## Original Article Identification of molecular mechanism and key biomarkers in membranous nephropathy by bioinformatics analysis

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Abstract: Objectives: Membranous nephropathy (MN) is an autoimmune nephropathy. The incidence of MN is increasing gradually in recent years. Previous studies focused on antibody production, complement activation and podocyte injury in MN. However, the etiology and underlying mechanism of MN remain to be further studied. Methods: GSE104948 and GSE108109 of glomerular expression profile were downloaded from Gene Expression Omnibus (GEO) database, GSE47184, GSE99325, GSE104954, GSE108112, GSE133288 of renal tubule expression profile, and GSE73953 of peripheral blood mononuclear cells (PBMCs) expression profile. After data integration by Networkanalyst, differentially expressed genes (DEGs) between MN and healthy samples were obtained. DEGs were enriched in gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG), and protein-protein interaction (PPI) networks of these genes were constructed through Metascape, etc. We further understood the function of hub genes through gene set enrichment analysis (GSEA). The diagnostic value of DEGs in MN was evaluated by receiver operating characteristic (ROC) analysis. Results: A total of 3 genes (TP53, HDAC5, and SLC2A3) were screened out. Among them, the up-regulated TP53 expression may be closely related to MN renal pathological changes. However, the expression of MN podocyte target antigen was not significantly different from that of healthy controls. In addition, the changes of Wnt signaling pathway in PBMCs and the effects of SLC2A3 on the differentiation of M2 monocyte need further study. Conclusion: It is difficult to unify a specific mechanism for the changes of glomerulus, renal tubules and PBMCs in MN patients. This may be related to the pathogenesis, pathology and immune characteristics of MN. MN podocyte target antigen may not be the root cause of the disease, but a stage result in the pathogenesis process.

Keywords: Membranous nephropathy, molecular mechanism, integrated bioinformatics, key biomarker

#### Introduction

Membranous nephropathy (MN), an autoimmune disease, is a common pathological type of primary glomerular diseases characterized by diffuse glomerular basement membrane thickening [1]. The main clinical manifestations are nephrotic syndrome with proteinuria, edema and hypoproteinemia [2]. Compared with other common autoimmune nephropathy, such as IgA nephropathy and lupus nephritis, MN is less common in hematuria and almost no gross hematuria [3, 4]. Some MN patients could have spontaneous remission [5, 6]. At the pathological level, local glomerular proliferation and infiltration of circulating immune cells were rare in this disease [1, 2]. At the immunological level, the autoantibodies deposited in the glomeruli were mainly IgG4 [1, 7]. The proportion of regulatory B cells in patients was higher than that in healthy controls [8, 9]. However, IgG4 and regulatory B cells are generally thought to inhibit inflammation and immune responses [8]. All these phenomena indicate that MN is a unique autoimmune disease.

In recent years, studies on the pathogenesis of MN have emerged in an endless stream, but

| Tissue       | Series GEO<br>accession | Series type                   | Number of<br>samples | Group                     | Organism     | Series<br>platform ID |
|--------------|-------------------------|-------------------------------|----------------------|---------------------------|--------------|-----------------------|
| Glomerular   | GSE104948               | Expression profiling by array | 25                   | MN (n = 21)<br>HC (n = 4) | Homo sapiens | GPL24120              |
|              | GSE108109               | Expression profiling by array | 50                   | MN (n = 44)<br>HC (n = 6) | Homo sapiens | GPL19983              |
| Renal tubule | GSE47184                | Expression profiling by array | 22                   | MN (n = 18)<br>HC (n = 4) | Homo sapiens | GPL14663              |
|              | GSE99325                | Expression profiling by array | 22                   | MN (n = 18)<br>HC (n = 4) | Homo sapiens | GPL19184              |
|              | GSE104954               | Expression profiling by array | 21                   | MN (n = 18)<br>HC (n = 3) | Homo sapiens | GPL24120              |
|              | GSE108112               | Expression profiling by array | 48                   | MN (n = 43)<br>HC (n = 5) | Homo sapiens | GPL19983              |
|              | GSE133288               | Expression profiling by array | 53                   | MN (n = 48)<br>HC (n = 5) | Homo sapiens | GPL19983              |
| PBMC         | GSE73953                | Expression profiling by array | 10                   | MN (n = 8)<br>HC (n = 2)  | Homo sapiens | GPL4133               |

HC, Healthy Control.

there are still many unexplained issues. In terms of the discovery of podocyte target antigen, Beck et al. in 2009 detected the presence of M-type phospholipase A2 antibody (PLA2R1) in the serum of patients, but not in the serum of other glomerular diseases and normal persons [7]. Subsequently, a large number of podocyte target antigens, such as THSD7A and NELL1, have been discovered by researchers [10]. But the mechanism of their exposure is not clear. In terms of pathogenic antibodies, immunofluorescence showed that IgG subclasses deposited on capillary walls of MN patients were mainly IgG4, and a small amount of IgG1, IgG2 or IgG3 existed [1]. Normally, IgG4 does not activate complement [11]. However, there is evidence of complement activation in MN patients [12, 13]. Therefore, some scholars believe that in MN patients complement is activated by non-IgG4 antibodies [14]. However, other scholars suggested that although IgG4 could not activate classical pathway, it could activate complement through alternative pathway or mannose-lectin pathway [15, 16]. In terms of the pathogenic factors of MN, although the target antigen was located in podocyte. Liu etc. believed that exposure of MN target antigen was located in the lung based on the correlation between PM2.5 and MN incidence [17]. This hypothesis has not yet been proven, but it is supported by fellow researchers [18, 19].

In recent studies, integrated bioinformatics is becoming more common. The integration of re-

lated bioinformatics studies can screen out differential genes more accurately and facilitate the exploration of potential mechanisms of diseases. When the results of multiple bioinformatics analyses are inconsistent or have no statistical significance, statistical analysis results close to the real situation can be obtained by using integrated bioinformatics analysis [20]. Unfortunately, to date, few bioanalyses have been performed specifically for membranous nephropathy. Therefore, we decided to use this approach to investigate the molecular mechanism of membranous nephropathy based on the genetic data of patients' glomerulus, renal tubules, and peripheral blood mononuclear cells (PBMCs).

#### Method

#### Access to GEO datasets

Gene series were screened by GEO database. Series of membranous nephropathy samples and healthy control samples were searched. Finally, GSE47184, GSE73953, GSE99325, GSE104948, GSE104954, GSE108109, GSE-108112, and GSE133288 were identified. The glomerular series were GSE104948 and GSE-108109. The renal tubules series were GSE-47184, GSE99325, GSE104954, GSE108112 and GSE133288. The PBMCs series is GSE-73953. The basic information for the selected dataset is shown in **Table 1**. The probes were transformed into the homologous gene symbol by means of the platform's annotation information.

# Data integration and differentially expressed genes identified

Since healthy controls are fewer in these genes series, we use Networkanalyst (http:// www.networkanalyst.ca) to integrate glomerular and renal tubular series, and identify differentially expressed genes (DEGs). Through "Multiple Gene Expression Table", the data were integrated and adjusted study batch effect was used to obtain the gene expression data of the combined glomerular and renal tubule samples. The principal component analysis (PCA) plot and density plot were plotted respectively (Supplementary Figure 1) [21]. "Fisher Method" is used to analyze the integrated data to generate a "CombinedTstat" representing difference and a "CombinedPval" representing combined P value. We compared data from MN patients with healthy controls, and perceived "CombinedPval" < 0.05 and a [CombinedTstat] > 50 to be statistically significant for the DEGs. For samples of PBMC series, we used GE-O2R (http://www.ncbi.nlm.nih.gov/geo/geo2r) for screening DEGs. The values for statistical significance were set as adjusted p value < 0.05 and |Fold change| > 2.5.

#### Functional annotation and pathway enrichment analysis

To functionally annotate the DEGs identified above, we annotated and visualized the enriched terms using Metascape (http://metascape.org/gp/index.html#/main/step1). For gene ontology (GO) terms and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis, we also applied web-based gene set analysis toolkit (WebGestalt, http://webgestalt.org/) to process these DEGs.

# Protein-protein interaction (PPI) networks and screening of hub genes

We drew PPI network by Metascape, and screened hub genes based on this. Using Venn diagram (http://bioinformatics.psb.ugent.be/ webtools/Venn/), we screened the common hub genes in glomerulus, renal tubules and PBMCs data sets. Receiver operating characteristic (ROC) analysis

We used SPSS20.0 to draw ROC for the above gene. We set MN as 1. Key biomarkers of MN were identified by observing area under curve (AUC). If AUC > 0.7 or < 0.3, it indicates that the abnormal expression of this gene has a certain suggestive effect on MN. If AUC > 0.9 or < 0.1, it suggests that this gene is a key biomarker of MN [22].

# Enrichment analysis by gene set enrichment analysis (GSEA)

Gene function was analyzed using GSEA 4.1.0 software from MSIGDB database on GSEA website (http://software.broadinstitute.org/gsea/ msigdb). The default weighted enrichment method was used for enrichment analysis. Set 1000 times randomly. GSEA analysis was used to enrich the GO and KEGG pathways with high and low expression of key biomarkers. To avoid false positive results by duplicate or nearly duplicate gene sets, the false discovery rate (FDR) should be less than 0.25. The Nominal (NOM) *p*-value used to evaluate the statistical significance of the genome enrichment score should be less than 0.05. Normalized enrichment score (NES) refers to the enrichment score of the gene set after normalization among the analyzed gene sets. Its absolute value should be greater than 1.

#### Result

#### Bioinformatic analysis of data description

Our flow chart is shown in **Figure 1**. Belonging to glomerular series, 21 MN samples and 3 healthy control samples were selected from GSE104948, and 44 MN samples and 6 healthy control samples were selected from GSE108109. Belonging to renal tubular series, 18 MN samples and 4 healthy control samples were selected from GSE47184, 18 MN samples and 4 healthy control samples from GSE-99325, 18 MN samples and 3 healthy control samples from GSE104954, 43 MN samples and 5 healthy control samples were selected from GSE108112, and 48 MN samples and 5 healthy control samples were selected from GSE133288. 8 MN samples and 2 healthy control samples were selected from GSE73953 belonging to PBMC series. After data integra-



tion and analysis, 94 up-regulated DEGs and 9 down-regulated DEGs were screened out from the glomerulus. We screened 312 up-regulated DEGs and 223 down-regulated DEGs from renal tubules. We screened 4 up-regulated DEGs and 389 down-regulated DEGs from PBMC. Specific DEGs were shown in <u>Supplementary Table 1</u>. Interestingly, podocyte target antigens, such as PLA2R1, THSD7A, NELL1, etc., are not DEGs.

#### Functional enrichment analyses

Based on Metascape functional enrichment analysis, it can be seen that the glomerular functions of MN patients are different from those of healthy controls in wound healing, angiogenesis, mesenchyme development, ameboidal-type cell migration, positive regulation of cell motility, hemostasis, interleukin-4 and interleukin-13 signaling, negative regulation of cell differentiation, response to peptide, lymphocyte activation, etc. (Figure 2A). The renal tubules of MN patients were different from those of healthy controls in terms of monocarboxylic acid metabolic process, small molecule catabolic process, small molecule biosynthetic process, nuclear receptors meta-pathway, response to extracellular stimulus, carbohydrate metabolic process, organic hydroxy compound metabolic process, response to xenobiotic stimulus, response to inorganic substance, response to lipopolysaccharide, etc. (Figure 2B). The PBMCs of MN patients were different from those of healthy controls in terms of signaling by WNT, regulation of kinase activity, RNA splicing, adaptive immune system, autophagy, cellular responses to stress, Inclusion body myositis, negative regulation of phosphorylation, neutrophil degranulation, nucleocytoplasmic transport, etc. (**Figure 2C**). Specific GO terms and KEGG pathway enrichment results were found in <u>Supplementary Table 2</u>. Glomerulus, renal tubules and PBMCs of MN patients were different from that of healthy controls in blood vessel development, coagulation, cellular response to peptide, MAPK signaling pathway, lymphocyte activation, etc.

#### PPI networks and hub gene screening

We screened hub genes through PPI network. In the glomerulus, the 2 clusters in the PPI network diagram contain 15 genes (**Figure 3A**, **3B**). The meanings of HDAC5, TP53, ANXA1, GATA3, RELA, TBXA2R, NOTCH1, GNA11, OGT, NFATC1 and GPR4 were response to peptide, regulation of endothelial cell migration, regulation of cell migration involved in sprouting angiogenesis, etc. The meanings of MYO1C, TMOD1, ARPC1B and ITGA5 were regulation of actin filament polymerization, regulation of actin filament length, etc.

In renal tubules, the 7 clusters in the PPI network diagram contain 111 genes (**Figure 3C**, **3D**). The meanings of HAO2, CAT, EPHX2, CROT, EHHADH, DAO, HMGCL, PIPOX, IDH1 were peroxisomal protein import, peroxisome, etc. The



**Figure 2.** Detailed information related to changes in the biological function of DEGs was provided in the dataset by enrichment analysis. Using Metascape, we performed functional enrichment analysis of glomerulus (A), renal tubules (B) and PBMCs (C).

meanings of a total of 31 genes, including ALDH3A2, MYLIP, NIT2, UBE2L6, CST3, JUN, ABAT, METTL7A, MTNR1A, C3, etc., were regulation of PTEN gene transcription, PTEN regulation, PIP3 activates AKT signaling, etc. The meanings of MYLIP, TRIP10, KDELR1, NECAP2, STX5, DNAJC6, TMED3, LDLR, TFRC, ANK3 and FOLR1 were membrane trafficking, vesicle-mediated transport, COPI-mediated anterograde transport, etc. The meanings of a total of 40 genes, including FOLR1, THBS1, S100A8, IFI35, PCGF2, IARS1, KIF16B, S100A9, SRSF5, ALDH2, FKBP2, etc., were tyrosine metabolism, response to ethanol, protein nitrosylation, etc. The meanings of JUNB, FOS, ETS2, ATF3, CDK4 and FOSB were PID ATF2 pathway, PID AP1 pathway, TGF-beta signaling pathway, etc. The meanings of STARD13, SRSF4, HMGCR, DDX5, NOP2, DUSP1, TNIP2, DUSP6, SLC2A3, WTAP, NUPR1 were regulation of mRNA splicing via spliceosome, negative regulation of phosphorylation, negative regulation of phosphate meta-



**Figure 3.** PPI network diagram of DEGs in glomerular and tubular. Metascape was used to construct the spatial distribution characteristics of the macroscopic PPI network model of glomerular DEGs (A), renal tubule DEGs (C) and PBMCs DEGs (E). The clusters of glomerular DEGs (B), renal tubule DEGs (D) and PBMCs DEGs (F) were selected.

bolic process, etc. The meanings of PDK4, HIBCH, ECI2 and PDK2 were atty acid metabolic process and monocarboxylic acid metabolic process. In PBMCs, the 10 clusters in the PPI network diagram contain 80 genes (Figure 3E, 3F). The meanings of UBE2G1, RNF114, HERC2, UBE-2M, LONRF1, CUL3, TRIP12, ANAPC13, PJA1,



**Figure 4.** Diagnostic properties of genes. We filtered these DEGs using Venn diagrams (A). ROC analysis was performed on the screened genes. The diagnostic performance of these genes in glomerulus (B) and renal tubules (C) was calculated according to the gene expression levels. AUC > 0.7 indicates that the gene is suggestive of MN.

UBE202 and MKRN1 were antigen processing: ubiquitination and proteasome degradation, class I MHC mediated antigen processing and presentation, adaptive immune system, etc. The meanings of EIF2S1, GFPT2, GNB1, DOHH, DNAJA2, DNAJA1, XPOT, GCH1 and DNAJA4 were response to heat, response to temperature stimulus, HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand, etc. The meanings of a total of 16 genes, including CAND1, RNF146, RNF20, HSP-90AA1, BRIX1, SRP68, RPL7, AJUBA, NSUN3, SUPT16H, etc., were ncRNA metabolic process, ncRNA processing, VEGFA-VEGFR2 signaling pathway, etc. The meanings of a total of 18 genes, including PRKAR1A, LAMTOR3, SNAP-23, PRKCB, APC, SPTA1, KRAS, LPCAT1, PPP-2CA, DYNC2LI1, etc., were signaling by WNT, AXIN missense mutants destabilize the destruction complex, signaling by AXIN mutants, etc. The meanings of CLP1, WBP4, HNRNPA1, SYF2, and LARP7 were RNA splicing, mRNA processing, mRNA splicing-major pathway, etc. The meaning of CYB5B, GOLGA5, FA2H, and RAB1A was endomembrane system organization. The meanings of ADORA2A, MTERF3, HNRNPA1L2, HNRNPH3, RCC1L, GPR20, LHB, and NGRN were ADORA2B mediated antiinflammatory cytokines production, G alpha (s) signaling events, leishmania parasite growth and survival, etc. The meanings of ASAH1, ACER1, and PLPP3 were sphingosine metabolic process, sphingoid metabolic process, diol metabolic process, etc. We found that it was difficult to obtain a unified meaning from the clusters of glomerulus, renal tubules and PBMCs. Therefore, we will re-conduct functional analysis on the intersection of these hub genes.

#### Diagnose significance of DEGs

Through the Venn diagram (Figure 4A), we found that the hub genes shared by glomerulus and renal tubules were TP53 and HDAC5. The hub gene shared by PBMCs and renal tubules was SLC2A3. To determine the diagnostic significance of these genes for MN patients, ROC analysis was performed to explore the sensitivity and specificity of these genes for MN diagnosis. Three target antigens, PLA2R1, THSD7A and NELL1, were also included in the analysis. The results showed that TP53 (AUC = 0.776) and HDAC5 (AUC = 0.750) had certain suggestive effects on MN in glomerulus (Figure 4B). However, the expression levels of PLA2R1, THSD7A and NELL1, as podocyte target antigens, showed low accuracy in suggesting MN (0.5 < AUC < 0.7). In renal tubules, TP53 (AUC = 0.734) and SLC2A3 (AUC = 0.293) had certain suggestive effects on MN (Figure 4C). HDAC5 had low accuracy in suggestive effects on MN (AUC = 0.567). Since there were only 2 healthy samples of PBMCs, the results lacked accuracy. In conclusion, the target antigens might not have very good diagnostic significance at the gene expression level. Comparatively, TP53 may have a certain suggestive effect on MN renal pathological changes.

# TP53, HDAC5 or SLC2A3 associated gene set enrichment analysis (GSEA)

Since there were only 2 samples in the HC group of PBMC, we only performed GSEA analysis for the above TP53, HDAC5 or SLC2A3 related functions in the series of glomerulus and renal tubules. In the glomerulus, we found that

the GO terms associated with TP53, negative regulation of macro-autophagy, disordered domain specific binding, and general transcription initiation factor binding were up-regulated (Figure 5A). TP53-related KEGG pathways, including apoptosis, chronic myeloid leukemia, glioma, and pancreatic cancer, were up-regulated (Figure 5B). In the GO terms related to HDAC5, the function of repressing transcription factor binding was up-regulated (Figure 5C). In renal tubules, astrocytoma function was upregulated in the GO terms related to TP53 (Figure 5D). In the GO terms related to SLC2A3, the function of addictive behavior was reduced (Figure 5E). Furthermore, it was interesting to note that glomerular and tubules did not share the same up-regulation function or pathway in the enrichment analysis. In conclusion, the related functions of TP53 are closely related to kidney injury.

#### Discussion

We made three significant observations. First of all, there are certain differences in gene expression in different parts of MN patients, so in the detection of protein expression, the glomerulus and renal tubules should be separated as far as possible, so as not to cause errors in the results. Second, TP53, HDAC5 and SLC2A3 may play a crucial role in the pathogenesis of MN. Third, the exposure of MN autoantigen is not necessarily the cause of the disease, but a staged result in the progression of the disease.

Glomerulus and tubules are difficult to unify the same mechanism because of the different causes of pathological injury. MN is also called membranous glomerulonephritis [1, 23, 24]. The glomerulus of the lesion is diffuse. The basement membrane is thickened because the antigen-antibody complex is mainly deposited on the capillary wall of the glomerular [12, 25]. The glomerular epithelial cells present diffuse fusion of foot processes [26, 27]. The mesangial cells in the glomerulus were only slightly proliferated in the early stage, but the mesangial matrix gradually increased in the later stage, leading to glomerulosclerosis [6, 28]. In the renal tubules, the pathological changes are mostly vacuolar or granular degeneration caused by proteinuria [29-31]. Endoplasmic retic-

ulum dilated, and phagocytic vesicles and lysosomes increased in renal tubular epithelial cells [31, 32]. There were no obvious changes in renal interstitium and arterioles. Thus, the pathological changes of glomerulus and renal tubules in MN are not identical, which makes it difficult to find the similarities between the two in terms of functional enrichment. This also explains why the three core genes we identified are not of great diagnostic value. Of course, our conclusions are not without suggestive implications. At the level of molecular mechanism, VEGF is closely related to kidney injury, and the correlation between MN and VEGF-related pathways has gradually come into view [33-35]. Therefore, attention should be paid to the role of VEGF-related pathways in mN-associated podocytes. In addition, MN podocyte showed upregulation of Wnt signaling pathway, which resulted in a series of aggravation of injury [36], and our results also showed that PBMCs of MN patients had abnormal Wnt signaling pathway. The Wnt pathway itself also has many connections with autoimmunity, and has a regulatory effect on a variety of dendritic cells, B cells, T cells and other immune cells [37-39]. Therefore, whether the control of Wht pathway can play a role in the prevention and treatment of MN is one of the directions of our next stage of research. Of course, the hub genes screened by us also have guiding significance for the pathogenesis and treatment of MN. This is because TP53, HDAC5 and SLC2A3 are all linked tenderly to autoimmune or kidney disease.

TP53, or tumor protein p53, plays an important role in cellular responses to DNA damage and other genomic aberrations. Activation of TP53 leads to cell cycle arrest, DNA repair or apoptosis. The expression level of TP53 will be up-regulated when the cells are exposed to genotoxic stress, hypoxia, carcinogenic stress and oxidative stress [40]. Meanwhile, TP53 can inhibit mTOR to enhance autophagy. TP53 is also associated with aging and cell senescence [41]. And these abnormalities are also present in MN kidney intrinsic cells [18, 27, 31]. In addition, TP53 is associated with the susceptibility to diffuse cutaneous systemic sclerosis, lichen sclerosis, in autoimmune disease [42, 43]. In renal disease, TP53 is also a major mediator of renal tubular cell injury and death [44].



**Figure 5.** Gene set enrichment analysis (GSEA) was used to analyze functional enrichment in MN. In glomerulus, GSEA was used to validate the gene signatures of TP53 in GO term (A) and KEGG pathway (B), and the gene signatures of HDAC5 in GO term (C). In renal tubules, GSEA was used to validate the gene signatures of TP53 in GO term (D), and the gene signatures of SLC2A3 in GO term (E). Normalized enrichment score (NES) indicated the analysis results across gene sets.

HDAC5, also known as histone deacetylase 5, changes the structure of chromosomes and affects the access of transcription factors to DNA by histone deacetylation. In diabetes, HD-AC5 leads to epithelial-mesenchymal transformation in renal tubular epithelial cells [45]. Blocking HDAC5 inhibits the development and progression of renal fibrosis in a mouse model of unilateral ureteral obstruction (UUO) [46]. HDAC5 also plays an important role in polycystic kidney disease [47]. Therefore, HDAC5 is also a key biomarker of renal tubular injury. In addition, on the immune side, the loss of HD-AC5 impedes the differentiation of regulatory T cells (Tregs) [48, 49]. And there is a study that shows that the mRNA expression levels of Foxp3 and TGF-B in the kidneys of MN patients are compared to that of anti-neutrophil cytoplasmic antigen-associated pauci-immune crescentic glomerulonephritis and membranoproliferative glomerulonephritis were up-regulated [50]. Foxp3 and TGF- $\beta$  are the markers that reflect the number and function of Treg [51]. Therefore, the upregulation of HDAC5 may be the key reason that differentiates MN kidney pathology from other autoimmune glomerular diseases.

SLC2A3, solute carrier family 2 member 3, also known as glucose transporter 3 (GLUT3), promotes glucose across mammalian cell membranes. In addition to being expressed in neurons, this protein is also found in sperm, embryos, leukocytes, carcinoma cells and so on [52-55]. In kidney, high glucose induces upregulation of SLC2A3 expression in human glomerular epithelial cells [56]. In immune cells, downregulation of SLC2A3 affects α-granule release and post-activation functions in platelets [57]. At the same time, the down-regulation of this protein may be influenced by hypoxia inducible factor (HIF) [58]. Interestingly, SLC2A3 can induce the kupffer cell, or hepatic macrophage, to secrete cytokines such as IL-10 and TGF-β [59]. The number of M2 monocytes also happened to increase in PBMCs of MN patients [60]. The M2 monocyte is a monocyte that secretes IL-10, and the number of the monocytes is positively correlated with the 24-hour urinary protein of MN and the serum anti-PLA2R1 antibody concentration. This may indicate that SLC2A3 plays an important role in immune abnormalities of MN.

Moreover, the diagnostic value of podocyte target antigen for MN is limited. The mechanism we have discovered may shed light on the underlying causes of antigen exposure. We found that there was no statistically significant difference in the expression levels of these autoantigens in MN patients compared with healthy controls. On the contrary, the above three factors that seem to be unrelated to MN have more significant differences. PLA2R1 is the most common autoantigen in MN patients, with a detection rate of about 70-80% [61]. Although no article has directly proved the relationship between TP53 and MN, activation of p53 pathway can increase PLA2R expression [62]. It has been documented that PLA2R1 inhibits inflammatory response by binding to PLA2 protein, and the increased expression of PLA2R1 is associated with inflammatory stimulation and TP53-related aging pathways [17, 62, 63]. These also prove that MN is more common in the elderly [1]. The incidence of the disease is associated with environmental pollution or the patient's history of pneumonia in adolescence [4, 64]. However, it has been reported that about 7% of patients are positive for anti-PLA2R1 antibodies in serum but negative for PLA2R1 in renal tissue [65]. There are also many cases of MN relapse after transplantation [66]. Cuarental et al. showed increased PLA2R1 expression in renal podocytes by injecting tweaking to 14-week-old C57/BL mice, but proteinuria was not reported in this study [67]. Moreover, PLA2R1 is not a protein specifically expressed in the kidney. In addition to glomerular epithelial cells, PLA2R1 is also expressed in alveolar macrophages, neutrophils, placenta, liver and skeletal muscle [17, 61, 68]. This may indicate that exposure to PLA2R1 as an antigen in kidney is not the root cause of MN morbidity. Antigen exposure is only a consequence of abnormal bodily function in the patient. Even if the autoimmune response is controlled with immunosuppressants, if the cause of antigen exposure is not ameliorated, the disease will still recur when the drug is discontinued [69-71]. In addition, THSD7A was originally described as an endothelial protein expressed in the placental vascular system that promotes endothelial cell migration during angiogenesis [72]. NELL1 is highly expressed in osteoblasts and promotes bone regeneration, as well as facilitating bone formation through the regenerative ability of



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**Figure 6.** Schematic diagram of MN mechanism hypothesis. Environmental factors (toxicity, inflammation, infection, etc.) lead to up-regulation of renal TP53 and down-regulation of SLC2A3 in PBMCs. Changes in the kidney expose podocyte target antigens. Changes in peripheral immune cells allow the persistence of a humoral immune response with IgG4 as the main antibody. Created with BioRender.com. Agreement number: S0245P2AW5.

stem cells [73, 74]. SEMA3B and PCDH7 are newly discovered antigens in recent years, but our understanding of them is not perfect [10]. And, SEMA3B accounts for only 1% of MN patients [75]. Therefore, we do not discuss these two autoantigens here. Meanwhile, this is also the reason why SEMA3B and PCDH7 were not selected for analysis. Taken together, these autoantigens are functionally different. There may be many autoantigens with different functions in the future. So, the exact mechanism of this phenomenon is unclear. Clinically, we did find increased expression of PLA2R and THSD7A on glomerular epithelial cells by immunohistochemical staining. This may indicate that the glomerular epithelial cells of MN patients have insufficient clearance capacity for PLA2R or THSD7A. However, the more different their functions are, the more it indicates that the root cause of MN is not these autoantigens. So, the genes for these podocyte target antigens are not enough by themselves to explain why some people have MN. Perhaps the disease itself is caused by a combination of toxic, inflammatory or infectious factors. In addition, these common podocyte target antigens are not expressed only in the kidney [61], but evidence of extrarenal disease is lacking. This oligo-inflammatory autoimmune glomerular disease may be the result of a combination of factors that lead to podocyte target antigen exposure and immune dysfunction in patients (**Figure 6**).

Of course, there are some limitations to our study. First, the study is analyzed based on GEO database. We can only observe differences in gene expression, which can not accurately reflect changes in protein structure. This makes our conclusions not entirely accurate. Therefore, further basic experiments are needed to confirm our results. Second, we can't categorize the data. The severity of MN affects the gene expression in glomerulus and renal tubules. This is the problem that online database research cannot solve. Third, there was only one series related to PBMCs, and there were only two healthy controls. This results in a lack of accuracy in our analysis of the patient's autoimmune environment. Therefore, PBMC of MN patients will be proactively collected for bioinformatics study.

#### Conclusions

As an autoimmune glomerular disease, the pathogenesis of MN remains to be further studied, especially the cause of antigen exposure, as well as strange pathological and immune characteristics. After completing the bioassay study of patients, we will conduct studies on these core genes to observe their effects on antigen exposure, Treg cells, M2 monocytes, and other immune cells.

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#### Disclosure of conflict of interest

None.

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**Supplementary Figure 1.** PCA plots and density plots. NetworkAnalyst was used to integrate gene expression profiles, and PCA plot (A) and density plot (B) of glomerulus, and PCA plot (C) and density plot (D) of renal tubules were drawn. The farther the distance between points or lines in the graph, the greater the difference between the suggested data.

| -              |  |
|----------------|--|
| Gene           | Gene title   |
| ECM1           | extracellular matrix protein 1   |
| MYOZ2          | myozenin 2   |
| BMP2           | bone morphogenetic protein 2   |
| FSCN1          | fascin actin-bundling protein 1  |
| ZYX            | zyxin  |
| TCIM           | transcriptional and immune response regulator  |
| CCND1          | cyclin D1  |
| ARPC1B         | actin related protein 2/3 complex subunit 1B   |
| IGFBP2         | insulin like growth factor binding protein 2   |
| TMOD1          | tropomodulin 1   |
| RAB31          | RAB31, member RAS oncogene family  |
| LRP10          | LDL receptor related protein 10  |
| ADM            | adrenomedullin   |
| PLD3           | phospholipase D family member 3  |
| WFS1           | wolframin ER transmembrane glycoprotein  |
| ADGRE5         | adhesion G protein-coupled receptor E5   |
| ARHGEF15       | Rho guanine nucleotide exchange factor 15  |
| AXL            | AXL receptor tyrosine kinase   |
| PLEKH01        | pleckstrin homology domain containing 01   |
| KIAA0040       | KIAA0040   |
| DAAM2          | dishevelled associated activator of morphogenesis 2  |
| TBXA2R         | thromboxane A2 receptor  |
| HLX            | H2.0 like homeobox   |
|                | post-glycosylphosphatidylinositol attachment to proteins 6   |
|                | apelin receptor  |
|                | dedicator of cytokinesis 6   |
|                | BMP and activin membrane bound inhibitor   |
|                | myosin IC  |
|                | TNF receptor superfamily member 12A  |
| ТМЕМЗ9В        | transmembrane protein 39B  |
| RRBP1          | ribosome binding protein 1   |
| LRRC32         | leucine rich repeat containing 32  |
| SEMA7A         | semaphorin 7A (John Milton Hagen blood group)  |
| NES            | nestin   |
|                | transient receptor potential cation channel subfamily C member 6   |
|                | H2B clustered histone 21   |
| KDELR3         | KDEL endoplasmic reticulum protein retention receptor 3  |
| ANXA1          | annexin A1   |
| JCAD           | junctional cadherin 5 associated   |
|                | RUN and SH3 domain containing 2  |
| HDAC5          | histone deacetylase 5  |
|                | melanoma cell adhesion molecule  |
|                | GATA binding protein 3   |
|                | kirre like nephrin family adhesion molecule 1  |
|                | biglycan   |
|                | syndecan 3   |
|                | transmembrane protein 45A  |
|                | ETS transcription factor ELK3  |
|                | ATPase cation transporting 13A2  |
|                |  |
| ATP13A2<br>HBB | hemoglobin subunit beta  |
|                | ECM1<br>MY0Z2<br>BMP2<br>FSCN1<br>ZYX<br>TCIM<br>CCND1<br>ARPC1B<br>IGFBP2<br>TMOD1<br>RAB31<br>LRP10<br>ADM<br>PLD3<br>WFS1<br>ADGRE5<br>ARHGEF15<br>AXL<br>PLEKH01<br>KIAA0040<br>DAAM2<br>TBXA2R<br>HLX<br>PLEKH01<br>KIAA0040<br>DAAM2<br>TBXA2R<br>HLX<br>PGAP6<br>APLNR<br>DOCK6<br>BAMBI<br>MY01C<br>TNFRSF12A<br>TMEM39B<br>RRBP1<br>LRRC32<br>SEMA7A<br>NES<br>TRPC6<br>H2BC21<br>KDELR3<br>ANXA1 |

#### Supplementary Table 1. The DEGs in the glomerulus, renal tubules and PBMCs of MN

| TIMP1             | TIMP metallopeptidase inhibitor 1  |
|-------------------|--|
| RELA              | RELA proto-oncogene, NF-KB subunit   |
| GADD45A           | growth arrest and DNA damage inducible alpha                                   |
| CAVIN1            | caveolae associated protein 1  |
| HK2               | hexokinase 2   |
| FGFR1             |  |
|                   | fibroblast growth factor receptor 1  |
| NOTCH1            | notch receptor 1   |
| KCTD12            | potassium channel tetramerization domain containing 12                         |
| BST2<br>GNA11     | bone marrow stromal cell antigen 2<br>G protein subunit alpha 11               |
| MY09B             |  |
| CENPB             | myosin IXB   |
| PEA15             | centromere protein B proliferation and apoptosis adaptor protein 15            |
| OAS1              |  |
|                   | 2'-5'-oligoadenylate synthetase 1  |
| FCER1G            | Fc fragment of IgE receptor Ig   |
| SLC35F6           | solute carrier family 35 member F6   |
| EFNB1             | ephrin B1  |
| SEMA4G            | semaphorin 4G  |
| ST3GAL2<br>MAP4K2 | ST3 beta-galactoside alpha-2,3-sialyltransferase 2                             |
| TAPBP             | mitogen-activated protein kinase kinase kinase kinase 2<br>TAP binding protein |
| SLC9A3R2          | SLC9A3 regulator 2   |
| ENC1              | ectodermal-neural cortex 1   |
| STN1              | STN1 subunit of CST complex  |
| CCDC85C           | coiled-coil domain containing 85C  |
| TAGLN2            | transgelin 2   |
| MFNG              | MFNG 0-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase                   |
| CD151             | CD151 molecule (Raph blood group)  |
| TGFB1             | transforming growth factor beta 1  |
| NFATC1            | nuclear factor of activated T cells 1  |
| CDK2AP2           | cyclin dependent kinase 2 associated protein 2                                 |
| DDA1              | DET1 and DDB1 associated 1   |
| SYT11             | synaptotagmin 11   |
| JPT1              | Jupiter microtubule associated homolog 1                                       |
| SPN               | sialophorin  |
| PRAF2             | PRA1 domain family member 2  |
| DAG1              | dystroglycan 1   |
| CRELD2            | cysteine rich with EGF like domains 2  |
| ITGA5             | integrin subunit alpha 5   |
| TMEM184B          | transmembrane protein 184B   |
| ADAM15            | ADAM metallopeptidase domain 15  |
| IQSEC1            | IQ motif and Sec7 domain ArfGEF 1  |
| TP53              | tumor protein p53  |
| SLC37A4           | solute carrier family 37 member 4  |
| ZNF189            | zinc finger protein 189  |
| SRSF5             | serine and arginine rich splicing factor 5                                     |
| MAOA              | monoamine oxidase A  |
| OGT               | O-linked N-acetylglucosamine (GlcNAc) transferase                              |
| AASS              | aminoadipate-semialdehyde synthase   |
| FRAS1             | Fraser extracellular matrix complex subunit 1                                  |
| CYP27B1           | cytochrome P450 family 27 subfamily B member 1                                 |
| PDK4              | pyruvate dehydrogenase kinase 4  |
| HBB               | hemoglobin subunit beta  |
|                   |  |

Tubules

| SLC29A3 | solute carrier family 29 member 3   |
|---------|---|
| FZD1    | frizzled class receptor 1   |
| MYLIP   | myosin regulatory light chain interacting protein   |
| CAPN3   | calpain 3   |
| B4GALT5 | beta-1,4-galactosyltransferase 5  |
| FHL3    | four and a half LIM domains 3   |
| ABCG1   | ATP binding cassette subfamily G member 1   |
| AKR7A3  | aldo-keto reductase family 7 member A3  |
| NREP    | neuronal regeneration related protein   |
| LIME1   | Lck interacting transmembrane adaptor 1   |
| CCND1   | cyclin D1   |
| FM01    | flavin containing dimethylaniline monoxygenase 1  |
| ABHD6   | abhydrolase domain containing 6, acylglycerol lipase                                      |
| PIPOX   | pipecolic acid and sarcosine oxidase  |
| CITED2  | $Cbp/p300\ interacting\ transactivator\ with\ Glu/Asp\ rich\ carboxy-terminal\ domain\ 2$ |
| PIK3R3  | phosphoinositide-3-kinase regulatory subunit 3  |
| DAO     | D-amino acid oxidase  |
| HNF1B   | HNF1 homeobox B   |
| RBM47   | RNA binding motif protein 47  |
| PCK2    | phosphoenolpyruvate carboxykinase 2, mitochondrial  |
| PDZD2   | PDZ domain containing 2   |
| XPNPEP2 | X-prolyl aminopeptidase 2   |
| CYP4F2  | cytochrome P450 family 4 subfamily F member 2   |
| KDM4A   | lysine demethylase 4A   |
| FAM168B | family with sequence similarity 168 member B  |
| HMGCL   | 3-hydroxy-3-methylglutaryl-CoA lyase  |
| GLYAT   | glycine-N-acyltransferase   |
| KMO     | kynurenine 3-monooxygenase  |
| DDC     | dopa decarboxylase  |
| CROT    | carnitine O-octanoyltransferase   |
| MXD4    | MAX dimerization protein 4  |
| FBP1    | fructose-bisphosphatase 1   |
| NR2F2   | nuclear receptor subfamily 2 group F member 2   |
| FABP1   | fatty acid binding protein 1  |
| PAH     | phenylalanine hydroxylase   |
| SLC22A2 | solute carrier family 22 member 2   |
| CRCP    | CGRP receptor component   |
| ILVBL   | ilvB acetolactate synthase like   |
| C1orf56 | chromosome 1 open reading frame 56  |
| CCDC51  | coiled-coil domain containing 51  |
| HADH    | hydroxyacyl-CoA dehydrogenase   |
| GATM    | glycine amidinotransferase  |
| DDX10   | DEAD-box helicase 10  |
| AMOT    | angiomotin  |
| METTL7A | methyltransferase like 7A   |
| IDH1    | isocitrate dehydrogenase (NADP(+)) 1  |
| LGALS1  | galectin 1  |
| ECHDC3  | enoyl-CoA hydratase domain containing 3   |
| TRIAP1  | TP53 regulated inhibitor of apoptosis 1   |
| COLEC11 | collectin subfamily member 11   |
| ALDOB   | aldolase, fructose-bisphosphate B   |
| GUCY1B1 | guanylate cyclase 1 soluble subunit beta 1  |
| C2CD2   | C2 calcium dependent domain containing 2  |
|         |   |

| CTDSP1   | CTD small phosphatase 1                             |
|----------|---|
| AQP1     | aquaporin 1 (Colton blood group)                    |
| HPD      | 4-hydroxyphenylpyruvate dioxygenase                 |
| SCARB1   | scavenger receptor class B member 1                 |
| GOLPH3L  | golgi phosphoprotein 3 like                         |
| GNPDA1   | glucosamine-6-phosphate deaminase 1                 |
| FLRT3    | fibronectin leucine rich transmembrane protein 3    |
| NAT8B    | N-acetyltransferase 8B (putative, gene/pseudogene)  |
| UBN1     | ubinuclein 1  |
| AKR7A2   | aldo-keto reductase family 7 member A2              |
| MSRB1    | methionine sulfoxide reductase B1                   |
| PTH1R    | parathyroid hormone 1 receptor                      |
| CALML4   | calmodulin like 4                                   |
| VAV3     | vav guanine nucleotide exchange factor 3            |
| HAO2     | hydroxyacid oxidase 2                               |
| NQO2     | N-ribosyldihydronicotinamide:quinone reductase 2    |
| CST3     | cystatin C  |
| LPCAT3   | lysophosphatidylcholine acyltransferase 3           |
| TNFSF10  | TNF superfamily member 10                           |
| GPD1     | glycerol-3-phosphate dehydrogenase 1                |
| RNH1     | ribonuclease/angiogenin inhibitor 1                 |
| GATAD2A  | GATA zinc finger domain containing 2A               |
| NPR3     | natriuretic peptide receptor 3                      |
| TDP2     | tyrosyl-DNA phosphodiesterase 2                     |
| ZGPAT    | zinc finger CCCH-type and G-patch domain containing |
| STAP2    | signal transducing adaptor family member 2          |
| GJB1     | gap junction protein beta 1                         |
| PLXNB1   | plexin B1   |
| UPB1     | beta-ureidopropionase 1                             |
| TMEM242  | transmembrane protein 242                           |
| CD320    | CD320 molecule                                      |
| FUT3     | fucosyltransferase 3 (Lewis blood group)            |
| GCHFR    | GTP cyclohydrolase I feedback regulator             |
| EPHX2    | epoxide hydrolase 2                                 |
| GPX4     | glutathione peroxidase 4                            |
| G6PC     | glucose-6-phosphatase catalytic subunit 1           |
| QDPR     | quinoid dihydropteridine reductase                  |
| ATP6V0E2 | ATPase H+ transporting V0 subunit e2                |
| RETSAT   | retinol saturase                                    |
| ALDH3A2  | aldehyde dehydrogenase 3 family member A2           |
| ACOT13   | acyl-CoA thioesterase 13                            |
| CRYL1    | crystallin lambda 1                                 |
| COL3A1   | collagen type III alpha 1 chain                     |
| RNPEPL1  | arginyl aminopeptidase like 1                       |
| DGLUCY   | D-glutamate cyclase                                 |
| ASS1     | argininosuccinate synthase 1                        |
| LRRC8D   | leucine rich repeat containing 8 VRAC subunit D     |
| TMEM159  | lipid droplet assembly factor 1                     |
| HDAC5    | histone deacetylase 5                               |
| MRPL57   | mitochondrial ribosomal protein L57                 |
| BPHL     | biphenyl hydrolase like                             |
| PATZ1    | POZ/BTB and AT hook containing zinc finger 1        |
| MASP1    | MBL associated serine protease 1                    |
| MAOF 1   | MBE associated serine protease I                    |

| COBL      | cordon-bleu WH2 repeat protein                                  |
|-----------|---|
| MYDGF     | myeloid derived growth factor                                   |
| HDAC6     | histone deacetylase 6   |
| MID1IP1   | MID1 interacting protein 1                                      |
| FUT6      | fucosyltransferase 6  |
| STX7      | syntaxin 7  |
| CUBN      | cubilin   |
| DHTKD1    | dehydrogenase E1 and transketolase domain containing 1          |
| SLC7A9    | solute carrier family 7 member 9                                |
| PEPD      | peptidase D   |
| GTF2H5    | general transcription factor IIH subunit 5                      |
| CYP4A11   | cytochrome P450 family 4 subfamily A member 11                  |
| AGPAT1    | 1-acylglycerol-3-phosphate 0-acyltransferase 1                  |
| OAZ2      | ornithine decarboxylase antizyme 2                              |
| КНК       | ketohexokinase  |
| MMUT      | methylmalonyl-CoA mutase  |
| REXO4     | REX4 homolog, 3'-5' exonuclease                                 |
| TRAM2     | translocation associated membrane protein 2                     |
| PPP6R1    | protein phosphatase 6 regulatory subunit 1                      |
| CBR4      | carbonyl reductase 4  |
| 0GG1      | 8-oxoguanine DNA glycosylase                                    |
| GLDC      | glycine decarboxylase   |
| GUCY1A1   | guanylate cyclase 1 soluble subunit alpha 1                     |
| CCNG2     | cyclin G2   |
| PCGF2     | polycomb group ring finger 2                                    |
| DOLPP1    | dolichyldiphosphatase 1   |
| MAN2B1    | mannosidase alpha class 2B member 1                             |
| FKBP2     | FKBP prolyl isomerase 2   |
| PLG       | plasminogen   |
| APOM      | apolipoprotein M  |
| ECI2      | enoyl-CoA delta isomerase 2                                     |
| PGAP2     | post-GPI attachment to proteins 2                               |
| ZNF106    | zinc finger protein 106   |
| FOLR1     | folate receptor alpha   |
| TCTN1     | tectonic family member 1  |
| STX5      | syntaxin 5  |
| PNP       | purine nucleoside phosphorylase                                 |
| CLDN10    | claudin 10  |
| CFDP1     | craniofacial development protein 1                              |
| TBC1D17   | TBC1 domain family member 17                                    |
| RBKS      | ribokinase  |
| TNFRSF11B | TNF receptor superfamily member 11b                             |
| LIAS      | lipoic acid synthetase  |
| EPHB4     | EPH receptor B4   |
| C1S       | complement C1s  |
| SERPINE2  | serpin family E member 2  |
| NFIX      | nuclear factor I X  |
| VEGFB     | vascular endothelial growth factor B                            |
| KEAP1     | kelch like ECH associated protein 1                             |
| EXTL2     | exostosin like glycosyltransferase 2                            |
| SMUG1     | single-strand-selective monofunctional uracil-DNA glycosylase 1 |
| IL10RB    | interleukin 10 receptor subunit beta                            |
| POP5      | POP5 homolog, ribonuclease P/MRP subunit                        |
| FUFU      | ו טו ט ווטוווטוטא, ווטטוועטובמסב דן ואוגר סטטעווונ              |

| SHMT1    | serine hydroxymethyltransferase 1  |
|----------|--|
| BEND5    | BEN domain containing 5  |
| RIDA     | reactive intermediate imine deaminase A homolog                          |
| KLHL24   | kelch like family member 24  |
| STX3     | syntaxin 3   |
| IGFBP4   | insulin like growth factor binding protein 4                             |
| TTC38    | tetratricopeptide repeat domain 38                                       |
| ZNF302   | zinc finger protein 302  |
| NECAP2   | NECAP endocytosis associated 2   |
| RMND1    | required for meiotic nuclear division 1 homolog                          |
| HIBCH    | 3-hydroxyisobutyryl-CoA hydrolase  |
| RFXANK   | regulatory factor X associated ankyrin containing protein                |
| ACE2     | angiotensin converting enzyme 2  |
| DNASE1L3 | deoxyribonuclease 1 like 3   |
| POLE3    | DNA polymerase epsilon 3, accessory subunit                              |
| ABAT     | 4-aminobutyrate aminotransferase   |
| OGDHL    | oxoglutarate dehydrogenase L   |
| TMEM63A  | transmembrane protein 63A  |
| SLC22A6  | solute carrier family 22 member 6  |
| HOMER3   | homer scaffold protein 3   |
| CDK4     | cyclin dependent kinase 4  |
| PHYH     | phytanoyl-CoA 2-hydroxylase  |
| PPIL2    | peptidylprolyl isomerase like 2  |
| BGN      | biglycan   |
| ALAD     | aminolevulinate dehydratase  |
| DTX4     | deltex E3 ubiquitin ligase 4   |
| CAT      | catalase   |
| SUGCT    | succinyl-CoA: glutarate-CoA transferase                                  |
| SPOP     | speckle type BTB/POZ protein   |
| TGFBRAP1 | transforming growth factor beta receptor associated protein 1            |
| ARPC1B   | actin related protein 2/3 complex subunit 1B                             |
| ALDH5A1  | aldehyde dehydrogenase 5 family member A1                                |
| FBX017   | F-box protein 17   |
| GNG11    | G protein subunit gamma 11   |
| GM2A     | GM2 ganglioside activator  |
| EHMT2    | euchromatic histone lysine methyltransferase 2                           |
| NIT2     | nitrilase family member 2  |
| TNFRSF21 | TNF receptor superfamily member 21                                       |
| MAPT     | microtubule associated protein tau                                       |
| MAN1B1   | mannosidase alpha class 1B member 1                                      |
| SSR4     | signal sequence receptor subunit 4                                       |
| S100A1   | S100 calcium binding protein A1  |
| PSPH     | phosphoserine phosphatase  |
| GLS      | glutaminase  |
| GLE1     | GLE1 RNA export mediator   |
| TPGS2    | tubulin polyglutamylase complex subunit 2                                |
| NAT8     | N-acetyltransferase 8 (putative)   |
| LEPROT   | leptin receptor overlapping transcript                                   |
| CD151    | CD151 molecule (Raph blood group)  |
| MGAT4B   | alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase B |
| ABCA1    | ATP binding cassette subfamily A member 1                                |
| ENAH     | ENAH actin regulator   |
| MSRA     | methionine sulfoxide reductase A   |
|          |  |

| KDELR1   | KDEL endoplasmic reticulum protein retention receptor 1     |
|----------|---|
| COL18A1  | collagen type XVIII alpha 1 chain                           |
| KCNJ15   | potassium inwardly rectifying channel subfamily J member 15 |
| RAB32    | RAB32, member RAS oncogene family                           |
| ISCA1    | iron-sulfur cluster assembly 1                              |
| PRRC2A   | proline rich coiled-coil 2A                                 |
| FMO4     | flavin containing dimethylaniline monoxygenase 4            |
| EHHADH   | enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase     |
| NUPR1    | nuclear protein 1, transcriptional regulator                |
| TBC1D19  | TBC1 domain family member 19                                |
| C2orf42  | chromosome 2 open reading frame 42                          |
| PXMP2    | peroxisomal membrane protein 2                              |
| CAMK2G   | calcium/calmodulin dependent protein kinase II gamma        |
| ARMT1    | acidic residue methyltransferase 1                          |
| KDM6B    | lysine demethylase 6B                                       |
| TP53     | tumor protein p53   |
| IGFBP6   | insulin like growth factor binding protein 6                |
| GBA3     | glucosylceramidase beta 3 (gene/pseudogene)                 |
| ATP6V1B2 | ATPase H+ transporting V1 subunit B2                        |
| NOP2     | NOP2 nucleolar protein                                      |
| PC       | pyruvate carboxylase  |
| ABHD10   | abhydrolase domain containing 10, depalmitoylase            |
| ATF7IP   | activating transcription factor 7 interacting protein       |
| CAPG     | capping actin protein, gelsolin like                        |
| INTS1    | integrator complex subunit 1                                |
| PEBP1    | phosphatidylethanolamine binding protein 1                  |
| PLEKHJ1  | pleckstrin homology domain containing J1                    |
| THBS1    | thrombospondin 1  |
| PALB2    | partner and localizer of BRCA2                              |
| DNAJB2   | DnaJ heat shock protein family (Hsp40) member B2            |
| NAXD     | NAD(P)HX dehydratase  |
| APOC1    | apolipoprotein C1   |
| NDUFS7   | NADH: ubiquinone oxidoreductase core subunit S7             |
| ANK3     | ankyrin 3   |
| SORBS2   | sorbin and SH3 domain containing 2                          |
| HDHD5    | haloacid dehalogenase like hydrolase domain containing 5    |
| PTOV1    | PTOV1 extended AT-hook containing adaptor protein           |
| DNAJC6   | DnaJ heat shock protein family (Hsp40) member C6            |
| GPR137B  | G protein-coupled receptor 137B                             |
| TRIM8    | tripartite motif containing 8                               |
| CA4      | carbonic anhydrase 4  |
| ADI1     | acireductone dioxygenase 1                                  |
| CLCN5    | chloride voltage-gated channel 5                            |
| NMRK1    | nicotinamide riboside kinase 1                              |
| RNASEL   | ribonuclease L  |
| HCFC1R1  | host cell factor C1 regulator 1                             |
| DEXI     | Dexi homolog  |
| SLC47A1  | solute carrier family 47 member 1                           |
| PPP1R3C  | protein phosphatase 1 regulatory subunit 3C                 |
| SLC25A38 | solute carrier family 25 member 38                          |
| RAB2A    | RAB2A, member RAS oncogene family                           |
| MPDZ     | multiple PDZ domain crumbs cell polarity complex component  |
| HOXB7    | homeobox B7   |

| PDZD3     | PDZ domain containing 3   |
|-----------|---|
| RNF167    | ring finger protein 167   |
| BRD30S    | BRD3 opposite strand  |
| ALDH2     | aldehyde dehydrogenase 2 family member                              |
| RENBP     | renin binding protein   |
| ZNF816    | zinc finger protein 816   |
| ZFP36L1   | ZFP36 ring finger protein like 1                                    |
| SLC25A1   | solute carrier family 25 member 1                                   |
| FAN1      | FANCD2 and FANCI associated nuclease 1                              |
| PDK2      | pyruvate dehydrogenase kinase 2                                     |
| MAOB      | monoamine oxidase B   |
| ZYX       | zyxin   |
| POLR3B    | RNA polymerase III subunit B  |
| DI01      | iodothyronine deiodinase 1  |
| CBX6      | chromobox 6   |
| SLC22A13  | solute carrier family 22 member 13                                  |
| PPCS      | phosphopantothenoylcysteine synthetase                              |
| SUOX      | sulfite oxidase   |
| FAM174C   | family with sequence similarity 174 member C                        |
| ARL6IP5   | ADP ribosylation factor like GTPase 6 interacting protein 5         |
| RRAGC     | Ras related GTP binding C   |
| SLC2A5    | solute carrier family 2 member 5                                    |
| SIVA1     | SIVA1 apoptosis inducing factor                                     |
| EHD2      | EH domain containing 2  |
| PPDPF     | pancreatic progenitor cell differentiation and proliferation factor |
| FAM98A    | family with sequence similarity 98 member A                         |
| LLGL2     | LLGL scribble cell polarity complex component 2                     |
| ZNF592    | zinc finger protein 592   |
| NEU1      | neuraminidase 1   |
| AMBRA1    | autophagy and beclin 1 regulator 1                                  |
| AMZ2      | archaelysin family metallopeptidase 2                               |
| PTER      | phosphotriesterase related  |
| DYRK1B    | dual specificity tyrosine phosphorylation regulated kinase 1B       |
| DIP2C     | disco interacting protein 2 homolog C                               |
| MTMR4     | myotubularin related protein 4                                      |
| SERPINI1  | serpin family I member 1  |
| AKR1A1    | aldo-keto reductase family 1 member A1                              |
| MLXIP     | MLX interacting protein   |
| WLS       | Wnt ligand secretion mediator                                       |
| MAZ       | MYC associated zinc finger protein                                  |
| TNFSF15   | TNF superfamily member 15   |
| PBLD      | phenazine biosynthesis like protein domain containing               |
| SLC25A10  | solute carrier family 25 member 10                                  |
| TIMM13    | translocase of inner mitochondrial membrane 13                      |
| ADH5      | alcohol dehydrogenase 5 (class III), chi polypeptide                |
| ACADM     | acyl-CoA dehydrogenase medium chain                                 |
| MAFF      | MAF bZIP transcription factor F                                     |
| PLPP3     | phospholipid phosphatase 3  |
| APH1B     | aph-1 homolog B, gamma-secretase subunit                            |
| VAMP5     | vesicle associated membrane protein 5                               |
| FADS3     | fatty acid desaturase 3   |
| CDKN1C    | cyclin dependent kinase inhibitor 1C                                |
| CYP51A1   | cytochrome P450 family 51 subfamily A member 1                      |
| OTI OTIAT |   |

| GSDMD         | gasdermin D  |
|---------------|--|
| SPAG4         | sperm associated antigen 4                               |
| C3            | complement C3  |
| PSMB9         | proteasome 20S subunit beta 9                            |
|               |  |
| STARD13       | StAR related lipid transfer domain containing 13         |
| SLC20A1       | solute carrier family 20 member 1                        |
| DOP1A         | DOP1 leucine zipper like protein A                       |
| BHLHE40       | basic helix-loop-helix family member e40                 |
| TRMT11        | tRNA methyltransferase 11 homolog                        |
| P3H2          | prolyl 3-hydroxylase 2                                   |
| NFASC         | neurofascin  |
| CDK2AP1       | cyclin dependent kinase 2 associated protein 1           |
| MON2          | MON2 homolog, regulator of endosome-to-Golgi trafficking |
| TBC1D8        | TBC1 domain family member 8                              |
| RARRES2       | retinoic acid receptor responder 2                       |
| SERPINE1      | serpin family E member 1                                 |
| RALGAPA1      | Ral GTPase activating protein catalytic subunit alpha 1  |
| SLC31A2       | solute carrier family 31 member 2                        |
| PDCD6IP       | programmed cell death 6 interacting protein              |
| ADM           | adrenomedullin   |
| TAS2R3        | taste 2 receptor member 3                                |
| CHD1          | chromodomain helicase DNA binding protein 1              |
| MIR22HG       | MIR22 host gene  |
| TAP1          | transporter 1, ATP binding cassette subfamily B member   |
| FKBP1B        | FKBP prolyl isomerase 1B                                 |
| TRIP10        | thyroid hormone receptor interactor 10                   |
| SLC2A3        | solute carrier family 2 member 3                         |
| FLOT2         | flotillin 2  |
| RAP1GDS1      | Rap1 GTPase-GDP dissociation stimulator 1                |
| TGFBR3        | transforming growth factor beta receptor 3               |
| HILPDA        |  |
| SLC52A2       | hypoxia inducible lipid droplet associated               |
|               | solute carrier family 52 member 2                        |
| ZP2           | zona pellucida glycoprotein 2                            |
| PTGER3        | prostaglandin E receptor 3                               |
| IFNAR2        | interferon alpha and beta receptor subunit 2             |
| PRSS22        | serine protease 22                                       |
| MTNR1A        | melatonin receptor 1A                                    |
| NR0B2         | nuclear receptor subfamily 0 group B member 2            |
| SOX9          | SRY-box transcription factor 9                           |
| EPB41L5       | erythrocyte membrane protein band 4.1 like 5             |
| ABCC5         | ATP binding cassette subfamily C member 5                |
| PHC2          | polyhomeotic homolog 2                                   |
| TACC2         | transforming acidic coiled-coil containing protein 2     |
| BTN2A2        | butyrophilin subfamily 2 member A2                       |
| PTPN1         | protein tyrosine phosphatase non-receptor type 1         |
| SQLE          | squalene epoxidase                                       |
| LBP           | lipopolysaccharide binding protein                       |
| <b>RPH3AL</b> | rabphilin 3A like (without C2 domains)                   |
| S100A8        | S100 calcium binding protein A8                          |
| YAF2          | YY1 associated factor 2                                  |
| SCML1         | Scm polycomb group protein like 1                        |
| UAP1          | UDP-N-acetylglucosamine pyrophosphorylase 1              |
| ARG2          | arginase 2   |
|               |  |

| LRP10    | LDL receptor related protein 10                             |
|----------|---|
| SASH1    | SAM and SH3 domain containing 1                             |
| TNFAIP3  | TNF alpha induced protein 3                                 |
| GAS2L1   | growth arrest specific 2 like 1                             |
| TMED3    | transmembrane p24 trafficking protein 3                     |
| TNIP2    | TNFAIP3 interacting protein 2                               |
| KIF16B   | kinesin family member 16B                                   |
| SECTM1   | secreted and transmembrane 1                                |
| CYBC1    | cytochrome b-245 chaperone 1                                |
| DNM1L    | dynamin 1 like  |
| NR1H4    | nuclear receptor subfamily 1 group H member 4               |
| KIF13B   | kinesin family member 13B                                   |
| FLOT1    | flotillin 1   |
| NR1H2    | nuclear receptor subfamily 1 group H member 2               |
| SRSF4    | serine and arginine rich splicing factor 4                  |
| ADIPOR2  | adiponectin receptor 2                                      |
| VWA5A    | von Willebrand factor A domain containing 5A                |
| HNRNPDL  | heterogeneous nuclear ribonucleoprotein D like              |
| HECA     | hdc homolog, cell cycle regulator                           |
| CCNH     | cyclin H  |
| IER3     | immediate early response 3                                  |
| GYG1     | glycogenin 1  |
| APCS     | amyloid P component, serum                                  |
| IDH3A    | isocitrate dehydrogenase (NAD(+)) 3 catalytic subunit alpha |
| SPSB1    | splA/ryanodine receptor domain and SOCS box containing 1    |
| AHI1     | Abelson helper integration site 1                           |
| FKBP5    | FKBP prolyl isomerase 5                                     |
| MAP3K14  | mitogen-activated protein kinase kinase kinase 14           |
| TOB1     | transducer of ERBB2, 1                                      |
| ARAP2    | ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2   |
| HMGCR    | 3-hydroxy-3-methylglutaryl-CoA reductase                    |
| SHFL     | shiftless antiviral inhibitor of ribosomal frameshifting    |
| SLC66A2  | solute carrier family 66 member 2                           |
| SCAPER   | S-phase cyclin A associated protein in the ER               |
| BIRC3    | baculoviral IAP repeat containing 3                         |
| IVNS1ABP | influenza virus NS1A binding protein                        |
| PAX8     | paired box 8  |
| RAB20    | RAB20, member RAS oncogene family                           |
| ZNF184   | zinc finger protein 184                                     |
| TCP11L1  | t-complex 11 like 1   |
| FERMT2   | FERM domain containing kindlin 2                            |
| LTN1     | listerin E3 ubiquitin protein ligase 1                      |
| ZDHHC6   | zinc finger DHHC-type palmitoyltransferase 6                |
| EIF2AK3  | eukaryotic translation initiation factor 2 alpha kinase 3   |
| NPC1     | NPC intracellular cholesterol transporter 1                 |
| FNBP4    | formin binding protein 4                                    |
| MALT1    | MALT1 paracaspase   |
| ZBTB16   | zinc finger and BTB domain containing 16                    |
| IARS1    | isoleucyl-tRNA synthetase 1                                 |
| ZNF189   | zinc finger protein 189                                     |
| WARS1    | tryptophanyl-tRNA synthetase 1                              |
| MTCP1    | mature T cell proliferation 1                               |
| CDH6     | cadherin 6  |
|          |   |

| KLF8            | Kruppel like factor 8  |
|-----------------|--|
| NFIL3           | nuclear factor, interleukin 3 regulated  |
| UBE2L6          | ubiquitin conjugating enzyme E2 L6   |
| TEAD4           | TEA domain transcription factor 4  |
| PNMA2           | PNMA family member 2   |
| IMPDH1          | inosine monophosphate dehydrogenase 1  |
| GOLGA3          |  |
| F3              | golgin A3  |
| гз<br>Р4НА1     | coagulation factor III, tissue factor  |
| IFI35           | prolyl 4-hydroxylase subunit alpha 1<br>interferon induced protein 35                      |
| TKT             | transketolase  |
| TACC1           | transforming acidic coiled-coil containing protein 1                                       |
| DBF4            | DBF4 zinc finger   |
| MCL1            | MCL1 apoptosis regulator, BCL2 family member   |
| SLCO4A1         |  |
| TSPYL2          | solute carrier organic anion transporter family member 4A1<br>TSPY like 2                  |
|                 |  |
| CXCL2           | C-X-C motif chemokine ligand 2   |
| WTAP<br>CREM    | WT1 associated protein   |
| RCL1            | cAMP responsive element modulator  |
| RARRES1         | RNA terminal phosphate cyclase like 1<br>retinoic acid receptor responder 1                |
| TFRC            |  |
| UBAP1           | transferrin receptor<br>ubiguitin associated protein 1                                     |
| LEFTY1          |  |
| TSC22D2         | left-right determination factor 1  |
| TRIM13          | TSC22 domain family member 2   |
| JUND            | tripartite motif containing 13   |
| IFRD1           | JunD proto-oncogene, AP-1 transcription factor subunit                                     |
| CARHSP1         | interferon related developmental regulator 1   |
| GPR3            | calcium regulated heat stable protein 1  |
| DUSP6           | G protein-coupled receptor 3   |
| AASS            | dual specificity phosphatase 6<br>aminoadipate-semialdehyde synthase                       |
| FAM131A         |  |
| FAMILSIA<br>F12 | family with sequence similarity 131 member A   |
| LRRFIP2         | coagulation factor XII<br>LRR binding FLII interacting protein 2                           |
| CGA             |  |
|                 | glycoprotein hormones, alpha polypeptide   |
| DDX5            | DEAD-box helicase 5  |
| FOSB            | FosB proto-oncogene, AP-1 transcription factor subunit<br>complement C1r subcomponent like |
| C1RL<br>IGFLR1  |  |
|                 | IGF like family receptor 1   |
| ABCA5           | ATP binding cassette subfamily A member 5  |
| ISG20           | interferon stimulated exonuclease gene 20  |
| GABARAPL1       | GABA type A receptor associated protein like 1   |
| IL1RL1          | interleukin 1 receptor like 1  |
| REG1B           | regenerating family member 1 beta  |
| CEMIP2          | cell migration inducing hyaluronidase 2  |
| IL6R            | interleukin 6 receptor   |
| ZNF331          | zinc finger protein 331  |
| PDE4D           | phosphodiesterase 4D   |
| S100A9          | S100 calcium binding protein A9  |
| KLF9            | Kruppel like factor 9  |
| DEPP1           | DEPP1 autophagy regulator  |
| HIVEP2          | HIVEP zinc finger 2  |

| SOD2     | superoxide dismutase 2  |
|----------|---|
| JUN      | Jun proto-oncogene, AP-1 transcription factor subunit   |
| BTG2     | BTG anti-proliferation factor 2   |
| SLC38A2  | solute carrier family 38 member 2   |
| C1R      | complement C1r  |
| VMP1     | vacuole membrane protein 1  |
| SMARCD3  | SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3 |
| RBBP8    | RB binding protein 8, endonuclease  |
| PPARGC1A | PPARG coactivator 1 alpha   |
| STAT1    | signal transducer and activator of transcription 1  |
| SLC39A14 | solute carrier family 39 member 14  |
| RIOX1    | ribosomal oxygenase 1   |
| RHOB     | ras homolog family member B   |
| KLF6     | Kruppel like factor 6   |
| PPP2R3A  | protein phosphatase 2 regulatory subunit B"alpha  |
| ETS2     | ETS proto-oncogene 2, transcription factor  |
| HES1     | hes family bHLH transcription factor 1  |
| SERPINA3 | serpin family A member 3  |
| CISH     | cytokine inducible SH2 containing protein   |
| LIPG     | lipase G, endothelial type  |
| CHI3L1   | chitinase 3 like 1  |
| NR4A3    | nuclear receptor subfamily 4 group A member 3   |
| SRSF5    | serine and arginine rich splicing factor 5  |
| IFIT5    | interferon induced protein with tetratricopeptide repeats 5                                       |
| ATF3     | activating transcription factor 3   |
| JUNB     | JunB proto-oncogene, AP-1 transcription factor subunit  |
| GADD45A  | growth arrest and DNA damage inducible alpha  |
| RGS2     | regulator of G protein signaling 2  |
| TSC22D3  | TSC22 domain family member 3  |
| NR4A1    | nuclear receptor subfamily 4 group A member 1   |
| SLC19A2  | solute carrier family 19 member 2   |
| TMEM100  | transmembrane protein 100   |
| PDK4     | pyruvate dehydrogenase kinase 4   |
| RGS3     | regulator of G protein signaling 3  |
| SOCS2    | suppressor of cytokine signaling 2  |
| LDLR     | low density lipoprotein receptor  |
| ELL2     | elongation factor for RNA polymerase II 2   |
| CEBPD    | CCAAT enhancer binding protein delta  |
| EFNA1    | ephrin A1   |
| AKAP13   | A-kinase anchoring protein 13   |
| APOLD1   | apolipoprotein L domain containing 1  |
| NEDD9    | neural precursor cell expressed, developmentally down-regulated 9                                 |
| GPX2     | glutathione peroxidase 2  |
| NFKBIA   | NFKB inhibitor alpha  |
| CCNL1    | cyclin L1   |
| CEBPB    | CCAAT enhancer binding protein beta   |
| PPP2R1B  | protein phosphatase 2 scaffold subunit Abeta  |
| FOS      | Fos proto-oncogene, AP-1 transcription factor subunit   |
| EGR1     | early growth response 1   |
| RETREG1  | reticulophagy regulator 1   |
| ZFP36    | ZFP36 ring finger protein   |
| TUBGCP3  | tubulin gamma complex associated protein 3  |
|          |   |

|       | 001/4      |   |
|-------|------------|---|
|       | SGK1       | serum/glucocorticoid regulated kinase 1                     |
|       | GADD45B    | growth arrest and DNA damage inducible beta                 |
|       | DUSP1      | dual specificity phosphatase 1                              |
|       | TIPARP     | TCDD inducible poly (ADP-ribose) polymerase                 |
|       | ZFAND5     | zinc finger AN1-type containing 5                           |
| PBMCs | GOLGA6L5P  | golgin A6 family like 5, pseudogene                         |
|       | ZDHHC22    | zinc finger DHHC-type palmitoyltransferase 22               |
|       | COTL1      | coactosin like F-actin binding protein 1                    |
|       | DICER1-AS1 | DICER1 antisense RNA 1                                      |
|       | ARL6IP1    | ADP ribosylation factor like GTPase 6 interacting protein 1 |
|       | HNRNPA1    | heterogeneous nuclear ribonucleoprotein A1                  |
|       | FZD5       | frizzled class receptor 5                                   |
|       | MAP4K4     | mitogen-activated protein kinase kinase kinase kinase 4     |
|       | GALE       | UDP-galactose-4-epimerase                                   |
|       | MXRA8      | matrix remodeling associated 8                              |
|       | PRKCB      | protein kinase C beta                                       |
|       | RNASE4     | ribonuclease A family member 4                              |
|       | MTDH       | metadherin  |
|       | CECR5      | haloacid dehalogenase like hydrolase domain containing 5    |
|       | USP34      | ubiquitin specific peptidase 34                             |
|       | MTMR9      | myotubularin related protein 9                              |
|       | GNA12      | G protein subunit alpha 12                                  |
|       | MAEA       | macrophage erythroblast attacher, E3 ubiquitin ligase       |
|       | TNP03      | transportin 3   |
|       | TEX11      | testis expressed 11   |
|       | XPOT       | exportin for tRNA   |
|       | METTL9     | methyltransferase like 9                                    |
|       | RYK        | receptor like tyrosine kinase                               |
|       | NFKB1      | nuclear factor kappa B subunit 1                            |
|       | DEPDC7     | DEP domain containing 7                                     |
|       | ZNF211     | zinc finger protein 211                                     |
|       | HMGN5      | high mobility group nucleosome binding domain 5             |
|       | TMEM43     | transmembrane protein 43                                    |
|       | RRAGC      |   |
|       | FAM57A     | Ras related GTP binding C                                   |
|       |            | TLC domain containing 3A                                    |
|       | DOHH       | deoxyhypusine hydroxylase                                   |
|       | TMSB4Y     | thymosin beta 4 Y-linked                                    |
|       | ANKRD11    | ankyrin repeat domain 11                                    |
|       | FEM1A      | fem-1 homolog A   |
|       | ZNF230     | zinc finger protein 230                                     |
|       | QARS       | glutamyl-prolyl-tRNA synthetase 1                           |
|       | PPP6R2     | protein phosphatase 6 regulatory subunit 2                  |
|       | RABGGTB    | Rab geranylgeranyltransferase subunit beta                  |
|       | FAM221A    | family with sequence similarity 221 member A                |
|       | ANXA7      | annexin A7  |
|       | RCSD1      | RCSD domain containing 1                                    |
|       | LARP7      | La ribonucleoprotein 7, transcriptional regulator           |
|       | ARV1       | ARV1 homolog, fatty acid homeostasis modulator              |
|       | RAP1GAP2   | RAP1 GTPase activating protein 2                            |
|       | CDK1       | cyclin dependent kinase 1                                   |
|       | HPS1       | HPS1 biogenesis of lysosomal organelles complex 3 subunit 1 |
|       | MAP3K4     | mitogen-activated protein kinase kinase kinase 4            |
|       | CLK3       | CDC like kinase 3   |
|       |            |   |

| USP31     | ubiquitin specific peptidase 31                                      |
|-----------|--|
| OPTN      | optineurin   |
| PARG      | poly (ADP-ribose) glycohydrolase                                     |
| CBR3      | carbonyl reductase 3   |
| NDRG3     | NDRG family member 3   |
| FMN1      | formin 1   |
| CASD1     | CAS1 domain containing 1   |
| INO80C    | INO80 complex subunit C  |
| PICALM    | phosphatidylinositol binding clathrin assembly protein               |
| SRP68     | signal recognition particle 68                                       |
| BTBD10    | BTB domain containing 10   |
| APC       | APC regulator of WNT signaling pathway                               |
| BTF3P11   | basic transcription factor 3 pseudogene 11                           |
|           |  |
| HBP1      | HMG-box transcription factor 1                                       |
| ITLN1     | intelectin 1   |
| ABCC5     | ATP binding cassette subfamily C member 5                            |
| EFS       | embryonal Fyn-associated substrate                                   |
| MED22     | mediator complex subunit 22  |
| BACE2     | beta-secretase 2   |
| MFAP1     | microfibril associated protein 1                                     |
| ST13      | ST13 Hsp70 interacting protein                                       |
| GOLGA5    | golgin A5  |
| LONRF1    | LON peptidase N-terminal domain and ring finger 1                    |
| ESC02     | establishment of sister chromatid cohesion N-acetyltransferase 2     |
| NGRN      | neugrin, neurite outgrowth associated                                |
| NEB       | nebulin  |
| UBE2G1    | ubiquitin conjugating enzyme E2 G1                                   |
| TRIM64    | tripartite motif containing 64                                       |
| BCAR3     | BCAR3 adaptor protein, NSP family member                             |
| ADORA2A   | adenosine A2a receptor   |
| SERPIND1  | serpin family D member 1   |
| CCM2L     | CCM2 like scaffold protein   |
| ANAPC13   | anaphase promoting complex subunit 13                                |
| RPAP3     | RNA polymerase II associated protein 3                               |
| HNRNPA1L2 | heterogeneous nuclear ribonucleoprotein A1 like 2                    |
| GMCL1     | germ cell-less 1, spermatogenesis associated                         |
| WNK1      | WNK lysine deficient protein kinase 1                                |
| ATP2C1    | ATPase secretory pathway Ca <sup>2+</sup> transporting 1             |
| HHEX      | hematopoietically expressed homeobox                                 |
| CLEC4E    | C-type lectin domain family 4 member E                               |
| PPID      | peptidylprolyl isomerase D   |
| MRFAP1L1  | Morf4 family associated protein 1 like 1                             |
| SNIP1     | Smad nuclear interacting protein 1                                   |
| CDH1      | cadherin 1   |
| PPM1A     | protein phosphatase, Mg <sup>2+</sup> /Mn <sup>2+</sup> dependent 1A |
| DYX1C1    | dynein axonemal assembly factor 4                                    |
| TDRKH     | tudor and KH domain containing                                       |
| DNAJA4    | DnaJ heat shock protein family (Hsp40) member A4                     |
| THAP11    | THAP domain containing 11  |
| ITGAD     | integrin subunit alpha D   |
| LAMP2     | lysosomal associated membrane protein 2                              |
| NSUN3     | NOP2/Sun RNA methyltransferase 3                                     |
| TMEM204   | transmembrane protein 204  |
|           | tanononorano protein 204   |

| PHF10         | PHD finger protein 10   |
|---------------|---|
| SOX4          | SRY-box transcription factor 4  |
| POC5          | POC5 centriolar protein   |
| BRIX1         | biogenesis of ribosomes BRX1  |
| HNRNPH2       | heterogeneous nuclear ribonucleoprotein H2                                    |
| MKRN1         | makorin ring finger protein 1   |
| KCTD18        | potassium channel tetramerization domain containing 18                        |
| RNF146        | ring finger protein 146   |
| TDRD12        | tudor domain containing 12  |
| INPP5F        | inositol polyphosphate-5-phosphatase F  |
| MRM2          | mitochondrial rRNA methyltransferase 2  |
| UBE2M         | ubiquitin conjugating enzyme E2 M   |
| IRS2          | insulin receptor substrate 2  |
| CDHR3         | cadherin related family member 3  |
| PCOLCE2       | procollagen C-endopeptidase enhancer 2  |
| PDCL3         | phosducin like 3  |
| ATP1A4        | ATPase Na <sup>+</sup> /K <sup>+</sup> transporting subunit alpha 4           |
| METTL3        | methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit |
| ALDH18A1      | aldehyde dehydrogenase 18 family member A1                                    |
| VMP1          | vacuole membrane protein 1  |
| COQ8A         | coenzyme Q8A  |
| AJUBA         | ajuba LIM protein   |
| KISS1R        | KISS1 receptor  |
| KDM3A         | lysine demethylase 3A   |
| TPRG1L        | tumor protein p63 regulated 1 like  |
| CHRD          | chordin   |
| C1orf229      | long intergenic non-protein coding RNA 2897                                   |
| TEPP          | testis, prostate and placenta expressed                                       |
| CSNK1A1       | casein kinase 1 alpha 1   |
| MTERF3        | mitochondrial transcription termination factor 3                              |
| FEN1          | flap structure-specific endonuclease 1  |
| DKFZP586I1420 | uncharacterized protein DKFZp586I1420   |
| NFKBIZ        | NFKB inhibitor zeta   |
| FAM69A        | divergent protein kinase domain 1A  |
| MTMR12        | myotubularin related protein 12   |
| ERP44         | endoplasmic reticulum protein 44  |
| HNRNPH3       | heterogeneous nuclear ribonucleoprotein H3                                    |
| CTSE          | cathepsin E   |
| SMCHD1        | structural maintenance of chromosomes flexible hinge domain containing 1      |
| NEUROG1       | neurogenin 1  |
| PLPP3         | phospholipid phosphatase 3  |
| FAM71E1       | family with sequence similarity 71 member E1                                  |
| CUL3          | cullin 3  |
| TRIP12        | thyroid hormone receptor interactor 12  |
| INTS5         | integrator complex subunit 5  |
| CTNNAL1       | catenin alpha like 1  |
| CCDC34        | coiled-coil domain containing 34  |
| PCMT1         | protein-L-isoaspartate (D-aspartate) O-methyltransferase                      |
| RAB27A        | RAB27A, member RAS oncogene family  |
| PLIN3         | perilipin 3   |
| ZNF487        | zinc finger protein 487   |
| PJA1          | praja ring finger ubiquitin ligase 1  |
| DYNC2H1       | dynein cytoplasmic 2 heavy chain 1  |
| 211102112     |   |

| UNC50        | unc-50 inner nuclear membrane RNA binding protein             |
|--------------|---|
| VSTM2A       | V-set and transmembrane domain containing 2A                  |
| SLC2A3       | solute carrier family 2 member 3                              |
| PAGE5        | PAGE family member 5  |
| ATCAY        | ATCAY kinesin light chain interacting caytaxin                |
| EGFEM1P      | EGF like and EMI domain containing 1, pseudogene              |
| IFRD1        | interferon related developmental regulator 1                  |
| CCDC82       | coiled-coil domain containing 82                              |
| TBC1D14      | TBC1 domain family member 14                                  |
| PSMC6        | proteasome 26S subunit, ATPase 6                              |
| ELF1         | E74 like ETS transcription factor 1                           |
| CAND1        | cullin associated and neddylation dissociated 1               |
| HGF          | hepatocyte growth factor                                      |
| ATP10D       | ATPase phospholipid transporting 10D (putative)               |
| KRAS         | KRAS proto-oncogene, GTPase                                   |
| EDEM1        | ER degradation enhancing alpha-mannosidase like protein $1$   |
| PRRC1        | proline rich coiled-coil 1                                    |
| HMCES        | 5-hydroxymethylcytosine binding, ES cell specific             |
| AFG3L2       | AFG3 like matrix AAA peptidase subunit 2                      |
| CLK1         | CDC like kinase 1   |
| DNAJB6       | DnaJ heat shock protein family (Hsp40) member B6              |
| SNX17        | sorting nexin 17  |
| RABEP1       | rabaptin, RAB GTPase binding effector protein 1               |
| API5         | apoptosis inhibitor 5   |
| ZNF285       | zinc finger protein 285                                       |
| GTF2B        | general transcription factor IIB                              |
| MORF4L1      | mortality factor 4 like 1                                     |
| TM2D3        | TM2 domain containing 3                                       |
| GIT2         | GIT ArfGAP 2  |
| PRKAR1A      | protein kinase cAMP-dependent type I regulatory subunit alpha |
| RAB28        | RAB28, member RAS oncogene family                             |
| KCTD15       | potassium channel tetramerization domain containing 15        |
| MRFAP1       | Morf4 family associated protein 1                             |
| STEAP3       | STEAP3 metalloreductase                                       |
| CNPY4        | canopy FGF signaling regulator 4                              |
| VTA1         | vesicle trafficking 1   |
| TARDBP       | TAR DNA binding protein                                       |
| ATAD3C       | ATPase family AAA domain containing 3C                        |
| LPCAT1       | lysophosphatidylcholine acyltransferase 1                     |
| CCDC126      | coiled-coil domain containing 126                             |
| FAM118A      | family with sequence similarity 118 member A                  |
| CAMTA1       | calmodulin binding transcription activator 1                  |
| TFCP2        | transcription factor CP2                                      |
| BORCS8-MEF2B | BORCS8-MEF2B readthrough                                      |
| RNF114       | ring finger protein 114                                       |
| NEK7         | NIMA related kinase 7   |
| PPP2CA       | protein phosphatase 2 catalytic subunit alpha                 |
| RAD51AP1     | RAD51 associated protein 1                                    |
| APMAP        | adipocyte plasma membrane associated protein                  |
| SURF6        | surfeit 6   |
| ANP32A       | acidic nuclear phosphoprotein 32 family member A              |
| CFDP1        | craniofacial development protein 1                            |
| EMC2         | ER membrane protein complex subunit 2                         |
| LIVIOZ       | En monorano protoni complex subunit 2                         |

| BRMS1L    | BRMS1 like transcriptional repressor  |
|-----------|---|
| RBM7      | RNA binding motif protein 7   |
| DNAJA1    | DnaJ heat shock protein family (Hsp40) member A1  |
| GFM2      | GTP dependent ribosome recycling factor mitochondrial 2   |
| RNPEP     | arginyl aminopeptidase  |
| GNB1      | G protein subunit beta 1  |
| ADH5      | alcohol dehydrogenase 5 (class III), chi polypeptide  |
| PDIA6     | protein disulfide isomerase family A member 6   |
| PPP3CA    | protein phosphatase 3 catalytic subunit alpha   |
| STIP1     | stress induced phosphoprotein 1   |
| SESN1     | sestrin 1   |
| NME7      | NME/NM23 family member 7  |
| TNXB      | tenascin XB   |
| AP2A2     | adaptor related protein complex 2 subunit alpha 2   |
| ELMO2     | engulfment and cell motility 2  |
| UTP6      | UTP6 small subunit processome component   |
| RUBCN     | rubicon autophagy regulator   |
| ARHGEF37  | Rho guanine nucleotide exchange factor 37   |
| TMEM9B    | TMEM9 domain family member B  |
| MYCBP     | MYC binding protein   |
| RPL7      | ribosomal protein L7  |
| IGF2R     | insulin like growth factor 2 receptor   |
| ADNP      | activity dependent neuroprotector homeobox  |
| C1orf116  | chromosome 1 open reading frame 116   |
| RAB9BP1   | RAB9B, member RAS oncogene family pseudogene 1  |
| TCERG1    | transcription elongation regulator 1  |
| FBX03     | F-box protein 3   |
| PSEN1     | presenilin 1  |
| ADD2      | adducin 2   |
| KIAA0232  | KIAA0232  |
| ZNF681    | zinc finger protein 681   |
| RNF20     | ring finger protein 20  |
| PER3      | period circadian regulator 3  |
| SAT1      | spermidine/spermine N1-acetyltransferase 1  |
| RILP      | Rab interacting lysosomal protein   |
| FOXJ2     | forkhead box J2   |
| SLC1A1    | solute carrier family 1 member 1  |
| RCC1L     | RCC1 like   |
| FAM135A   | family with sequence similarity 135 member A  |
| E2F3      | E2F transcription factor 3  |
| CDK8      | cyclin dependent kinase 8   |
| BLOC1S6   | biogenesis of lysosomal organelles complex 1 subunit 6  |
| ZNF263    | zinc finger protein 263   |
| FAM120C   | family with sequence similarity 120C  |
| BEX4      | brain expressed X-linked 4  |
| TMCO1     | transmembrane and coiled-coil domains 1   |
| PAGE2     | PAGE family member 2  |
| HERC2     | HECT and RLD domain containing E3 ubiquitin protein ligase 2 $% \left( {{\left[ {{{\rm{B}}_{\rm{T}}} \right]}} \right)$ |
| HAT1      | histone acetyltransferase 1   |
| LINC01123 | long intergenic non-protein coding RNA 1123   |
| ACAT1     | acetyl-CoA acetyltransferase 1  |
| SCP2      | sterol carrier protein 2  |
| RWDD4     | RWD domain containing 4   |
|           |   |

| CD59         | CD59 molecule (CD59 blood group)   |
|--------------|--|
| LHX1         | LIM homeobox 1   |
| PAIP2        | poly(A) binding protein interacting protein 2                                |
| TECPR2       | tectonin beta-propeller repeat containing 2                                  |
| DNAJA2       | DnaJ heat shock protein family (Hsp40) member A2                             |
| KDELC1       | protein O-glucosyltransferase 2  |
| PCID2        | PCI domain containing 2  |
| DAPK1        | death associated protein kinase 1  |
| ZNF827       | zinc finger protein 827  |
| ALDH5A1      | aldehyde dehydrogenase 5 family member A1                                    |
| TSNAX        | translin associated factor X   |
| C9orf78      | chromosome 9 open reading frame 78   |
| ASAH1        | N-acylsphingosine amidohydrolase 1   |
| BMX          | BMX non-receptor tyrosine kinase   |
| PRTN3        | proteinase 3   |
| NPBWR1       | neuropeptides B and W receptor 1   |
| IDH3A        | isocitrate dehydrogenase (NAD(+)) 3 catalytic subunit alpha                  |
| CRK          | CRK proto-oncogene, adaptor protein  |
| KCNE2        | potassium voltage-gated channel subfamily E regulatory subunit 2             |
| NAP1L4       | nucleosome assembly protein 1 like 4   |
| ZNF282       | zinc finger protein 282  |
| GPR20        | G protein-coupled receptor 20  |
| PAN3         | poly(A) specific ribonuclease subunit PAN3                                   |
| TMEM245      | transmembrane protein 245  |
| TIFA         | TRAF interacting protein with forkhead associated domain                     |
| SPON1        | spondin 1  |
| SHQ1         | SHQ1, H/ACA ribonucleoprotein assembly factor                                |
| TMC5         | transmembrane channel like 5   |
| PAPPA2       | pappalysin 2   |
| GALNT5       | polypeptide N-acetylgalactosaminyltransferase 5                              |
| FRMD4A       | FERM domain containing 4A  |
| SLTM         | SAFB like transcription modulator  |
| RPL22        | ribosomal protein L22  |
| ATP6V1E1     | ATPase H+ transporting V1 subunit E1   |
| ETS1         | ETS proto-oncogene 1, transcription factor                                   |
| LOC100422526 | proteasome activator subunit 3 pseudogene                                    |
| BRD7P3       | bromodomain containing 7 pseudogene 3  |
| JMJD1C       | jumonji domain containing 1C   |
| KRTAP4-1     | keratin associated protein 4-1   |
| EIF4E        | eukaryotic translation initiation factor 4E                                  |
| ZMAT4        | zinc finger matrin-type 4  |
| FAM168B      | family with sequence similarity 168 member B                                 |
| SEC23B       | SEC23 homolog B, COPII coat complex component                                |
| CAPZA2       | capping actin protein of muscle Z-line subunit alpha 2                       |
| HSP90AA1     | heat shock protein 90 alpha family class A member 1                          |
| HSD3B1       | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 |
| CLP1         | cleavage factor polyribonucleotide kinase subunit 1                          |
| SOX17        | SRY-box transcription factor 17  |
| XRN2         | 5'-3' exoribonuclease 2  |
| RIPK4        | receptor interacting serine/threonine kinase 4                               |
| CORIN        | corin, serine peptidase  |
| CUTC         | cutC copper transporter  |
| CEACAM6      | CEA cell adhesion molecule 6   |
|              |  |

| 470454       |   |
|--------------|---|
| ATPAF1       | ATP synthase mitochondrial F1 complex assembly factor 1     |
| HRASLS2      | phospholipase A and acyltransferase 2                       |
| RFX4         | regulatory factor X4  |
| FCER1A       | Fc fragment of IgE receptor la                              |
| MAFG-AS1     | MAFG divergent transcript                                   |
| HMGCS1       | 3-hydroxy-3-methylglutaryl-CoA synthase 1                   |
| CAND2        | cullin associated and neddylation dissociated 2 (putative)  |
| PSEN2        | presenilin 2  |
| ANXA3        | annexin A3  |
| UBFD1        | ubiquitin family domain containing 1                        |
| SUPT16H      | SPT16 homolog, facilitates chromatin remodeling subunit     |
| EFNA1        | ephrin A1   |
| FA2H         | fatty acid 2-hydroxylase                                    |
| SYF2         | SYF2 pre-mRNA splicing factor                               |
| CCDC115      | coiled-coil domain containing 115                           |
| WBP4         | WW domain binding protein 4                                 |
| RAD17        | RAD17 checkpoint clamp loader component                     |
| MRGPRF       | MAS related GPR family member F                             |
| MSANTD2      | Myb/SANT DNA binding domain containing 2                    |
| PAQR9        | progestin and adipoQ receptor family member 9               |
| TMEM232      | transmembrane protein 232                                   |
| GCH1         | GTP cyclohydrolase 1  |
| NUPL2        | nucleoporin 42  |
| TTC33        | tetratricopeptide repeat domain 33                          |
| TPMT         | thiopurine S-methyltransferase                              |
| MINOS1P1     | MICOS10 pseudogene 1  |
| HEPACAM2     | HEPACAM family member 2                                     |
| RBMX2        | RNA binding motif protein X-linked 2                        |
| SNAP23       | synaptosome associated protein 23                           |
| ATRNL1       | attractin like 1  |
| PSMD10       | proteasome 26S subunit, non-ATPase 10                       |
| SPTA1        | spectrin alpha, erythrocytic 1                              |
| LOC101928068 | uncharacterized LOC101928068                                |
| B4GALNT3     | beta-1,4-N-acetyl-galactosaminyltransferase 3               |
| ZNF12        | zinc finger protein 12                                      |
| CACUL1       | CDK2 associated cullin domain 1                             |
| SDHC         | succinate dehydrogenase complex subunit C                   |
| TMEM167B     | transmembrane protein 167B                                  |
| HCFC1        | host cell factor C1   |
| IQCC         | IQ motif containing C                                       |
| FOXJ1        | forkhead box J1   |
| CYB5B        | cytochrome b5 type B  |
| ARL13B       | ADP ribosylation factor like GTPase 13B                     |
| KRT1         | keratin 1   |
| DKK3         | dickkopf WNT signaling pathway inhibitor 3                  |
| AXIN2        | axin 2  |
| MAF          | MAF bZIP transcription factor                               |
| SARAF        | store-operated calcium entry associated regulatory factor   |
| DYNC2LI1     | dynein cytoplasmic 2 light intermediate chain 1             |
| FOXB1        | forkhead box B1   |
| EIF2S1       | eukaryotic translation initiation factor 2 subunit alpha    |
| LAMTOR3      | late endosomal/lysosomal adaptor, MAPK and MTOR activator 3 |
| UBE2Q2       | ubiquitin conjugating enzyme E2 Q2                          |
|              | ,,  |

| MTM1      | myotubularin 1  |
|-----------|---|
| RAB1A     | RAB1A, member RAS oncogene family                                   |
| ADAR      | adenosine deaminase RNA specific                                    |
| SLC35B3   | solute carrier family 35 member B3                                  |
| GFPT2     | glutamine-fructose-6-phosphate transaminase 2                       |
| GLDC      | glycine decarboxylase   |
| KARS      | lysyl-tRNA synthetase 1   |
| HSPB9     | heat shock protein family B (small) member 9                        |
| CD1D      | CD1d molecule   |
| ASPHD1    | aspartate beta-hydroxylase domain containing 1                      |
| LRP3      | LDL receptor related protein 3                                      |
| FAM173B   | ATP synthase c subunit lysine N-methyltransferase                   |
| TGFA      | transforming growth factor alpha                                    |
| KLF5      | Kruppel like factor 5   |
| GPR31     | G protein-coupled receptor 31                                       |
| WDTC1     | WD and tetratricopeptide repeats 1                                  |
| MSTN      | myostatin   |
| BTNL3     | butyrophilin like 3   |
| CLPSL2    | colipase like 2   |
| NLGN4Y    | neuroligin 4 Y-linked   |
| IFI27     | interferon alpha inducible protein 27                               |
| LHB       | luteinizing hormone subunit beta                                    |
| ACER1     | alkaline ceramidase 1   |
| ENC1      | ectodermal-neural cortex 1  |
| PLCXD2    | phosphatidylinositol specific phospholipase C X domain containing 2 |
| TAPBP     | TAP binding protein   |
| LINC00476 | long intergenic non-protein coding RNA 476                          |
|           |   |

### Supplementary Table 2. Detailed results of DEGs functional enrichment

| Names         | total | elements   |
|---------------|-------|--|
| Glom PBMC Tub | 48    | positive regulation of transferase activity            |
|               |       | negative regulation of cellular component organization |
|               |       | actin filament-based process                           |
|               |       | Endometrial cancer                                     |
|               |       | hemostasis   |
|               |       | regeneration   |
|               |       | glial cell differentiation                             |
|               |       | regulation of cell adhesion                            |
|               |       | negative regulation of protein modification process    |
|               |       | MAPK signaling pathway                                 |
|               |       | liver development                                      |
|               |       | Pathways in cancer                                     |
|               |       | regulation of kinase activity                          |
|               |       | regulation of body fluid levels                        |
|               |       | regulation of protein serine/threonine kinase activity |
|               |       | regulation of protein kinase activity                  |
|               |       | positive regulation of kinase activity                 |
|               |       | Pancreatic cancer                                      |
|               |       | response to inorganic substance                        |
|               |       | blood vessel morphogenesis                             |
|               |       | actin cytoskeleton organization                        |
|               |       | lymphocyte activation                                  |
|         |     | blood coagulation   |
|---------|-----|---|
|         |     | response to wounding  |
|         |     | negative regulation of catalytic activity   |
|         |     | negative regulation of catabolic process  |
|         |     | regulation of neuron death  |
|         |     | cellular response to nitrogen compound  |
|         |     | Melanoma  |
|         |     |   |
|         |     | pattern specification process   |
|         |     | Corticotropin-releasing hormone signaling pathway   |
|         |     | blood vessel development  |
|         |     | VEGFA-VEGFR2 signaling pathway  |
|         |     | positive regulation of protein phosphorylation  |
|         |     | hepaticobiliary system development  |
|         |     | positive regulation of protein kinase activity  |
|         |     | cellular component disassembly  |
|         |     | viral process   |
|         |     | cellular response to peptide  |
|         |     | wound healing   |
|         |     | coagulation   |
|         |     | Neural crest differentiation  |
|         |     | Non-small cell lung cancer  |
|         |     | Pancreatic adenocarcinoma pathway   |
|         |     | regulation of cell-cell adhesion  |
|         |     | gland development   |
|         |     | Glioma  |
|         |     | cellular response to organonitrogen compound  |
| lom Tub | 272 | positive regulation of cell activation  |
|         |     | regulation of viral process   |
|         |     | regulation of epithelial cell differentiation   |
|         |     | muscle organ development  |
|         |     | regulation of angiogenesis  |
|         |     | muscle cell differentiation   |
|         |     | cellular response to environmental stimulus   |
|         |     | regulation of steroid biosynthetic process  |
|         |     | DNA damage response   |
|         |     | connective tissue development   |
|         |     | nephron epithelium development  |
|         |     | cellular response to peptide hormone stimulus   |
|         |     | response to oxidative stress  |
|         |     | regulation of transforming growth factor beta receptor signaling pathway  |
|         |     | leukocyte cell-cell adhesion  |
|         |     | vasculogenesis  |
|         |     | negative regulation of response to external stimulus  |
|         |     | regulation of cellular ketone metabolic process   |
|         |     | mononuclear cell differentiation  |
|         |     | epithelial tube morphogenesis   |
|         |     | cytokine-mediated signaling pathway   |
|         |     | Spinal cord injury  |
|         |     | kidney development  |
|         |     | regulation of cytokine production   |
|         |     | mesenchymal cell differentiation  |
|         |     | nephron tubule development  |
|         |     | - Provide and a second s |

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positive regulation of cell death positive regulation of angiogenesis hormone biosynthetic process Notch signaling pathway pyruvate metabolic process T-cell activation SARS-CoV-2 Gastrin signaling pathway endothelial cell migration regulation of tissue remodeling Chagas disease (American trypanosomiasis) taxis regulation of epithelial cell proliferation animal organ regeneration regulation of apoptotic signaling pathway T-cell receptor (TCR) signaling pathway negative regulation of cell differentiation Folate metabolism regulation of steroid metabolic process positive regulation of pri-miRNA transcription by RNA polymerase II Transcriptional Regulation by VENTX response to BMP regulation of epithelial cell migration cellular ketone metabolic process Signaling by Interleukins Measles fat cell differentiation response to steroid hormone glucose metabolic process adenylate cyclase-modulating G protein-coupled receptor signaling pathway in utero embryonic development regulation of defense response tissue morphogenesis multi-multicellular organism process cellular response to growth factor stimulus Epstein-Barr virus infection MAPK cascade regulation of inflammatory response regulation of endothelial cell migration muscle structure development regulation of neuron apoptotic process cellular response to insulin stimulus skeletal muscle organ development tissue migration osteoblast differentiation regulation of cellular response to growth factor stimulus AGE-RAGE signaling pathway in diabetic complications cellular response to molecule of bacterial origin Integrated breast cancer pathway positive regulation of cell-cell adhesion cell growth Cell cycle mesenchyme development insulin receptor signaling pathway

autophagy of mitochondrion response to estradiol p53 signaling pathway response to ketone mitochondrion disassembly positive regulation of programmed cell death Cytokine Signaling in Immune system regulation of chemotaxis skeletal system development cell migration involved in sprouting angiogenesis axon development response to decreased oxygen levels Colorectal cancer renal system process Senescence and autophagy in cancer HTLV-I infection regulation of cell activation negative regulation of proteolysis Breast cancer female pregnancy positive regulation of cellular component movement cellular response to abiotic stimulus renal tubule development response to lipopolysaccharide embryonic organ development Interleukin-4 and Interleukin-13 signaling lymphocyte proliferation positive regulation of apoptotic process epithelial cell migration positive regulation of cellular component biogenesis Chromosomal and microsatellite instability in colorectal cancer neuron death urogenital system development renal system development protein kinase B signaling Chronic myeloid leukemia purine ribonucleotide metabolic process response to growth factor negative regulation of cellular component movement response to reactive oxygen species cellular response to lipopolysaccharide embryonic morphogenesis regulation of vasculature development leukocyte differentiation skeletal muscle tissue development **RHOA GTPase cycle** rhythmic process Metabolism of carbohydrates reactive oxygen species metabolic process T cell proliferation response to mechanical stimulus tissue remodeling hexose metabolic process

response to vitamin response to nutrient levels transmembrane receptor protein serine/threonine kinase signaling pathway embryo development ending in birth or egg hatching Leishmania infection negative regulation of endothelial cell migration regulation of lipid metabolic process PI3K-Akt signaling pathway negative regulation of small molecule metabolic process embryonic epithelial tube formation Hepatitis C and hepatocellular carcinoma negative regulation of cell motility positive regulation of leukocyte activation response to transforming growth factor beta Vitamin D receptor pathway positive regulation of apoptotic signaling pathway hormone metabolic process Prolactin signaling pathway neuron apoptotic process reproductive structure development G1 to S cell cycle control monosaccharide metabolic process regulation of hormone biosynthetic process organelle disassembly secretion by cell positive regulation of vasculature development Diseases of metabolism ameboidal-type cell migration second-messenger-mediated signaling regulation of hormone metabolic process PID AP1 PATHWAY carbohydrate biosynthetic process response to nutrient response to glucocorticoid endocytosis endocrine system development response to molecule of bacterial origin epithelial cell proliferation cellular response to lipid **RHOC GTPase cycle** cellular response to hormone stimulus Hair follicle development: cytodifferentiation-part 3 of 3 DNA damage response (only ATM dependent) IL-18 signaling pathway regulation of endocytosis Thyroid cancer regulation of transmembrane receptor protein serine/threonine kinase signaling pathway transmembrane receptor protein tyrosine kinase signaling pathway response to oxygen levels viral life cycle transforming growth factor beta receptor signaling pathway positive regulation of locomotion response to alcohol

ossification regulation of DNA-templated transcription in response to stress regulation of reactive oxygen species metabolic process response to extracellular stimulus leukocyte proliferation positive regulation of reactive oxygen species metabolic process Hepatitis C cellular response to chemical stress response to corticosteroid T cell activation Adipogenesis Breast cancer pathway tube formation Herpes simplex infection negative regulation of cell migration cellular response to reactive oxygen species Hemostasis cellular response to ionizing radiation Endocrine resistance cellular response to transforming growth factor beta stimulus **RHOB GTPase cycle** negative regulation of cell cycle pri-miRNA transcription by RNA polymerase II Signaling by NOTCH kidney morphogenesis reproductive system development regulation of lipid biosynthetic process positive regulation of cell motility carbohydrate metabolic process regulation of pri-miRNA transcription by RNA polymerase II regulation of growth sprouting angiogenesis positive regulation of endocytosis epithelium migration GPCR downstream signalling regulation of viral life cycle negative regulation of cell population proliferation cellular response to biotic stimulus cellular response to hydrogen peroxide negative regulation of apoptotic signaling pathway response to peptide hormone negative regulation of cell-cell adhesion Viral carcinogenesis response to ionizing radiation chordate embryonic development Tuberculosis regulation of glucose metabolic process Platelet activation, signaling and aggregation morphogenesis of an epithelium PID REG GR PATHWAY heart morphogenesis chemotaxis regulation of leukocyte cell-cell adhesion

|    | response to bacterium   |
|----|---|
|    | cellular response to BMP stimulus   |
|    | positive regulation of cytokine production                                      |
|    | response to radiation   |
|    | small molecule biosynthetic process   |
|    | positive regulation of cell migration   |
|    | regulation of small molecule metabolic process                                  |
|    | response to insulin   |
|    | angiogenesis  |
|    | response to hypoxia   |
|    | apoptotic signaling pathway   |
|    |   |
|    | blood vessel endothelial cell migration<br>smooth muscle cell differentiation   |
|    |   |
|    | Overlap between signal transduction pathways contributing to LMNA laminopathies |
|    | Small cell lung cancer  |
|    | regulation of carbohydrate metabolic process                                    |
|    | cellular response to external stimulus<br>aging                                 |
|    | mononuclear cell proliferation  |
|    | Transcriptional regulation by RUNX2   |
|    | negative regulation of cell adhesion  |
|    | TGF-beta signaling pathway  |
|    | nephron development   |
|    |   |
|    | response to hydrogen peroxide   |
|    | regulation of cellular response to transforming growth factor beta stimulus     |
|    | heart development   |
|    | regulation of cell growth   |
|    | epithelial cell differentiation   |
|    | response to peptide   |
|    | gastrulation  |
|    | positive regulation of cell adhesion  |
|    | developmental growth  |
|    | cellular response to oxidative stress   |
|    | regulation of leukocyte activation  |
| 25 | cell junction organization  |
|    | cell-cell signaling by wnt  |
|    | regulation of canonical Wnt signaling pathway                                   |
|    | canonical Wnt signaling pathway   |
|    | cell morphogenesis involved in differentiation                                  |
|    | determination of left/right symmetry  |
|    | regulation of MAP kinase activity   |
|    | membrane protein proteolysis  |
|    | regulation of Wnt signaling pathway   |
|    | positive regulation of canonical Wnt signaling pathway                          |
|    | Wnt signaling pathway   |
|    | positive regulation of MAP kinase activity                                      |
|    | positive regulation of Wnt signaling pathway                                    |
|    | Sphingolipid signaling pathway  |
|    | positive regulation of protein binding  |
|    | regulation of cellular component size   |
|    | forebrain development   |
|    | cell surface receptor signaling pathway involved in cell-cell signaling         |
|    | positive regulation of binding  |

Glom PBMC

|     | Prostate cancer   |
|-----|---|
|     | Wnt signaling   |
|     | regulation of binding   |
|     | Head and neck squamous cell carcinoma                           |
|     | positive regulation of protein serine/threonine kinase activity |
| ~ 1 | regulation of anatomical structure size                         |
| 81  | head development  |
|     | inclusion body assembly   |
|     | anterior/posterior pattern specification                        |
|     | Cellular responses to stimuli                                   |
|     | amyloid-beta metabolic process                                  |
|     | regulation of lipid localization                                |
|     | Neutrophil degranulation  |
|     | Metabolism of lipids  |
|     | Autophagy-animal  |
|     | Butanoate metabolism  |
|     | Nuclear receptors meta-pathway                                  |
|     | response to temperature stimulus                                |
|     | lipid catabolic process   |
|     | positive regulation of protein transport                        |
|     | Hypertrophy model   |
|     | cognition   |
|     | regulation of organic acid transport                            |
|     | negative regulation of phosphorus metabolic process             |
|     | learning or memory  |
|     | regulation of protein transport<br>Transport of small molecules |
|     | PIP3 activates AKT signaling                                    |
|     | Intracellular signaling by second messengers                    |
|     | regulation of cellular amide metabolic process                  |
|     | PID HIF2PATHWAY   |
|     | positive regulation of protein secretion                        |
|     | regulation of establishment of protein localization             |
|     | negative regulation of transferase activity                     |
|     | positive regulation of catabolic process                        |
|     | import into cell  |
|     | Signaling by Receptor Tyrosine Kinases                          |
|     | positive regulation of amino acid transport                     |
|     | B cell receptor signaling pathway                               |
|     | glutamate metabolic process                                     |
|     | dicarboxylic acid transport                                     |
|     | lipid biosynthetic process                                      |
|     | macromolecule methylation                                       |
|     | Cellular responses to stress                                    |
|     | negative regulation of cysteine-type endopeptidase activity     |
|     | protein processing  |
|     | macroautophagy  |
|     | lipid modification  |
|     | regulation of proteolysis                                       |
|     | Bladder cancer  |
|     | process utilizing autophagic mechanism                          |
|     | Signaling by NTRK1 (TRKA)                                       |
|     | alcohol metabolic process                                       |
|     |   |

PBMC Tub

|     | response to amine   |
|-----|---|
|     | response to topologically incorrect protein   |
|     | regulation of protein stability   |
|     | protein maturation  |
|     | negative regulation of kinase activity  |
|     | endomembrane system organization  |
|     | positive regulation of protein catabolic process  |
|     | methylation   |
|     | Insulin signaling   |
|     | protein stabilization   |
|     | autophagy   |
|     | steroid biosynthetic process  |
|     | PTEN Regulation   |
|     | vesicle organization  |
|     | Regulation of autophagy   |
|     | negative regulation of protein phosphorylation  |
|     | regulation of protein catabolic process   |
|     | regionalization   |
|     | steroid metabolic process   |
|     | Vesicle-mediated transport  |
|     | metanephros morphogenesis   |
|     | negative regulation of autophagy  |
|     | negative regulation of cellular catabolic process   |
|     | positive regulation of lipid storage  |
|     | positive regulation of cellular catabolic process   |
|     | negative regulation of phosphate metabolic process  |
|     | Focal adhesion: PI3K-Akt-mTOR-signaling pathway   |
|     | regulation of autophagy   |
|     | negative regulation of phosphorylation  |
|     | PID CMYB PATHWAY  |
|     | astrocyte development   |
|     | Signaling by NTRKs  |
|     | import across plasma membrane   |
|     | PID P53 DOWNSTREAM PATHWAY  |
| 360 | tissue regeneration   |
|     | Extracellular matrix organization   |
|     | Development of ureteric collection system   |
|     | CD4-positive, alpha-beta T cell differentiation   |
|     | regulation of cell cycle G1/S phase transition  |
|     | positive regulation of transmembrane receptor protein serine/threonine kinase signaling pathway   |
|     | tumor necrosis factor superfamily cytokine production   |
|     | mononuclear cell migration  |
|     | cellular component assembly involved in morphogenesis<br>negative regulation of T cell activation |
|     | regulation of cytokine production involved in immune response                                     |
|     |   |
|     | histone deacetylation<br>alpha-beta T cell differentiation  |
|     | heart valve development   |
|     | Pre-NOTCH Expression and Processing   |
|     | actin filament organization   |
|     | ion homeostasis   |
|     | Central carbon metabolism in cancer   |
|     | chondrocyte differentiation   |
|     |   |

Fcgamma receptor (FCGR) dependent phagocytosis regulation of nervous system development regulation of exocytosis positive regulation of immune effector process regulation of anoikis axon guidance Hypertrophic cardiomyopathy (HCM) epithelial cell differentiation involved in kidney development regulation of lymphocyte activation extracellular matrix assembly receptor metabolic process muscle organ morphogenesis negative regulation of chemotaxis positive regulation of hemopoiesis positive regulation of calcium ion transport negative regulation of cell development cartilage development regulation of CD4-positive, alpha-beta T cell differentiation Initiation of transcription and translation elongation at the HIV-1 LTR regulation of tumor necrosis factor production mucopolysaccharide metabolic process cell activation involved in immune response cell cycle G1/S phase transition neural crest cell differentiation cellular response to radiation NABA MATRISOME ASSOCIATED positive regulation of gliogenesis positive regulation of extracellular matrix organization regulation of Notch signaling pathway positive regulation of cell development negative regulation of neuron death Cytokine-cytokine receptor interaction GPCR ligand binding cellular ion homeostasis muscle cell development oligodendrocyte differentiation negative regulation of cell growth positive regulation of transcription from RNA polymerase II promoter involved in cellular response to chemical stimulus positive regulation of leukocyte cell-cell adhesion Proteoglycans in cancer regulation of adaptive immune response phagocytosis angiogenesis involved in wound healing integrin-mediated signaling pathway negative regulation of nervous system development negative regulation of DNA metabolic process Pre-NOTCH Transcription and Translation regulation of extracellular matrix organization morphogenesis of an epithelial sheet protein deacylation bone mineralization T cell differentiation

regulation of G1/S transition of mitotic cell cycle actomyosin structure organization negative regulation of cell cycle G1/S phase transition Th17 cell differentiation regulation of cytoskeleton organization cell part morphogenesis regulation of muscle cell differentiation positive regulation of T cell activation BMP signaling pathway regulation of epithelial to mesenchymal transition endocardial cushion formation Glioblastoma signaling pathways regulation of cell shape regulation of viral genome replication external encapsulating structure organization regulation of vesicle-mediated transport regulation of T cell activation regulation of biomineralization regulation of protein-containing complex assembly regulation of CD4-positive, alpha-beta T cell activation negative regulation of growth plasma membrane bounded cell projection morphogenesis regulation of gliogenesis Hepatitis B cardiac ventricle morphogenesis negative regulation of G1/S transition of mitotic cell cycle epithelial to mesenchymal transition extracellular matrix organization blood vessel remodeling T cell differentiation involved in immune response Signaling by TGFB family members glycosaminoglycan metabolic process positive regulation of epithelial cell migration Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) negative regulation of locomotion cellular response to interferon-gamma Amoebiasis Epithelial to mesenchymal transition in colorectal cancer Osteoblast differentiation and related diseases negative regulation of biomineral tissue development Elastic fibre formation Primary focal segmental glomerulosclerosis (FSGS) cellular metal ion homeostasis cardiac ventricle development positive regulation of neuron differentiation negative regulation of immune effector process regulation of histone methylation Hippo-Merlin signaling dysregulation lymphocyte activation involved in immune response morphogenesis of a branching epithelium regulation of ossification regulation of alpha-beta T cell activation

regulation of tumor necrosis factor superfamily cytokine production cell differentiation involved in kidney development cardiac muscle tissue morphogenesis regulation of lymphocyte proliferation alpha-beta T cell activation involved in immune response negative regulation of cellular response to growth factor stimulus positive regulation of MAPK cascade regulation of vascular permeability positive regulation of cytoskeleton organization response to estrogen cardiac chamber morphogenesis CD4-positive, alpha-beta T cell activation apoptotic mitochondrial changes negative regulation of cytokine production Th1 and Th2 cell differentiation Parasite infection Ras protein signal transduction negative regulation of cell migration involved in sprouting angiogenesis biomineral tissue development biomineralization cytokine production involved in immune response positive regulation of lymphocyte activation cation homeostasis Glycosaminoglycan metabolism morphogenesis of a branching structure RAC1 GTPase cycle negative regulation of epithelial cell migration regulation of Ras protein signal transduction positive regulation of glial cell differentiation negative regulation of leukocyte cell-cell adhesion ventricular septum development mitochondrial membrane organization ECM proteoglycans positive regulation of histone modification Shigellosis gliogenesis tumor necrosis factor production protein deacetylation regulation of membrane permeability positive regulation of leukocyte proliferation regulation of alpha-beta T cell differentiation cardiac septum development CD4-positive, alpha-beta T cell differentiation involved in immune response regulation of cytosolic calcium ion concentration Thyroid hormones production and peripheral downstream signaling effects leukocyte activation involved in immune response regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains immune effector process regulation of cell migration involved in sprouting angiogenesis endocardial cushion development T-helper 1 type immune response Platelet degranulation

regulation of leukocyte differentiation negative regulation of anoikis receptor internalization Non-integrin membrane-ECM interactions vesicle fusion Cell surface interactions at the vascular wall divalent inorganic cation homeostasis developmental maturation peptidyl-tyrosine phosphorylation NABA ECM GLYCOPROTEINS cell surface receptor signaling pathway involved in heart development extracellular structure organization regulation of production of molecular mediator of immune response semi-lunar valve development Leishmania phagocytosis Response to elevated platelet cytosolic Ca2+ endocardial cushion morphogenesis cardiac septum morphogenesis inorganic ion homeostasis positive regulation of T cell proliferation positive regulation of production of molecular mediator of immune response vascular associated smooth muscle cell differentiation alpha-beta T cell activation metal ion homeostasis cell projection morphogenesis defense response to bacterium regulation of blood vessel endothelial cell migration response to interferon-alpha aminoglycan metabolic process positive regulation of protein-containing complex assembly Signaling by GPCR PID NOTCH PATHWAY Heart development Transcriptional regulation by RUNX3 cell-substrate adhesion exocytosis neural crest cell migration lymphocyte differentiation positive regulation of epithelial to mesenchymal transition Inflammatory bowel disease (IBD) Nervous system development mesenchymal cell development negative regulation of Wnt signaling pathway NABA ECM AFFILIATED extracellular matrix disassembly cellular divalent inorganic cation homeostasis heart valve morphogenesis negative regulation of striated muscle cell differentiation regulation of small GTPase mediated signal transduction adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains T-helper 1 cell differentiation cell-cell junction organization

negative regulation of lymphocyte activation negative regulation of leukocyte activation extrinsic apoptotic signaling pathway positive regulation of T cell differentiation T cell activation involved in immune response neural crest cell development adenylate cyclase-activating G protein-coupled receptor signaling pathway Notch signaling pathway (Netpath) endothelial cell proliferation negative regulation of neurogenesis miRNA regulation of DNA damage response negative regulation of cell activation positive regulation of lymphocyte differentiation cell cycle phase transition regulation of T cell proliferation regulation of actin cytoskeleton organization regulation of extrinsic apoptotic signaling pathway Factors involved in megakaryocyte development and platelet production response to interferon-gamma positive regulation of nervous system development positive regulation of stress-activated protein kinase signaling cascade stem cell differentiation regulation of cell development neuron projection morphogenesis Burn wound healing peptidyl-tyrosine modification organelle membrane fusion T-helper 2 cell differentiation regulation of mononuclear cell proliferation cellular cation homeostasis regulation of histone modification positive regulation of organelle organization calcium ion homeostasis regulation of immune effector process ear development regulation of phagocytosis response to X-ray inner ear development B cell activation positive regulation of epithelial cell proliferation anatomical structure maturation negative regulation of blood vessel endothelial cell migration negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway neuron projection guidance histone modification alpha-beta T cell differentiation involved in immune response regulation of oligodendrocyte differentiation regulation of receptor signaling pathway via STAT regulation of protein kinase B signaling positive regulation of endothelial cell migration regulation of type 2 immune response aortic valve development lymphocyte migration

positive regulation of neurogenesis skin development type 2 immune response negative regulation of biomineralization regulation of neurogenesis HIF-1 signaling pathway small GTPase mediated signal transduction regulation of leukocyte apoptotic process Ebola virus pathway in host gland morphogenesis NABA CORE MATRISOME PID LYSOPHOSPHOLIPID PATHWAY negative regulation of immune system process cardiac chamber development cell morphogenesis involved in neuron differentiation mesenchyme morphogenesis sensory organ development Lung fibrosis Diseases of glycosylation macromolecule deacylation regulation of neuron differentiation Dilated cardiomyopathy regulation of hemopoiesis response to light stimulus myotube differentiation regulation of actin filament-based process response to UV Neovascularisation processes regulation of leukocyte proliferation Basal cell carcinoma hematopoietic progenitor cell differentiation regulation of biomineral tissue development muscle tissue morphogenesis Axon guidance negative regulation of transforming growth factor beta receptor signaling pathway muscle adaptation negative regulation of mitotic cell cycle PID THROMBIN PAR1 PATHWAY regulation of mitochondrial membrane permeability MicroRNAs in cancer regulation of glial cell differentiation regulation of extracellular matrix assembly FCGR3A-mediated phagocytosis axonogenesis negative regulation of protein catabolic process cellular response to vascular endothelial growth factor stimulus cell fate commitment regulation of lymphocyte differentiation Regulation of actin dynamics for phagocytic cup formation positive regulation of cytosolic calcium ion concentration positive regulation of endothelial cell proliferation positive regulation of leukocyte differentiation aortic valve morphogenesis

|      | stem cell development   |
|------|---|
|      | regulation of protein binding                                       |
|      | positive regulation of ERK1 and ERK2 cascade                        |
|      | anoikis   |
|      | T-helper cell differentiation                                       |
|      | platelet activation   |
|      | thyroid hormone signaling pathway                                   |
|      | negative regulation of muscle cell differentiation                  |
|      | Acute viral myocarditis   |
|      | positive regulation of stress-activated MAPK cascade                |
|      | regulation of bone mineralization                                   |
|      | leukocyte apoptotic process   |
|      | Deubiquitination  |
|      | atrioventricular valve development                                  |
|      | leukocyte migration   |
|      | cellular component morphogenesis                                    |
|      | striated muscle cell differentiation                                |
|      | G alpha (q) signalling events                                       |
|      | regulation of endothelial cell proliferation                        |
|      | positive regulation of protein kinase B signaling                   |
|      | regulation of MAPK cascade  |
|      | cellular calcium ion homeostasis                                    |
|      | G1/S transition of mitotic cell cycle                               |
|      | positive regulation of blood vessel endothelial cell migration      |
|      | regulation of neural precursor cell proliferation                   |
|      | cardiac epithelial to mesenchymal transition                        |
|      | regulation of striated muscle cell differentiation                  |
| 1008 | Ovarian infertility   |
|      | regulation of amino acid import across plasma membrane              |
|      | detoxification  |
|      | Defects in cobalamin (B12) metabolism                               |
|      | Citrate cycle (TCA cycle)   |
|      | Neural crest cell migration in cancer                               |
|      | response to zinc ion  |
|      | PID AVB3 OPN PATHWAY  |
|      | energy derivation by oxidation of organic compounds                 |
|      | negative regulation of viral process                                |
|      | p53 transcriptional gene network                                    |
|      | amino sugar metabolic process                                       |
|      | MyD88 dependent cascade initiated on endosome                       |
|      | plasma lipoprotein particle organization                            |
|      | regulation of ion transport   |
|      | aspartate family amino acid metabolic process                       |
|      | Regulation of TLR by endogenous ligand                              |
|      | regulation of nuclear-transcribed mRNA poly(A) tail shortening      |
|      | deoxyribose phosphate metabolic process                             |
|      | Transmission across Chemical Synapses                               |
|      | chronic inflammatory response                                       |
|      | negative regulation of macrophage derived foam cell differentiation |
|      | Tryptophan metabolism   |
|      | glucan metabolic process  |
|      | Glutamate Neurotransmitter Release Cycle                            |
|      | carboxylic acid transmembrane transport                             |
|      |   |

Tub

supramolecular fiber organization negative regulation of ion transport cholesterol storage response to xenobiotic stimulus regulation of phospholipid metabolic process catecholamine biosynthetic process NIK/NF-kappaB signaling fatty acid biosynthetic process NF-kappaB signaling pathway regulation of transcription from RNA polymerase II promoter in response to stress Initial triggering of complement renal vesicle development alpha-amino acid metabolic process alpha-amino acid catabolic process response to salt stress regulation of biological process involved in symbiotic interaction peptide secretion SREBF and miR33 in cholesterol and lipid homeostasis organophosphate ester transport interleukin-5 production deoxyribonucleotide metabolic process PID P38 ALPHA BETA DOWNSTREAM PATHWAY alpha-amino acid biosynthetic process establishment of protein localization to extracellular region **Oxidative Stress Induced Senescence** Signaling by Nuclear Receptors Carbon metabolism positive regulation of cysteine-type endopeptidase activity involved in apoptotic process organic hydroxy compound biosynthetic process endothelium development positive regulation of sterol transport fatty acid oxidation nitrogen cycle metabolic process regulation of sterol transport regulation of endopeptidase activity MECP2 regulates neuronal receptors and channels pteridine-containing compound metabolic process negative regulation of response to wounding NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux Proximal tubule transport primary alcohol metabolic process positive regulation of neuron death ABC transporters protein-lipid complex subunit organization peptidyl-proline modification positive regulation of heart contraction cellular modified amino acid metabolic process receptor-mediated endocytosis negative regulation of mitochondrion organization oligosaccharide metabolic process regulation of cholesterol transport aspartate family amino acid catabolic process regulation of nucleotide metabolic process

cardiocyte differentiation NR1H2 and NR1H3-mediated signaling MAPK targets/Nuclear events mediated by MAP kinases phospholipid biosynthetic process positive regulation of glucose transmembrane transport regulation of ATP metabolic process glycosyl compound catabolic process regulation of system process lipid homeostasis response to arsenic-containing substance neutral lipid biosynthetic process leukocyte migration involved in inflammatory response sphingolipid metabolic process regulation of peptidase activity nucleic acid phosphodiester bond hydrolysis PID P75 NTR PATHWAY serine family amino acid catabolic process Staphylococcus aureus infection protein localization to membrane Longevity regulating pathway Thyroid stimulating hormone (TSH) signaling pathway behavior Defects in vitamin and cofactor metabolism thioester metabolic process cellular response to toxic substance TP53 Regulates Transcription of DNA Repair Genes cellular response to interleukin-4 response to cold toll-like receptor 4 signaling pathway regulation of coagulation positive regulation of response to wounding platelet-derived growth factor receptor signaling pathway positive regulation of leukocyte chemotaxis regulation of type B pancreatic cell proliferation regulation of ketone biosynthetic process positive regulation of fatty acid oxidation cellular response to lipoprotein particle stimulus ATP generation from ADP regulation of generation of precursor metabolites and energy nucleoside phosphate metabolic process PID ATF2 PATHWAY organelle fusion regulation of cellular carbohydrate metabolic process GABA biosynthesis, eukaryotes, putrescine  $\geq$  GABA Toll-like receptor signaling pathway regulation of interleukin-5 production regulation of cholesterol efflux positive regulation of blood coagulation protein dephosphorylation T cell apoptotic process maintenance of gastrointestinal epithelium catecholamine metabolic process response to organophosphorus

positive regulation of macrophage activation protein peptidyl-prolyl isomerization lipid localization Cholesterol biosynthesis folic acid transport macrophage derived foam cell differentiation cellular response to growth hormone stimulus Proximal tubule bicarbonate reclamation fatty acid catabolic process MyD88: MAL (TIRAP) cascade initiated on plasma membrane metanephric epithelium development protein localization to extracellular region Resolution of Abasic Sites (AP sites) Alanine, aspartate and glutamate metabolism protein secretion regulation of hemostasis Alanine and aspartate metabolism activation of cysteine-type endopeptidase activity involved in apoptotic process smooth muscle cell proliferation amino acid import fatty acid metabolic process regulation of secretion monosaccharide biosynthetic process NAD metabolic process Estrogen receptor pathway metanephric nephron development response to mineralocorticoid Ethanol effects on histone modifications Regulation of toll-like receptor signaling pathway high-density lipoprotein particle remodeling glycogen metabolic process circadian entrainment positive regulation of immune response release of cytochrome c from mitochondria Protein localization cholesterol homeostasis negative regulation of myeloid cell differentiation cellular response to reactive nitrogen species programmed necrotic cell death SLC-mediated transmembrane transport Transcriptional misregulation in cancer regulation of phosphatidylinositol 3-kinase activity G1/S Transition nephron epithelium morphogenesis sterol transport regulation of toll-like receptor 3 signaling pathway intracellular cholesterol transport nucleoside diphosphate metabolic process reverse cholesterol transport Toll Like Receptor 10 (TLR10) Cascade Golgi to endosome transport negative regulation of plasminogen activation protein homotetramerization

Oxysterols derived from cholesterol PID NFKAPPAB CANONICAL PATHWAY vitamin transport Interferon Signaling Citrate cycle (TCA cycle, Krebs cycle) regulation of peptide hormone secretion mesonephric epithelium development PID MYC REPRESS PATHWAY macrophage activation I-kappaB kinase/NF-kappaB signaling regulation of lipoprotein particle clearance regulation of transmembrane transport positive regulation of digestive system process positive regulation of coagulation neutral lipid metabolic process carbohydrate derivative catabolic process Metabolism of amino acids and derivatives urea metabolic process aromatic amino acid family metabolic process Gluconeogenesis, oxaloacetate ≥ fructose-6P regulation of kidney development Defective Intrinsic Pathway for Apoptosis positive regulation of branching involved in ureteric bud morphogenesis positive regulation of cellular response to transforming growth factor beta stimulus cellular response to amino acid starvation regulation of protein processing positive regulation of lipid transport tertiary alcohol metabolic process Cholesterol metabolism with Bloch and Kandutsch-Russell pathways Glycolysis/Gluconeogenesis response to cAMP regulation of epidermal cell differentiation amide transport Phenylalanine metabolism oligosaccharide catabolic process myeloid leukocyte activation TGF-beta receptor signaling acute inflammatory response Growth hormone receptor signaling Vitamin digestion and absorption glucosamine-containing compound metabolic process Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects intracellular sterol transport regulation of cholesterol storage regulation of epidermis development negative regulation of tissue remodeling NOD-like receptor signaling pathway positive regulation of peptidase activity response to endoplasmic reticulum stress vitamin transmembrane transport nucleoside phosphate biosynthetic process Influenza A PID HIF1 TFPATHWAY

Toll Like Receptor 7/8 (TLR7/8) Cascade Starch and sucrose metabolism 2-oxoglutarate metabolic process vascular process in circulatory system nucleotide phosphorylation vascular wound healing PID RB 1PATHWAY regulation of DNA-templated transcription, initiation regulation of smooth muscle cell proliferation SA G1 AND S PHASES regulation of phosphatidylcholine catabolic process glycoprotein metabolic process generation of precursor metabolites and energy amine biosynthetic process Circadian rhythm genes cholesterol metabolic process multicellular organismal homeostasis PID TAP63 PATHWAY Statin inhibition of cholesterol production L-phenylalanine catabolic process protein-containing complex remodeling Toll Like Receptor TLR1:TLR2 Cascade purine nucleoside bisphosphate metabolic process dephosphorylation Transcriptional Regulation by E2F6 positive regulation of smooth muscle cell proliferation Toll Like Receptor 2 (TLR2) Cascade Cellular response to chemical stress regulation of triglyceride biosynthetic process nucleotide-binding oligomerization domain containing signaling pathway regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay erythrose 4-phosphate/phosphoenolpyruvate family amino acid catabolic process positive regulation of lipid metabolic process Glyoxylate metabolism and glycine degradation inositol lipid-mediated signaling regulation of bone remodeling positive regulation of organic acid transport Endochondral ossification steroid hormone biosynthetic process mesonephric tubule development response to aluminum ion myeloid leukocyte migration bone resorption regulation of protein maturation pentose-phosphate shunt negative regulation of peptidase activity Pertussis zymogen activation cellular response to starvation Apoptosis glycerolipid catabolic process cellular response to extracellular stimulus Jak-STAT signaling pathway

sterol homeostasis otic vesicle development ribonucleotide metabolic process plasminogen activation labyrinthine layer development Scavenging by Class A Receptors viral transcription catechol-containing compound biosynthetic process Glucocorticoid receptor pathway regulation of cysteine-type endopeptidase activity insulin secretion response to hexose Arginine biosynthesis membrane fusion carboxylic acid biosynthetic process PID SMAD2 3NUCLEAR PATHWAY hormone secretion regulation of T cell apoptotic process Immune response to tuberculosis regulation of gonad development organic anion transport positive regulation of blood pressure FOXO-mediated transcription of oxidative stress, metabolic and neuronal genes blood vessel diameter maintenance PID RXR VDR PATHWAY N-acetylglucosamine metabolic process regulation of leukocyte chemotaxis Mitochondrial Fatty Acid Beta-Oxidation viral gene expression carbohydrate derivative transport nucleoside bisphosphate metabolic process cellular response to glucocorticoid stimulus notochord development PID FOXO PATHWAY regulation of mitochondrial fusion cellular response to glucose stimulus tricarboxylic acid metabolic process regulation of macrophage activation negative regulation of nucleotide metabolic process cellular lipid catabolic process Photodynamic therapy-induced HIF-1 survival signaling TRIF (TICAM1)-mediated TLR4 signaling Malonate semialdehyde pathway, propanoyl-CoA ≥ acetyl-CoA TNF signaling pathway cellular response to corticosteroid stimulus Urea cycle and metabolism of amino groups peptidyl-cysteine S-nitrosylation glycerolipid metabolic process cellular aldehyde metabolic process cellular response to inorganic substance blood circulation phospholipid efflux Orexin receptor pathway

cellular amino acid catabolic process defense response to symbiont sterol metabolic process NAD biosynthetic process phosphate ion transport Glutathione metabolism glucose homeostasis Peroxisomal protein import cellular response to xenobiotic stimulus cholesterol transport L-alpha-amino acid transmembrane transport positive regulation of proteolysis regulation of I-kappaB kinase/NF-kappaB signaling amino acid transport Fatty acid biosynthesis regulation of bone resorption MECP2 and associated Rett syndrome Phenylalanine and tyrosine metabolism lipoprotein metabolic process regulation of carbohydrate catabolic process Apoptosis-related network due to altered Notch3 in ovarian cancer Pyruvate metabolism regulation of peptide transport doxorubicin metabolic process carbohydrate derivative biosynthetic process polyketide metabolic process type B pancreatic cell proliferation mesoderm development negative regulation of glycolytic process positive regulation of inflammatory response positive regulation of steroid metabolic process 2'-deoxyribonucleotide metabolic process response to fatty acid circadian regulation of gene expression PPAR signaling pathway intracellular lipid transport positive regulation of cysteine-type endopeptidase activity PPARA activates gene expression renal water homeostasis medium-chain fatty acid metabolic process Complement and coagulation cascades ER-nucleus signaling pathway Nonalcoholic fatty liver disease beta-Alanine metabolism Pentose phosphate pathway plasma lipoprotein particle assembly protein-lipid complex remodeling Cyclin D associated events in G1 phenol-containing compound metabolic process Oxytocin signaling pathway TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation amino acid transmembrane transport regulation of lipid storage

FOXO-mediated transcription acylglycerol metabolic process **Dissolution of Fibrin Clot** Retinoid metabolism and transport PID TELOMERASE PATHWAY cellular nitrogen compound catabolic process acetyl-CoA metabolic process organophosphate catabolic process Mitophagy-animal cellular biogenic amine metabolic process cholesterol efflux positive regulation of I-kappaB kinase/NF-kappaB signaling vasodilation biological process involved in symbiotic interaction positive regulation of response to external stimulus negative regulation of cold-induced thermogenesis negative regulation of blood coagulation negative regulation of anion transport regulation of purine nucleotide metabolic process protein nitrosylation regulation of blood coagulation PID HNF3B PATHWAY response to osmotic stress Transcriptional regulation of white adipocyte differentiation heterocycle catabolic process NRF2 pathway Toll Like Receptor TLR6:TLR2 Cascade metanephric nephron tubule morphogenesis PID FRA PATHWAY water-soluble vitamin metabolic process monocarboxylic acid biosynthetic process pancreas development Glycolysis and gluconeogenesis epithelial cell apoptotic process cellular response to metal ion leukocyte aggregation myeloid cell differentiation organic acid transport Arachidonic acid metabolism low-density lipoprotein particle clearance cellular biogenic amine biosynthetic process Glucose metabolism regulation of anion transmembrane transport cellular response to hypoxia PID ERBB1 DOWNSTREAM PATHWAY response to monosaccharide regulation of toll-like receptor signaling pathway negative regulation of protein serine/threonine kinase activity glucose 6-phosphate metabolic process digestion fructose metabolic process SNARE interactions in vesicular transport muscle cell proliferation

**Biological oxidations** regulation of plasma lipoprotein particle levels regulation of mitochondrion organization positive regulation of lipid localization amino acid import across plasma membrane STING pathway in Kawasaki-like disease and COVID-19 Influence of laminopathies on Wnt signaling Asparagine N-linked glycosylation response to cadmium ion regulation of phosphatidylcholine metabolic process **RNA Polymerase I Transcription Initiation** G protein-coupled receptor signaling pathway involved in heart process response to testosterone PID AURORA A PATHWAY protein tetramerization nucleotide biosynthetic process regulation of systemic arterial blood pressure mediated by a chemical signal monocarboxylic acid metabolic process MyD88-independent TLR4 cascade regulation of branching involved in ureteric bud morphogenesis regulation of acute inflammatory response response to calcium ion fatty acid beta-oxidation intestinal absorption Diseases of carbohydrate metabolism leukocyte chemotaxis phosphatidylcholine catabolic process negative regulation of fibrinolysis erythrose 4-phosphate/phosphoenolpyruvate family amino acid metabolic process foam cell differentiation high-density lipoprotein particle assembly pancreatic juice secretion neural tube formation regulation of amino acid transmembrane transport secondary alcohol metabolic process C21-steroid hormone biosynthetic process PID CD40 PATHWAY positive regulation of cholesterol transport glycosphingolipid catabolic process ribose phosphate biosynthetic process response to toxic substance Propanoate metabolism Ferroptosis Regulation of lipid metabolism by PPARalpha regulation of macrophage derived foam cell differentiation Potential therapeutics for SARS Fatty acid degradation Photodynamic therapy-induced NFE2L2 (NRF2) survival signaling acyl-CoA metabolic process neurotransmitter metabolic process cell proliferation involved in kidney development pyridine-containing compound biosynthetic process

signal release regulation of hormone levels positive regulation of hemostasis purine ribonucleoside diphosphate metabolic process mesonephros development Wnt signaling pathway and pluripotency nucleobase-containing small molecule metabolic process defense response to Gram-negative bacterium RIPK1-mediated regulated necrosis growth hormone receptor signaling pathway lipid storage positive regulation of muscle tissue development Nuclear receptors in lipid metabolism and toxicity Dopaminergic synapse positive regulation of epithelial cell differentiation regulation of macroautophagy NADP metabolic process astrocyte differentiation positive regulation of hydrolase activity nucleotide metabolic process Osteoclast differentiation anion transmembrane transport regulation of cyclin-dependent protein kinase activity cellular carbohydrate catabolic process homotypic cell-cell adhesion carbohydrate homeostasis negative regulation of viral transcription amine transport NADH metabolic process negative regulation of bone remodeling regulation of digestive system process Myometrial relaxation and contraction pathways PID TOLL ENDOGENOUS PATHWAY IL-5 signaling pathway nicotinamide nucleotide biosynthetic process movement in host environment negative regulation of macroautophagy negative regulation of epithelial cell proliferation epithelial tube formation entry into host **ETS2-FOS-JUN** complex Leishmaniasis cellular amino acid biosynthetic process negative regulation of bone resorption regulation of homotypic cell-cell adhesion positive regulation of anion transport mitochondrion organization phospholipid homeostasis regulation of secretion by cell positive regulation of DNA-binding transcription factor activity toll-like receptor signaling pathway **DNA Repair** IL-4 signaling pathway

skeletal muscle cell differentiation smooth muscle tissue development lymphocyte apoptotic process negative regulation of protein kinase activity cellular response to fatty acid response to activity DNA repair pathways, full network Phagosome ribonucleoside diphosphate metabolic process Salmonella infection regulation of fatty acid metabolic process regulation of progesterone biosynthetic process autocrine signaling regulation of fibrinolysis TCA cycle and deficiency of pyruvate dehydrogenase complex (PDHc) cold-induced thermogenesis IRAK4 deficiency (TLR2/4) catechol-containing compound metabolic process modulation of process of other organism response to magnesium ion Insulin signaling pathway regulation of protein secretion c-Fos-c-Jun-SAF-1 complex positive regulation of secretion regulation of osteoblast differentiation cellular carbohydrate metabolic process negative regulation of amino acid transport G1 Phase Copper homeostasis cellular response to oxygen levels TGF-beta receptor signaling in skeletal dysplasias positive regulation of fat cell differentiation negative regulation of lipid localization SARS-CoV-2 innate immunity evasion and cell-specific immune response dicarboxylic acid metabolic process Lysine degradation protein-lipid complex assembly carbohydrate catabolic process regulation of myeloid cell differentiation toll-like receptor 3 signaling pathway positive regulation of nitric-oxide synthase activity NADPH regeneration  $O_2/CO_2$  exchange in erythrocytes Farnesoid X receptor pathway MyD88 deficiency (TLR2/4) defense response to virus glycerophospholipid metabolic process intrinsic apoptotic signaling pathway negative regulation of coagulation response to growth hormone Defective binding of RB1 mutants to E2F1, (E2F2, E2F3) L-amino acid transport

Protein digestion and absorption Vitamin B12 disorders AMPK signaling pathway serine family amino acid metabolic process tricarboxylic acid cycle phospholipid catabolic process organic cyclic compound catabolic process PID HNF3A PATHWAY regulation of lipid catabolic process Type I collagen synthesis in the context of osteogenesis imperfecta maintenance of location Unfolded Protein Response (UPR) acetyl-CoA biosynthetic process Metapathway biotransformation Phase I and II Cholesterol biosynthesis pathway ureteric bud development insulin resistance Diseases of Immune System p38MAPK cascade pyrimidine deoxyribonucleotide catabolic process deoxyribonucleotide catabolic process Eicosanoid metabolism via cytochrome P450 monooxygenases (CYP) pathway ceramide catabolic process Neuronal System hormone transport purine-containing compound metabolic process **Circadian Clock** PPAR-alpha pathway Sterol regulatory element-binding proteins (SREBP) signaling regulation of lipid kinase activity protein localization to plasma membrane purine nucleotide biosynthetic process acute-phase response anion transport Oncostatin M signaling pathway regulation of amino acid transport NADH oxidation regulation of systemic arterial blood pressure Photodynamic therapy-induced AP-1 survival signaling neuroepithelial cell differentiation bone remodeling lipid oxidation hexose biosynthetic process negative regulation of hydrolase activity RANKL/RANK signaling pathway Neuroinflammation and glutamatergic signaling N-glycan antennae elongation in the medial/trans-Golgi Amphetamine addiction RHO GTPase cycle regulation of peptide secretion coenzyme A metabolic process Programmed Cell Death

PID CD8 TCR DOWNSTREAM PATHWAY Tyrosine metabolism response to vitamin E organic hydroxy compound transport viral entry into host cell carboxylic acid catabolic process cellular response to low-density lipoprotein particle stimulus PID NFAT TFPATHWAY positive regulation of cellular respiration regulation of phospholipid catabolic process SARS-CoV Infections Plasma lipoprotein assembly, remodeling, and clearance amyloid fibril formation negative regulation of lipid storage thioester biosynthetic process Erythrocytes take up oxygen and release carbon dioxide Selenium micronutrient network regulation of blood pressure Arginine and proline metabolism cellular amino acid metabolic process interleukin-2 production positive regulation of defense response glycolytic process regulation of toll-like receptor 4 signaling pathway olefinic compound biosynthetic process organic hydroxy compound metabolic process Mitochondrial long chain fatty acid beta-oxidation Fat digestion and absorption Glycogen storage diseases positive regulation of cholesterol efflux quinone metabolic process negative regulation of T cell apoptotic process fibrinolysis cellular response to carbohydrate stimulus response to lead ion daunorubicin metabolic process Angiopoietin-like protein 8 regulatory pathway organic cation transport myoblast differentiation positive regulation of hormone metabolic process Gluconeogenesis positive regulation of transcription from RNA polymerase II promoter in response to stress negative regulation of lipid transport sulfur compound metabolic process nicotinamide nucleotide metabolic process Adipocytokine signaling pathway beta-Oxidation PID BCR 5PATHWAY pyridine nucleotide metabolic process activation of NF-kappaB-inducing kinase activity cellular glucan metabolic process positive regulation of chemotaxis Apelin signaling pathway

regulation of cysteine-type endopeptidase activity involved in apoptotic process high-density lipoprotein particle clearance phosphatidylinositol 3-kinase signaling amyloid-beta clearance PID IL6 7 PATHWAY RAF-independent MAPK1/3 activation olefinic compound metabolic process negative regulation of organic acid transport response to tumor necrosis factor T-cell antigen receptor (TCR) pathway during Staphylococcus aureus infection PDGF pathway cyclic-nucleotide-mediated signaling activation of immune response MyD88 cascade initiated on plasma membrane intracellular receptor signaling pathway cell chemotaxis Host-pathogen interaction of human coronaviruses-interferon induction response to ethanol regulation of lipid transport organic acid catabolic process Fluid shear stress and atherosclerosis protein complex oligomerization aromatic amino acid family catabolic process metanephric tubule development acyl-CoA biosynthetic process regulation of phosphatidylinositol 3-kinase signaling cellular detoxification thyroid hormone generation Toll Like Receptor 9 (TLR9) Cascade regulation of carbohydrate biosynthetic process triglyceride metabolic process Metabolism of water-soluble vitamins and cofactors Erythrocytes take up carbon dioxide and release oxygen circadian rhythm cardiac neural crest cell development involved in heart development Valine, leucine and isoleucine degradation glycosyl compound metabolic process positive regulation of fatty acid metabolic process L-phenylalanine metabolic process peptide hormone secretion pyridine nucleotide biosynthetic process regulation of plasminogen activation negative regulation of cysteine-type endopeptidase activity involved in apoptotic process PID ERA GENOMIC PATHWAY granulocyte migration acylglycerol biosynthetic process pyrimidine deoxyribonucleotide metabolic process muscle system process regulation of response to wounding pattern recognition receptor signaling pathway negative regulation of cholesterol storage RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known **Cellular Senescence** 

granulocyte chemotaxis Regulation of PTEN gene transcription Toll Like Receptor 3 (TLR3) Cascade positive regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress peptide transport positive regulation of hormone biosynthetic process plasma lipoprotein particle clearance muscle tissue development cellular response to thyroid hormone stimulus ATM signaling pathway positive regulation of triglyceride biosynthetic process Glycerolipid metabolism response to corticosterone Histidine metabolism regulation of transcription initiation from RNA polymerase II promoter cellular oxidant detoxification regulation of viral transcription response to carbohydrate regulation of fat cell differentiation regulation of interleukin-2 production response to interleukin-4 positive regulation of NF-kappaB transcription factor activity Neuroinflammation negative regulation of wound healing positive regulation of neuron apoptotic process response to glucose regulation of DNA-binding transcription factor activity cAMP signaling pathway progesterone biosynthetic process gastrulation with mouth forming second amine metabolic process androgen metabolic process regulation of tube diameter ceramide metabolic process positive regulation of intrinsic apoptotic signaling pathway Plasma lipoprotein clearance neurotransmitter catabolic process regulation of cold-induced thermogenesis PGC-1-SRp40-SRp55-SRp75 complex Endochondral ossification with skeletal dysplasias Negative regulation of MAPK pathway Activation of gene expression by SREBF (SREBP) regulation of neurotransmitter levels Creation of C4 and C2 activators PID PDGFRB PATHWAY progesterone metabolic process regulation of transcription from RNA polymerase II promoter in response to hypoxia membrane raft organization SUMOylation of transcription cofactors TP53 network Peroxisomal lipid metabolism transcription initiation from RNA polymerase II promoter

negative regulation of hemostasis Fluoropyrimidine activity response to metal ion left/right axis specification TNF-related weak inducer of apoptosis (TWEAK) signaling pathway pyrimidine nucleotide catabolic process regulation of monocyte differentiation Transport to the Golgi and subsequent modification Metabolic reprogramming in colon cancer Metabolism of vitamins and cofactors positive regulation of cold-induced thermogenesis Glyoxylate and dicarboxylate metabolism GABA metabolism (aka GHB) deoxyribose phosphate catabolic process cellular amine metabolic process monocarboxylic acid catabolic process plasma lipoprotein particle remodeling glycolipid catabolic process IL-2 signaling pathway morphogenesis of embryonic epithelium lipid transport positive regulation of wound healing body fluid secretion pronephros development purine-containing compound biosynthetic process SA B CELL RECEPTOR COMPLEXES mitophagy embryonic placenta development Complement activation purine nucleoside diphosphate metabolic process nucleoside diphosphate phosphorylation aminoglycoside antibiotic metabolic process regulation of intrinsic apoptotic signaling pathway Neural crest cell migration during development Amino acid metabolism Nuclear Receptor transcription pathway metanephric nephron tubule development Genotoxicity pathway response to purine-containing compound negative regulation of purine nucleotide metabolic process positive regulation of lipid biosynthetic process response to fructose triglyceride biosynthetic process kidney epithelium development Bile secretion regulation of epithelial cell apoptotic process cellular response to organic cyclic compound Lysine degradation, lysine  $\geq$  saccharopine  $\geq$  acetoacetyl-CoA glycerolipid biosynthetic process metanephric nephron morphogenesis Vitamin B12 metabolism digestive system process phospholipid transport

regulation of insulin secretion cellular response to decreased oxygen levels Binding and Uptake of Ligands by Scavenger Receptors nephron tubule morphogenesis Apoptosis modulation and signaling MAP kinase activation phospholipid metabolic process positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay cardiac neural crest cell differentiation involved in heart development cellular response to steroid hormone stimulus hydrogen peroxide metabolic process modified amino acid transport ribonucleoside bisphosphate metabolic process endocrine pancreas development axis specification toxin metabolic process regulation of triglyceride metabolic process regulation of cyclin-dependent protein serine/threonine kinase activity lipopolysaccharide-mediated signaling pathway T cell receptor signaling pathway negative regulation of endopeptidase activity Glycine, serine and threonine metabolism Ectoderm differentiation glycoside metabolic process regulation of glycolytic process Toll Like Receptor 5 (TLR5) Cascade Oxidative damage response biological process involved in interaction with host Interleukin-17 signaling Peroxisome Phase I-Functionalization of compounds amino sugar catabolic process **Regulated Necrosis** cellular response to osmotic stress neutral amino acid transport gluconeogenesis DNA-templated transcription, initiation temperature homeostasis cellular polysaccharide metabolic process Metabolism of amine-derived hormones Complement cascade Toll Like Receptor 4 (TLR4) Cascade cellular carbohydrate biosynthetic process cellular response to nutrient levels renal vesicle morphogenesis regulation of anion transport cellular response to hexose stimulus neural tube development **Toll-like Receptor Cascades** regulation of astrocyte differentiation sterol biosynthetic process PID PS1 PATHWAY PID IL2 1PATHWAY

response to selenium ion regulation of nucleotide biosynthetic process nucleobase-containing compound catabolic process organophosphate biosynthetic process response to electrical stimulus **RNA Polymerase III Transcription Termination** organ growth striated muscle tissue development regulation of cellular response to stress Blood clotting cascade Regulation of necroptotic cell death Epithelial cell signaling in Helicobacter pylori infection Sudden infant death syndrome (SIDS) susceptibility pathways ribose phosphate metabolic process positive regulation of small molecule metabolic process positive regulation of blood circulation IL-17 signaling pathway metanephric tubule morphogenesis Oxidative stress response Neurotransmitter release cycle positive regulation of triglyceride metabolic process positive regulation of nuclear-transcribed mRNA poly(A) tail shortening Metabolic pathway of LDL, HDL and TG, including diseases regulation of fatty acid oxidation Transcriptional Regulation by MECP2 Nuclear Events (kinase and transcription factor activation) positive regulation of cellular amine metabolic process positive regulation of transforming growth factor beta receptor signaling pathway Network map of SARS-CoV-2 signaling pathway Cobalamin (Cbl, vitamin B12) transport and metabolism Diseases associated with the TLR signaling cascade Transcriptional Regulation by TP53 carboxylic acid transport ESR-mediated signaling regulation of purine nucleotide biosynthetic process development of primary sexual characteristics Biosynthesis of amino acids regulation of wound healing organic acid biosynthetic process Modulators of TCR signaling and T cell activation Complement system aromatic compound catabolic process purine nucleotide metabolic process cellular response to tumor necrosis factor NGF-stimulated transcription adaptive thermogenesis ADP metabolic process negative regulation of ATP metabolic process cellular response to salt stress phosphatidylinositol-mediated signaling complement activation regulation of cholesterol metabolic process positive regulation of endopeptidase activity

|      |     | protein homooligomerization   |
|------|-----|---|
|      |     | cGMP-mediated signaling   |
|      |     | Fatty acid metabolism   |
|      |     | gonad development   |
|      |     | Mitotic G1 phase and G1/S transition                                  |
|      |     | regulation of tube size   |
|      |     | foxo signaling pathway  |
|      |     | left/right pattern formation  |
|      |     | secondary metabolic process   |
|      |     | glutamine family amino acid metabolic process                         |
|      |     | pyridine-containing compound metabolic process                        |
|      |     | electron transport chain  |
|      |     | Galanin receptor pathway  |
|      |     | response to starvation  |
|      |     | circulatory system process  |
|      |     | dopamine metabolic process  |
|      |     | negative regulation of intracellular signal transduction              |
|      |     | small molecule catabolic process                                      |
|      |     | cellular response to monosaccharide stimulus                          |
|      |     | metanephric nephron epithelium development                            |
|      |     | organic acid transmembrane transport                                  |
|      |     | glycine metabolic process   |
|      |     | sulfur compound transport   |
|      |     |   |
|      |     | cellular glucose homeostasis  |
|      |     | positive regulation of steroid biosynthetic process                   |
|      |     | nephron morphogenesis   |
|      |     | Antiviral and anti-inflammatory effects of Nrf2 on SARS-CoV-2 pathway |
|      |     | cellular respiration  |
|      |     | vitamin metabolic process   |
|      |     | animal organ formation  |
|      |     | Transcription factor regulation in adipogenesis                       |
|      |     | Interferon alpha/beta signaling                                       |
| PBMC | 252 | autophagosome assembly  |
|      |     | Adaptive Immune System  |
|      |     | production of miRNAs involved in gene silencing by miRNA              |
|      |     | Macroautophagy  |
|      |     | sphingoid metabolic process   |
|      |     | spermatogenesis   |
|      |     | regulation of receptor recycling                                      |
|      |     | protein polyubiquitination  |
|      |     | regulation of translation   |
|      |     | amyloid-beta formation  |
|      |     | Inclusion body myositis   |
|      |     | DNA repair  |
|      |     | dorsal/ventral pattern formation                                      |
|      |     | Malignant pleural mesothelioma  |
|      |     | regulation of protein ubiquitination                                  |
|      |     | Membrane Trafficking  |
|      |     | Alzheimer's disease   |
|      |     | positive regulation of telomerase activity                            |
|      |     |   |
|      |     | IncRNA in canonical Wht signaling and colorectal cancer               |
|      |     | Interleukin-1 induced activation of NF-KB                             |
|      |     | Autophagy   |

protein folding MAPK family signaling cascades Cellular response to starvation protein localization to nucleus regulation of JUN kinase activity establishment of vesicle localization Alzheimer's disease and miRNA effects sphingosine metabolic process Ciliary landscape negative regulation of translation Nuclear Envelope Breakdown peptidyl-serine modification regulation of GTPase activity male meiotic nuclear division T41 mutants of beta-catenin aren't phosphorylated regulation of embryonic development RNA polymerase II preinitiation complex assembly H19 action Rb-E2F1 signaling and CDK-Beta-catenin activity Golgi organization regulation of vascular endothelial growth factor receptor signaling pathway negative regulation of protein-containing complex disassembly Ca2+ pathway nucleobase-containing compound transport VEGFA-VEGFR2 Pathway pigment granule transport S33 mutants of beta-catenin aren't phosphorylated T cell receptor and co-stimulatory signaling WNT SIGNALING Signaling by APC mutants Disassembly of the destruction complex and recruitment of AXIN to the membrane mRNA processing regulation of DNA metabolic process cell junction assembly Canonical and non-canonical Notch signaling Ion transport by P-type ATPases response to heat mTORC1-mediated signalling protein K48-linked ubiquitination ncRNA metabolic process Amino acids regulate mTORC1 melanosome transport amyloid precursor protein catabolic process mRNA metabolic process modification-dependent protein catabolic process cellular response to leukemia inhibitory factor regulation of chromosome organization Protein processing in endoplasmic reticulum Signaling by AMER1 mutants Fc epsilon receptor (FCERI) signaling positive regulation of transmembrane transport pigment granule localization mRNA splicing, via spliceosome regulation of mitotic cell cycle

peptidyl-serine phosphorylation male gamete generation protein refolding amyloid precursor protein metabolic process Antigen processing: Ubiquitination & Proteasome degradation Factors and pathways affecting insulin-like growth factor (IGF1)-Akt signaling Cohesin complex-Cornelia de Lange syndrome positive regulation of protein localization to nucleus skeletal system morphogenesis positive regulation of nucleocytoplasmic transport meiotic cell cycle determination of bilateral symmetry positive regulation of cell cycle PID FAK PATHWAY S37 mutants of beta-catenin aren't phosphorylated phospholipid dephosphorylation vacuole organization diol metabolic process import into nucleus regulation of cellular protein localization positive regulation of DNA metabolic process Signaling by GSK3beta mutants response to leukemia inhibitory factor Degradation of AXIN Gastric cancer network 2 PID MET PATHWAY transport across blood-brain barrier COPII-coated vesicle budding negative regulation of transport fibroblast apoptotic process regulation of nuclear division MAPK1/MAPK3 signaling **RNA** splicing regulation of RNA splicing Regulation of Wnt/B-catenin signaling by small molecule compounds alcohol biosynthetic process modulation of chemical synaptic transmission regulation of trans-synaptic signaling ubiquitin-dependent protein catabolic process Energy dependent regulation of mTOR by LKB1-AMPK nucleus organization response to unfolded protein APC truncation mutants have impaired AXIN binding post-embryonic development regulation of neuron projection regeneration glial cell development specification of symmetry positive regulation of amyloid precursor protein catabolic process **RHOQ GTPase cycle** metanephros development Cell Cycle limbic system development production of small RNA involved in gene silencing by RNA

**RHOJ GTPase cycle** ncRNA processing proteolysis involved in cellular protein catabolic process postsynaptic modulation of chemical synaptic transmission regulation of mitochondrial gene expression Extracellular vesicle-mediated signaling in recipient cells vesicle localization brain development Cell Cycle, Mitotic melanosome localization G2/M Transition segmentation Diseases of signal transduction by growth factor receptors and second messengers MTOR signalling nuclear membrane organization positive regulation of telomere maintenance via telomerase Golgi vesicle transport regulation of mitochondrial translation negative regulation of defense response Class I MHC mediated antigen processing & presentation Metabolism of RNA heterotypic cell-cell adhesion Signaling by the B Cell Receptor (BCR) L-glutamate import phosphatidylinositol dephosphorylation telencephalon development DARPP-32 events mitotic cell cycle phase transition C-type lectin receptors (CLRs) mitotic cell cycle checkpoint signaling ncRNAs involved in Wnt signaling in hepatocellular carcinoma cellular response to DNA damage stimulus regulation of intracellular transport EPH-ephrin mediated repulsion of cells regulation of mRNA metabolic process G protein signaling pathways S45 mutants of beta-catenin aren't phosphorylated PID BETA CATENIN NUC PATHWAY PCP/CE pathway regulation of protein import establishment of pigment granule localization chorion development L-glutamate transmembrane transport mTOR signaling pathway diol biosynthetic process Beta-catenin independent WNT signaling RAF/MAP kinase cascade PID IL8 CXCR2 PATHWAY regulation of protein import into nucleus PIWI-interacting RNA (piRNA) biogenesis Long-term depression dsRNA processing establishment of protein localization to organelle

Signaling by AXIN mutants receptor recycling regulation of inclusion body assembly PTK6 Regulates RHO GTPases, RAS GTPase and MAP kinases extraembryonic membrane development response to amphetamine Regulated proteolysis of p75NTR negative regulation of organelle organization positive regulation of protein import into nucleus RNA splicing, via transesterification reactions with bulged adenosine as nucleophile RNA splicing, via transesterification reactions Downstream signaling events of B Cell Receptor (BCR) Truncations of AMER1 destabilize the destruction complex positive regulation of protein import acidic amino acid transport PID WNT CANONICAL PATHWAY Kisspeptin/kisspeptin receptor system in the ovary Synthesis of PIPs at the early endosome membrane HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand positive regulation of DNA biosynthetic process gamete generation vesicle-mediated transport to the plasma membrane cellular pigmentation spinal cord development L-glutamate import across plasma membrane multivesicular body sorting pathway Ubiquitin mediated proteolysis PI Metabolism MET in type 1 papillary renal cell carcinoma Chaperone Mediated Autophagy protein import into nucleus negative regulation of lipid biosynthetic process Degradation of beta-catenin by the destruction complex Mesodermal commitment pathway nuclear transport Signaling by WNT Renal cell carcinoma Signaling by EGFR in Cancer proteasomal protein catabolic process negative regulation of cellular amide metabolic process astrocyte activation establishment of melanosome localization Wnt/beta-catenin signaling pathway in leukemia regulation of proteolysis involved in cellular protein catabolic process Mitotic G2-G2/M phases PID MYC ACTIV PATHWAY somitogenesis hyaluronan metabolic process vesicle budding from membrane Mitochondrial gene expression Signaling by CTNNB1 phospho-site mutants PID BETA CATENIN DEG PATHWAY PID ECADHERIN KERATINOCYTE PATHWAY

PID ANGIOPOIETIN RECEPTOR PATHWAY nucleocytoplasmic transport Rab regulation of trafficking EGFR tyrosine kinase inhibitor resistance synaptic vesicle cycle AXIN missense mutants destabilize the destruction complex modification-dependent macromolecule catabolic process protein-containing complex disassembly positive regulation of establishment of protein localization protein import membrane protein ectodomain proteolysis Sphingolipid pathway Signaling by WNT in cancer TCF dependent signaling in response to WNT regulation of transcription elongation from RNA polymerase II promoter vascular transport vesicle cargo loading Beta-catenin phosphorylation cascade regulation of cellular protein catabolic process