483        |
| RORA        | 14          | 0.001493| 299584         | 0.282187        |
| LARP1B      | 14          | 0.004683| 546700         | 0.321708        |
| ACSL4       | 14          | 0.005208| 423594         | 0.320388        |
| ESRRG       | 14          | 0.001317| 573474         | 0.244687        |
| MXD1        | 13          | 6.21E-04| 548286         | 0.273427        |
| GET4        | 13          | 0.001988| 297146         | 0.321113        |
| NFE2        | 13          | 0.001758| 361494         | 0.277475        |
| SCNN1B      | 13          | 0.001794| 293352         | 0.321863        |
| TBX3        | 11          | 0.00107 | 660104         | 0.254826        |
| RORA        | 14          | 0.001493| 299584         | 0.282187        |
| LARP1B      | 14          | 0.004683| 546700         | 0.321708        |
| ACSL4       | 14          | 0.005208| 423594         | 0.320388        |
| ESRRG       | 14          | 0.001317| 573474         | 0.244687        |
| MXD1        | 13          | 6.21E-04| 548286         | 0.273427        |
| GET4        | 13          | 0.001988| 297146         | 0.321113        |
| NFE2        | 13          | 0.001758| 361494         | 0.277475        |
| SCNN1B      | 13          | 0.001794| 293352         | 0.321863        |
| TBX3        | 11          | 0.00107 | 660104         | 0.254826        |
| RORA        | 14          | 0.001493| 299584         | 0.282187        |
| LARP1B      | 14          | 0.004683| 546700         | 0.321708        |
| ACSL4       | 14          | 0.005208| 423594         | 0.320388        |
| ESRRG       | 14          | 0.001317| 573474         | 0.244687        |
| MXD1        | 13          | 6.21E-04| 548286         | 0.273427        |
| GET4        | 13          | 0.001988| 297146         | 0.321113        |
| NFE2        | 13          | 0.001758| 361494         | 0.277475        |
| SCNN1B      | 13          | 0.001794| 293352         | 0.321863        |
| TBX3        | 11          | 0.00107 | 660104         | 0.254826        |
| RORA        | 14          | 0.001493| 299584         | 0.282187        |
| LARP1B      | 14          | 0.004683| 546700         | 0.321708        |
| ACSL4       | 14          | 0.005208| 423594         | 0.320388        |
| ESRRG       | 14          | 0.001317| 573474         | 0.244687        |
| MXD1        | 13          | 6.21E-04| 548286         | 0.273427        |
| GET4        | 13          | 0.001988| 297146         | 0.321113        |
| NFE2        | 13          | 0.001758| 361494         | 0.277475        |
| SCNN1B      | 13          | 0.001794| 293352         | 0.321863        |
| TBX3        | 11          | 0.00107 | 660104         | 0.254826        |
| RORA        | 14          | 0.001493| 299584         | 0.282187        |
| LARP1B      | 14          | 0.004683| 546700         | 0.321708        |
| ACSL4       | 14          | 0.005208| 423594         | 0.320388        |
| ESRRG       | 14          | 0.001317| 573474         | 0.244687        |
| MXD1        | 13          | 6.21E-04| 548286         | 0.273427        |
| GET4        | 13          | 0.001988| 297146         | 0.321113        |
| NFE2        | 13          | 0.001758| 361494         | 0.277475        |
| SCNN1B      | 13          | 0.001794| 293352         | 0.321863        |
| TBX3        | 11          | 0.00107 | 660104         | 0.254826        |
| RORA        | 14          | 0.001493| 299584         | 0.282187        |
| LARP1B      | 14          | 0.004683| 546700         | 0.321708        |
| ACSL4       | 14          | 0.005208| 423594         | 0.320388        |
| ESRRG       | 14          | 0.001317| 573474         | 0.244687        |
| MXD1        | 13          | 6.21E-04| 548286         | 0.273427        |
| GET4        | 13          | 0.001988| 297146         | 0.321113        |
| Gene   | Down | DE   | FDR   | p-value | p-adjusted | Fold Change | q-value | 
|--------|------|------|-------|---------|------------|-------------|--------|
| MYL9   | 60   | 0.008098 | 2479906 | 0.335361 |
| DMT1   | 58   | 0.008481 | 2242228 | 0.32726  |
| TCY1   | 54   | 0.009445 | 2760706 | 0.330279 |
| MRPL34 | 52   | 0.006656 | 17810170| 0.236106 |
| CCND3  | 51   | 0.003239 | 1930616 | 0.32283  |
| TCF4   | 54   | 0.008618 | 1694556 | 0.33133  |
| DIMT1  | 58   | 0.008481 | 2242228 | 0.32726  |
| MRPL34 | 52   | 0.006656 | 17810170| 0.236106 |
| CCND3  | 51   | 0.003239 | 1930616 | 0.32283  |
| TCF4   | 54   | 0.008618 | 1694556 | 0.33133  |
| Down | miRNA | Hub Genes | Degree | MIcroRNA | Regulation | Hub Genes | Degree | TF |
|------|-------|-----------|--------|----------|------------|-----------|--------|----|
| NDN  | 15    | 0.003831  | 473694 | 0.322239 |            |           |        |    |
| ADAM15 | 15    | 0.001982  | 294010 | 0.331283 |            |           |        |    |
| ARHGEF2 | 15    | 9.41E-04  | 262476 | 0.330396 |            |           |        |    |
| PMT  | 14    | 0.005116  | 629532 | 0.29664  |            |           |        |    |
| VWF  | 14    | 0.001828  | 345586 | 0.275097 |            |           |        |    |
| OXTR | 14    | 0.001359  | 122180 | 0.23325  |            |           |        |    |
| FRYL | 14    | 0.001994  | 332012 | 0.321598 |            |           |        |    |
| ARHGEF6 | 13    | 0.001032  | 179796 | 0.326573 |            |           |        |    |
| TSC2D3 | 13    | 1.34E-04  | 119696 | 0.32391  |            |           |        |    |
| IMPDH1 | 13    | 0.002712  | 390200 | 0.321554 |            |           |        |    |
| NME4 | 12    | 0.003215  | 901430 | 0.301583 |            |           |        |    |
| EHD2 | 12    | 0.003128  | 309602 | 0.320717 |            |           |        |    |
| RGL1 | 12    | 5.53E-04  | 670384 | 0.247308 |            |           |        |    |
| COL18A1 | 12    | 0.001098  | 309928 | 0.266008 |            |           |        |    |
| ADGRA2 | 12    | 8.13E-04  | 196338 | 0.301583 |            |           |        |    |
| FMOD | 11    | 2.68E-04  | 98450  | 0.300385 |            |           |        |    |
| SLIT3 | 10    | 6.95E-05  | 22762  | 0.24207  |            |           |        |    |
| COL5A1 | 3     | 4.31E-05  | 14682  | 0.244636 |            |           |        |    |
| TGFBI | 3     | 8.62E-06  | 14986  | 0.248607 |            |           |        |    |
| RASIP1 | 2     | 1.64E-06  | 1660   | 0.251732 |            |           |        |    |
| CAS2 | 2     | 0        | 0      | 0.258536 |            |           |        |    |
| PCOLCE | 2     | 3.25E-05  | 6584   | 0.246761 |            |           |        |    |
| COL4A2 | 2     | 0        | 0      | 0.208517 |            |           |        |    |
| SVIL | 2     | 0        | 0      | 0.262801 |            |           |        |    |
| SMTN | 2     | 7.00E-06  | 2536   | 0.261073 |            |           |        |    |
| COL4A5 | 2     | 7.45E-06  | 6672   | 0.244776 |            |           |        |    |
| FSCN1 | 2     | 2.41E-06  | 2090   | 0.268585 |            |           |        |    |
| ADAMTS1 | 2     | 5.19E-05  | 3268   | 0.250857 |            |           |        |    |
| CTSC | 1     | 0        | 0      | 0.244559 |            |           |        |    |
| FEZ1 | 1     | 0        | 0      | 0.21526  |            |           |        |    |
| MALL | 1     | 0        | 0      | 0.269357 |            |           |        |    |
| LYL1 | 1     | 0        | 0      | 0.248489 |            |           |        |    |
| SEMA3A | 1    | 0        | 0      | 0.27858  |            |           |        |    |
| ENPP2 | 1     | 0        | 0      | 0.195022 |            |           |        |    |
| BST2 | 1     | 0        | 0      | 0.24757  |            |           |        |    |
| F3 | 1     | 0        | 0      | 0.236738 |            |           |        |    |
| COL16A1 | 1    | 0        | 0      | 0.204978 |            |           |        |    |
| ANGPTL2 | 1    | 0        | 0      | 0.252724 |            |           |        |    |
| NCA LD | 1     | 0        | 0      | 0.250508 |            |           |        |    |
| RASL12 | 1    | 0        | 0      | 0.228262 |            |           |        |    |
| PPP1R14A | 1    | 0        | 0      | 0.273923 |            |           |        |    |
| FCGR7 | 1     | 0        | 0      | 0.243872 |            |           |        |    |
| CN2 | 1     | 0        | 0      | 0.268139 |            |           |        |    |
| EHBP1 | 1     | 0        | 0      | 0.242848 |            |           |        |    |
| COL3A1 | 1    | 0        | 0      | 0.216264 |            |           |        |    |
| DDIT4 | 1     | 0        | 0      | 0.25408  |            |           |        |    |
| ITM2C | 1     | 0        | 0      | 0.249441 |            |           |        |    |
| GAS6 | 1     | 0        | 0      | 0.257007 |            |           |        |    |
| FERMT2 | 1    | 0        | 0      | 0.252751 |            |           |        |    |
| RAPGEF5 | 1    | 0        | 0      | 0.246424 |            |           |        |    |
| APCDD1 | 1    | 0        | 0      | 0.230588 |            |           |        |    |
| MMP23B | 1    | 0        | 0      | 0.200599 |            |           |        |    |
| PTPRD | 1     | 0        | 0      | 0.274549 |            |           |        |    |
| RSPO3 | 1     | 0        | 0      | 0.249441 |            |           |        |    |
| COL6A1 | 1    | 0        | 0      | 0.243745 |            |           |        |    |
| DDR2 | 1     | 0        | 0      | 0.247805 |            |           |        |    |
| NEK6 | 1     | 0        | 0      | 0.244776 |            |           |        |    |
| COL5A2 | 1    | 0        | 0      | 0.205788 |            |           |        |    |
| TSPAN4 | 1    | 0        | 0      | 0.244559 |            |           |        |    |
| IFITM3 | 1    | 0        | 0      | 0.27858  |            |           |        |    |
| HES4 | 1     | 0        | 0      | 0.261875 |            |           |        |    |
| FAT1 | 1     | 0        | 0      | 0.242521 |            |           |        |    |

**Table 6**: miRNA - hub gene and TF – hub gene interaction
| Sl. No/ Code | EGFR PDB: 4UV7 (Energy) | -C docker Interaction Energy | HSP90AA1 PDB: 5NJX (Energy) | -C docker Interaction Energy | PAK1 PDB: 3Q4Z (Energy) | -C docker Interaction Energy | RBX1 PDB: 3FN1 (Energy) | -C docker Interaction Energy |
|-------------|------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|-----------------------------|---------------------------|-----------------------------|
| AJA         | -56.02                 | -10.57                      | 18.17                       | -77.05                      | 21.66                    | -196.65                     | 13.03                     | 43.86                       | -113.94                    | 5.61                      | 37.90                      |
| ALE         | -22.04                 | -17.45                      | 10.55                       | -16.93                      | 12.00                    | -58.34                      | -2.81                     | 24.49                       | -24.28                     | -9.71                     | 18.84                      |
| ALO         | -6.22                   | -25.19                      | 8.57                        | -2.69                       | 9.65                     | -4.41                       | -19.09                    | 14.60                       | -11.36                     | -18.02                    | 15.96                      |
| ARA         | -50.94                  | -28.62                      | 19.50                       | -57.53                      | 26.43                    | -159.25                     | 8.76                      | 57.02                       | -83.85                     | -16.52                    | 33.54                      |
| ARJ         | -43.98                  | 17.23                       | 28.38                       | -39.56                      | 18.14                    | 25.73                       | -119.99                   | 33.00                       | 43.82                      | -39.87                    | 26.58                      | 31.46                      |
| ARG         | -49.90                  | 20.57                       | 23.74                       | -61.58                      | 22.29                    | 25.37                       | -151.03                   | 40.87                       | 47.08                      | -7.21                     | -116.32                    | 22.65                      |
| ANA         | -65.59                  | -68.87                      | 32.04                       | -89.71                      | 51.76                    | -245.05                     | -79.05                    | 83.86                       | -61.60                     | 21.05                     | 41.01                      |
| ALL         | -118.34                 | -47.02                      | 34.21                       | -168.97                     | 50.42                    | 39.91                       | -139.90                   | 62.54                       | -18.62                     | -15.64                    | 14.90                      |
| CAR         | -86.83                  | 19.53                       | 35.26                       | -45.09                      | 19.64                    | 36.45                       | -131.24                   | 58.34                       | -48.59                     | -55.20                    | 21.22                      |
| CAJ         | -6.67                   | -21.05                      | 9.42                        | -6.26                       | 20.34                    | -9.30                       | -16.06                    | 13.09                       | -47.54                     | 28.64                     | 30.02                      |
| CAP         | -35.79                  | -58.29                      | 19.06                       | -42.81                      | 28.01                    | -172.32                     | -28.95                    | 57.88                       | -6.63                      | -25.87                    | 30.85                      |
| CAV         | -65.69                  | 22.19                       | 25.24                       | -53.63                      | 25.00                    | 27.33                       | -136.49                   | 43.84                       | 47.47                      | -46.65                    | 19.83                      | 28.55                      |
| CHA         | -4.05                   | -30.55                      | 21.32                       | -35.08                      | 30.24                    | 21.35                       | -107.73                   | -7.42                       | 44.11                      | -27.07                    | 13.28                      | 14.79                      |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
| CHL | -14.17 | 8.84 | 17.63 | -49.92 | 15.28 | 24.60 | -81.41 | 27.24 | 34.82 | -80.66 | -26.20 | 43.47 |
| CIN | -50.02 | 12.60 | 14.67 | -27.06 | 11.55 | 13.70 | -92.97 | 18.99 | 21.39 | -29.49 | -17.74 | 24.17 |
| CUR | -61.32 | -38.90 | 27.73 | -64.69 | -22.71 | 40.68 | -276.18 | 16.00 | 87.65 | -61.40 | 18.48 | 32.45 |
| ELL | -40.77 | -22.62 | 18.69 | -34.20 | -24.49 | 16.72 | -137.67 | 1.59 | 41.48 | -73.55 | 20.96 | 35.11 |
| EUG | -71.25 | 14.65 | 28.33 | -71.08 | 13.46 | 27.19 | -149.04 | 30.21 | 46.83 | -40.14 | -27.96 | 25.52 |
| FER | -84.22 | 11.92 | 24.50 | -38.93 | 14.41 | 25.46 | -157.42 | 32.92 | 48.59 | -74.77 | -97.25 | 24.35 |
| GIN | -26.63 | -36.38 | 14.98 | -51.74 | -30.08 | 21.65 | -135.45 | -15.24 | 39.95 | -47.21 | 14.33 | 17.68 |
| GNS | -36.67 | 10.71 | 17.53 | -41.60 | 12.11 | 20.48 | -132.64 | 26.84 | 30.74 | -84.78 | -82.04 | 29.12 |
| GYM | -41.53 | -84.64 | 23.43 | -52.36 | -79.44 | 27.80 | -110.88 | -55.77 | 55.03 | -78.34 | -164.85 | 26.81 |
| GYA | -75.68 | -162.34 | 32.37 | -86.27 | -145.33 | 40.68 | -160.78 | -122.08 | 67.89 | -75.89 | 20.89 | 41.44 |
| GMT | -4.26 | -99.21 | 17.86 | -72.64 | -91.68 | 25.64 | -109.57 | -79.81 | 40.10 | -47.57 | 30.04 | 32.56 |
| HYD | -68.08 | 19.53 | 34.12 | -125.59 | 23.82 | 41.37 | -158.25 | 41.54 | 59.92 | -20.94 | 20.67 | 23.23 |
| INO | -50.91 | 24.87 | 26.12 | -43.89 | 24.42 | 27.14 | -87.39 | 39.52 | 44.59 | -28.20 | 15.41 | 23.15 |
| LEU | -38.73 | 18.54 | 21.60 | -26.25 | 15.39 | 18.10 | -122.22 | 27.38 | 32.75 | -48.37 | 26.66 | 39.62 |
| LEP | -16.17 | 7.13 | 15.51 | -21.35 | 8.09 | 16.21 | -62.06 | 19.28 | 25.76 | -31.27 | 18.48 | 20.64 |
| LIR | -53.70 | 9.95 | 22.56 | -84.07 | 18.36 | 27.30 | -142.76 | 31.85 | 41.89 | -29.11 | -73.02 | 27.80 |
| MAL | -58.66 | 21.70 | 30.45 | -34.92 | 23.71 | 32.09 | -138.59 | 36.48 | 50.57 | -24.50 | -15.13 | 18.76 |
| MHC | -28.62 | 13.37 | 15.74 | -32.04 | 13.89 | 16.17 | -33.87 | 21.61 | 22.73 | -40.19 | -77.90 | 31.36 |
| MYR | -22.60 | -74.73 | 29.54 | -51.69 | -68.66 | 31.40 | -94.78 | -45.63 | 63.61 | -48.31 | 20.69 | 36.63 |
| NIM | -17.29 | -20.00 | 11.23 | -22.94 | -18.68 | 12.75 | -39.38 | -11.59 | 19.23 | -73.77 | 21.14 | 30.96 |
| MPO | -26.31 | -85.18 | 28.60 | -27.95 | -81.28 | 30.13 | -62.20 | -67.23 | 48.83 | -49.69 | -107.43 | 17.79 |
| PHE | -52.17 | 12.68 | 21.80 | -59.98 | 17.35 | 28.95 | -140.57 | 34.70 | 49.40 | -51.52 | -95.45 | 20.50 |
| PUN | -23.27 | -121.88 | 26.67 | -62.56 | 19.02 | 28.47 | -100.15 | 27.33 | 36.00 | -6.35 | 3.83 | 17.39 |
| PUC | -22.94 | -98.54 | 23.93 | -110.98 | -114.66 | 31.90 | -147.91 | -67.17 | 73.20 | -25.35 | -112.29 | 24.27 |
| QUE | -25.04 | -95.41 | 19.39 | -29.38 | -88.29 | 31.16 | -182.08 | -73.82 | 62.28 | -119.62 | 14.22 | 41.65 |
| SHA | -62.78 | 4.01 | 17.60 | -97.71 | -87.07 | 28.88 | -133.51 | -71.22 | 39.42 | -38.98 | 22.34 | 28.18 |
| SYR | -42.02 | -112.72 | 18.53 | -57.33 | 0.94 | 14.08 | -111.64 | 16.61 | 30.08 | -28.67 | 15.86 | 22.42 |
| TER | -48.17 | 3.01 | 26.96 | -45.14 | -109.25 | 24.75 | -88.49 | -99.19 | 31.30 | -55.95 | 20.86 | 33.04 |
| TPN | -48.96 | 17.76 | 22.80 | -58.53 | 5.58 | 30.24 | -151.71 | 24.04 | 55.75 | -38.43 | 15.22 | 28.09 |
| VIC | -49.26 | 11.32 | 17.70 | -60.62 | 17.96 | 23.33 | -150.32 | 32.32 | 43.25 | -15.63 | 21.72 | 55.13 |
| GLY | -49.25 | 15.93 | 28.98 | -46.36 | 9.39 | 14.16 | -83.17 | 23.57 | 29.57 | -25.71 | 18.79 | 28.22 |
Figures

**Volcano plot**

Fig. 1. 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. 2. Heat map of differentially expressed genes. Legend on the top left indicate log fold change of genes. (A1 – A38 = Gestational diabetes mellitus; B1 – B70 = Gestational diabetes mellitus)

Fig. 3. PPI network of DEGs. The PPI network of DEGs was constructed using Cytoscap. Up regulated genes are marked in green; down regulated genes are marked in red.
Fig. 4. Modules of isolated form PPI of DEGs. (A) The most significant module was obtained from PPI network with 16 nodes and 32 edges for up regulated genes (B) The most significant module was obtained from PPI network with 16 nodes and 34 edges for down regulated genes. Up regulated genes are marked in green; down regulated genes are marked in red.

Fig. 5. MiRNA - hub gene regulatory network. The light purple color diamond nodes represent the key miRNAs; up regulated genes are marked in green; down regulated genes are marked in red.
Fig. 6. TF - hub gene regulatory network. The yellow color triangle nodes represent the key TFs; up regulated genes are marked in green; down regulated genes are marked in red.

Fig. 7. ROC curve validated the sensitivity, specificity of hub genes as a predictive biomarker for GDM prognosis.
A) HSP90AA1 B) EGFR C) RPS13 D) RBX1 E) PAK1 F) FYN G) ABL1 H) SMAD3 I) STAT3 J) PRKCA
Fig. 8 Validation of hub genes by RT-PCR. A) HSP90AA1 B) EGFR C) RPS13 D) RBX1 E) PAK1 F) FYN G) ABL1 H) SMAD3 I) STAT3 J) PRKCA
Fig 9. Chemical Structures of Phytoconstituents
**Fig. 10** Structure of ALO

**Fig. 11** Structure of MAL

**Fig. 12** 3D Binding of ALO with 3FN1

**Fig. 13** 3D Binding of MAL with 3Q4Z
**Fig. 14** 2D Binding of ALO with 3FN1

**Fig. 15** 2D Binding of MAL with 3Q4Z