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# Bioinformatics enriched analysis for identification of novel candidate genes and pathways for cystic fibrosis

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## Abstract

Cystic Fibrosis, an inherited disorder, is primarily found in white American society. It arises due to alteration in the CFTR gene. Several pieces of evidence insight oxidative stress as one of the primary reasons behind this disorder. Thus, with the aim of finding the physiopathology of this disorder and its association with oxidative stress, a comparative transcriptomic study of CF with control was performed. A transcriptomic dataset (GSE ID: 39843) was accessed through Gene Expression Omnibus. Differentially Expressed Genes were enriched, and novel DEGs were sorted out. A protein-protein interaction network was constructed, followed by Gene Ontology and KEGG pathway enrichment. Our analysis revealed a total of 704 DEGs with 556 up-regulated and 148 downregulated genes. Comparison with the reported gene list (obtained through OMIM and Gene Cards) lead to the identification of 156 novel DEGs (125 up-regulated and 31 downregulated). PPI network constructed for the respective DEGs consists of 233 nodes and 1304 edges. POLR2D,CUL1,RAN,MANF,LNX1,GMNN, and STOM were identified as hub nodes through networking. GO and KEGG enrichment study identifies some major significant processes and pathways like Pyrimidine metabolism, Glutathione metabolism, Pentose phosphate pathway, Ubiquitin mediated proteolysis. ABC transporters up-regulated DEGs while cytokine receptor, Cell adhesion molecules, tight junction, leukocyte transendothelial for down-regulated DEGs. POLR2D,CUL1,RAN,MANF,LNX1,GMNN, and STOM genes may represent novel candidate biomarkers related to CF disease, as also revealed through our present findings. The current work reveals a new outlook to detect potential targets behind the cause of CF occurrence.

**Abstract**

**Background:** Cystic Fibrosis, an inherited disorder, is mainly found in white American society. It arises due to alteration in the CFTR gene. Several pieces of evidence insight oxidative stress as one of the primary reasons behind this disorder. Thus, with the aim of finding the physiopathology of this disorder and its association with oxidative stress, a comparative transcriptomic study of CF with control was performed.

**Methods:** A transcriptomic dataset (GSE ID: 39843) was accessed through Gene Expression Omnibus. Differentially Expressed Genes were enriched, and novel DEGs were sorted out. A protein-protein interaction network was constructed, followed by Gene Ontology and KEGG pathway enrichment.

**Results:**Our analysis revealed a total of 704 DEGs with 556 up-regulated and 148 downregulated genes. Comparison with the reported gene list (obtained through OMIM and Gene Cards) lead to the identification of 156 novel DEGs (125 up-regulated and 31 downregulated). PPI network constructed for the respective DEGs consists of 233 nodes and 1304 edges. POLR2D,CUL1,RAN,MANF,LNX1,GMNN, and STOM were identified

as hub nodes through networking. GO and KEGG enrichment study identifies some major significant processes and pathways like Pyrimidine metabolism, Glutathione metabolism, Pentose phosphate pathway, Ubiquitin mediated proteolysis, and ABC-transporters for up-regulated DEGs while cytokine receptor, Cell adhesion molecules, tight junction, leukocyte transendothelial for down-regulated DEGs.

**Conclusions:**

POLR2D,CUL1,RAN,MANF,LNX1,GMNN, and STOM genes may represent novel candidate biomarkers related to CF disease, as also revealed through our present findings. The current work reveals a new outlook to detect potential targets behind the cause of CF occurrence.

INTRODUCTION

Cystic Fibrosis (CF), an autosomal recessive disorder, is a disease associated mainly with the respiratory system. It iscommonly found in Caucasians [1]. It occurs due to mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTRis situated on the long arm of chromosome 7 and encodes a transmembrane protein (CFTR), an epithelial ion channel that plays an essential role in regulating epithelial ion and water transport and fluid homeostasis [2]. Moreover, being a lethal genetic disease, it is related to shortening (40-50 years) of expected life span[3]. Symptoms like respiratory and pulmonary infection are often at the forefront of the clinical scenario and cause morbidity [4]. Also, earlier steatorrhea persists during this disorder and is dominated upon the beginning of digestive problems [5].

Many facts reveal that oxidative stress is a characteristic of CF [6]and may involve in Nitric Oxide bioavailability reduction and followed by endothelial abnormalities [7]. The variation between the production of free radicals and radicals neutralization via antioxidants occurs due to constant, elevated immune stimulation [8] and, together with diet deficiency and exogenic antioxidants malabsorption [9]. Though antioxidants administration orally has been performed to decrease oxidative stress and vascular function improvement temporarily was found [10];however, the oxidative stress role in CF patients with vascular abnormalities is still undetermined [6].

Thus, to find the physiopathology of this disorder and its association with oxidative stress, a comparative study of CF and non CF was performed. Since fewer genes have been reported with CF diseases' pathogenicity, our aim was to find more novel genes and reveal the overall molecular mechanism via in silico method using various bioinformatics tools. The main aim behind the current study is screening potent candidate genes of CF disorder. In this study, the gene expression profile (ID: GSE39843) analysis was performed to find differential gene expressions (DEGs). The Protein-Protein Interactions (PPI ) network based on the combined scores was constructed. Moreover, a Functional and gene enrichment-based study was also carried out.

**2 Materials and methods**

2.1 Samples retrieval

Raw gene expression profile (GSE ID GSE39843) was acquired from the GEO NCBI database. The raw dataset which was retrieved for the expression profiling was based on CF air duct cell lines provided with oxidative stress condition. The array profile consists of twelve samples and one platform (GPL570[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array) [11]. Several in silico tools were used for the present work to find the DEGs of CF samples and downstream processing of DEGs.

2.2 Pre-processing of samples

Using Benjamini and Hochberg algorithm, pre-processing of raw expression profile was performed to compute the adjusted p-value. Also, eluding force normalization and Limma precision weights log transformation was applied to the expression profile[12]. The significant cutoff level was adjusted to 0.05. Probe level conversion to gene-level symbols was also accomplished using GEO2R.

2.3 DEGs retrieval

The retrieval of DEGs from the present dataset was carried out depending on the parameters with adjustable p values <0.05 and log fold change values >0.1 for overexpressed and <0.1 for under-expressed genes GEO2R.Visualization of the selected DEGs, highlighting overexpressed and underexpressed genes via volcano plot, log2 fold variation versus log2 average gene expression values through mean difference (MD) graph, and selected genes that coincide among various available contrasts through Venn Diagram was implemented. Construction of all these graphs through GEO2R with the available LIMMA package[13].

2.4 PPI network and subnetwork formation

Through the online tool STRING v 10.5 (https://www.string-db.org/), functional relation among proteins were found [14]. This software computes the combined scores within gene pairs for protein-protein interactions. So for the current study, DEGs selected lists were provided to the software, and a combined score > 0.4 was applied as a parameter for this analysis. Then Cytoscape v 3.2.1 (http://www.cytoscape.org) and in silico software package were used to construct numerous network and sub-networks [15]. Degree and edge betweenness criteria were initiated for the construction of networks.

2.5 GO and KEGG pathway interpretation

DAVID (Database for Annotation, Visualisation, And Integrated Discovery) (https://david.abcc.ncifcrf.gov) server involves an extensive list of genes dataset to merge reasonable sets of functional annotation [16]. Gene Ontology (GO) analysis reveals cellular component (CC),molecular function (MF), and biological process (BP) through DAVID v 6.8. Depending on the hypergeometric distribution, DAVID constructs complete gene datasets with related or nearby functions.

**3. RESULTS**

3.1 DEGs enrichment for CF.

Using GEO2R, normalization of gene expression dataset was performed. Box plot shows that all data have median centred value (Fig. 1A). Uniform Manifold Approximation and Projection shows the distribution of the samples and the number of nearest neighbors used in the calculation i.e. nbrs=5 (Fig. 1B). DEGs screening identified a total of 704 DEGs with 556 up-regulated and 148 downregulated genes were found (Supplementary file 1). For determining DEGs, p-value < 0.05 and | $\log_2$ FC > 0.1were used as parameters. On the basis of mean values of average gene expression, DEGs were screened. Furthermore, comparisons of DEGs with gene listobtained from OMIM and Gene Cards leads to the identification of a total of 156 reported DEGs (125 up-regulated and 31 down-regulated) while548 novel DEGS (117 up-regulated and 431 down-regulated)(Fig. 2A,2B). Construction of Volcano plot and MD graph of determined DEGs with over and under-expressed genes were visualized (Fig. 2C, 2D).

3.2 Construction of Principal Component and Heatmap plot.

Analysis of Principal Component for CF through scatter graph represents a total 58.9% variance on x-axis equivalent to principal component 1, and 11.2% variance on the y axis equivalent to principal component 2 (Fig. 3A). Representation of heat map through numerical differences for DEGs through data matrix with the colorful prototype was also produced (Fig. 3B).

3.3. Creation of PPI network

All DEGs were used to create a protein-protein interaction network (Fig. 4A). A separate PPI network was constructed for DEGs with the combined score greater than 0.9 generated by STRING (Fig. 4B). PPI network constructed for the respective DEGs consists of 233 nodes and 1304 edges. Blue and Red colors constitute the down and up-regulated genes of the generated DEGs. Degree and edge betweenness were implemented for hub node creation. Genes involved in forming hub nodes were UBC (Ubiquitin C), POLR2D(RNA Polymerase II Subunit D), CUL1(Cullin 1), HSP90( Heat Shock Protein 90), RAN (Ras-related nuclear protein), PLAUR (Plasminogen Activator Urokinase Receptor ), MANF (Mesencephalic Astrocyte Derived Neurotrophic Factor) as up-regulated genes while NOTCH1(NOTCH Receptor 1), STAT3(Signal Transducer And Activator Of Transcription 3), LNX1(Ligand Of Numb-Protein X 1), GMNN (Geminin DNA Replication Inhibitor), ADAM10(ADAM Metallopeptidase Domain 10) and, STOM (Stomatin) as downregulated genes association of these hub nodes with genes of recognized disease and being novel were considered as potential candidate genes for CF.

Some DEGs established five separate networks from the major network, which were considered sub-networks (Fig. 4C). The first sub-network consists of 6 nodes and 12 edges (Fig. 4C1). The second subnetwork consists of 4 nodes and six edges (Fig. 4C2). The third subnetwork consists of 4 nodes and eight edges (Fig. 4C3). The fourth subnetwork consists of 9 nodes and 72 edges (Fig. 4C4). Furthermore, the fifth subnetwork consists of 5 nodes and 20 edges (Fig. 4C5). Depending on the degree and combined scores, a total of ten DEGs were screened out as novel biomarkers.

3.4. Construction of GO Enrichment and KEGG pathways.

In the network, all the DEGs were intensified for their processes, component, and functions. The present study reveals that most overexpressed DEGs with significant values ($p<0.05$) regulates the processes of induction of apoptosis, cell cycle, response to oxidative stress, negative regulation of cellular protein, positive regulation of protein ubiquitination, positive regulation of ligase activity, cell redox homeostasis, and proteasomal protein catabolic process (Fig. 5A). Also, under-expressed DEGs with significant values ($p<0.05$) regulates positive regulation of epidermis development, positive regulation of apoptosis, somatic stem cell division, regulation of cell growth, cell junction, negative regulation of cell adhesion, response to hormone stimulus, regulation of secretion, regulation of cell growth, calcium-independent cell cell adhesion processes (Fig. 5B).
Through KEGG enrichment study, it was found that Pyrimidine metabolism, Glutathione metabolism, Pentose phosphate pathway, Ubiquitin mediated proteolysis, ABC transporters for up-regulated genes and cytokine receptor, Cell adhesion molecules, tight junction, leukocyte transendothelial for down-regulated genes were the main pathways for this DEGs enrichment (Fig 5C).

**Discussion**

Cystic Fibrosis is a progressive genetic disorder that leads to frequent infections in the lungs. Despite the increasing CF occurrence, there is still a lack of suitable therapeutic targets [5]. In the current study, we have applied numerous bioinformatics tools to find CF's mechanism at the molecular level. In the present in silico approach, UBC, POLR2D, CUL1, HSP90, RAN, PLAUR, MANF, NOTCH1, STAT3, LNX1, GMNN, ADAM10, and STOM were found as novel DEGs in the samples of CF disorder with oxidative stress.
The UBC gene depicts the Ubiquitin gene. It encodes proteins that are involved in DNA repair and cell cycle regulation. These protein impairments lead to CF. U.Griesenbach et al. revealed through their studies the crucial role of the UBC gene in chronic lung disorders, cancer, and CF and related genetic therapy[17]. Since few studies disclosed UBC gene association with CF, thus provides a potent target for CF.
POLR2D genes are responsible for RNA pol II formation that induces Eukaryotic mRNA synthesis. R Marcotte et al. suggested through their work mutational POLR2D role in breast cancer progression [18]. However, to date, the POLR2D gene role was not found in CF, but its role in the transcription process, as shown in our present work, may prove to be a novel candidate for CF treatment.
CUL1 gene mediates its role with ubiquitination, cell cycle progression, and an important role in the WNT signaling pathway. Ye-Fei Huang et al. through gene expression profiling CUL1 overexpression in breast carcinoma[19]. Lan Chen et al. investigated through their studies overexpression of CUL1 in the proliferation of melanoma cells [20]. Though CUL1 gene association with CF was not found until now, its association with the cell cycle process and ubiquitination revealed through our work may prove to be a novel target for CF.
Kaisheng Liu et al. revealed the involvement of the HSP90 gene with CFTR membrane and regulating phosphorylation of the AKT pathway and its crucial role in colorectal carcinoma [21]. RT Youker et al. disclosed the onset of CF due to deletion of Phe 508 in the Hsp90 chaperone [22]. Thus, Hsp90 relation with CF unveils an essential marker for therapeutics.
Ran gene-encoded protein associated with DNA synthesis, cell cycle progression, and induces microtubules nucleation. Zied Boudhraa et al. reported that Ran GTPase tumorigenic role in cancer [23]. However, the Ran gene's role in CF is still unknown, but its involvement in a mitotic cell cycle as represented in our work may serve as a novel biomarker for CF disorder.
PLAUR gene encodes a urokinase protein that promotes the formation of plasmin. S Shetty et al., through DEGs analysis, disclosed the PLAUR gene as one of the overexpressed genes of urokinase receptors in fibroblast [24]. Sheila et al. investigated through their studies PLAUR polymorphism with lung dysfunction and asthma [25]. Varrie Ogilvie et al. PLAUR gene plays a crucial role in the regulation of TGF beta in tissue repairment and fibrosis [26]. C E Stewart et al. suggested PLAUR gene polymorphism and its involvement in CF [27], which indicates a promising candidate for curing CF.
MANF gene up-regulation leads to ER stress. Y Kim et al. disclosed through their work that overexpression of the MANF gene leads to genetic skeletal disorders [28]. Apostolou A et al. revealed MANF gene dysfunction inhibits cell proliferation and ER stress leading to cellular death [29]. Although MANF gene association with CF disease was not found to date, its involvement with cell proliferation which is also proved through our work, may provide a potent key for treatment.
NOTCH1 gene encodes a transmembrane protein that regulates adjacent cell interaction and is involved in the survival and proliferation of cells. According to Biao Hu et al., NOTCH1 is involved in signaling pathways of

airways fibrosis[30]. Y C Wang et al. concluded through their work the overexpression of the NOTCH1 gene in the pulmonary duct leading to fibrosis[31]. However, some works suggested the role of the NOTCH1 gene in promoting CF, which may prove to be one of the biomarkers of CF disease.

STAT3 gene in the phosphorylated form is found involved in cellular growth and apoptotic-related pathways. M. Pedroza et al. found through their studies phosphorylated STAT3 elevated levels in lung fibroids [32]. However, D. Chakraborty et al. suggested STAT3 gene association with fibroblast formation and any change leads to tissue fibrosis [33].AC Tang et al. indicated that STAT3 increased level leads to ER stress, causing inflammation in the airways, leading to CF [34] since the STAT3 gene association with CF was represented through some works, which may provide a clue for CF treatment.

LNX1 gene encodes a proteasomal protein involved in degradation and ubiquitination. RPark et al. revealed LNX1 gene downregulates stable p53, promoting tumorigenesis[35]. S.Baisiwala et al. indicated the role of LNX1 gene modulating NOTCH1, which leads to glioma stem cell expansion [36]. Although the LNX1 gene role in CF is still unknown, its involvement in proteasomal degradation, as also suggested through our work, can provide a novel candidate for CF disorder.

GMNN gene is found in regulation of cell cycle, especially in metaphase to the anaphase transition phase. Christelle de Renty et al. found GMNN gene role in the replication process and DNA ablation [37]. Also, P.P Kushwaha et al. suggested through their work GMNN gene association with developmental process and cancer pathobiology [38]. M R Salbat et al. investigated GMNN overexpression in pancreatic carcinoma [39]. However, CF's GMNN gene role is unknown to date, but its involvement in cell cycle regulation may prove to be a novel candidate for CF treatment.

ADAM 10 gene encodes a protein involved in proteasomal degradation and is found involved in the cell adhesion process. P R Manzine et al. revealed ADAM 10 as a crucial player in proteolytic processing and cell adhesion in Alzheimer's disease [40]. M Muller et al. found that ADAM10 protein cleaves Ephrin B2, leading to fibrosis in pulmonary tracts[41]. Thus, ADAM10's relation with CF through some studies has proven to be potential CF disease targets.

The STOM gene encodes proteins that are found integrated into the RBC membrane and regulates ion channels. M T Landi et al. proposed through their work the overexpression of STOM gene in lung carcinoma [42]. M Nikpay et al. found the STOM gene's crucial role in coronary artery diseases [43]. Although STOM gene relation with CF is unknown until now, their function in ion channel regulation, which was also indicated through our current study, may be assigned as a novel lead for CF diseases.

In conclusion, POLR2D, CUL1, RAN, MANF, LNX1, GMNN, and STOM genes may represent novel candidate biomarkers related to CF disease as these genes have been found to play an essential role in apoptosis, cell cycle, response to oxidative stress. The current work reveals a new outlook to detect potential targets behind the cause of CF occurrence and the role of oxidative stress in the progression of the disease. However, in vivo and in vitro works are needed to be carried out for validation of results.

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**Figure Legends:**

**Fig.1:Microarray data normalization for GSE39843. A. Box plot. It shows that all datasets have median centered values distribution of values data for the selected samples. The lines in the box are coincident, indicating that these chips have been highly normalized. B. UMAP plot. It shows the distribution of data.**

**Fig. 2: Reported and novel DEGs. A. Venn diagram: All DEGs were compared with reported gene list obtained from the Gene Cards and OMIM to reveal the novel DEGs. B. Out of total DEGs identified, 548 genes were found to be novel while 156 were found to be reported. C. MD plot: Total identified DEGs were visualised through C. MD plot and D. Volcano plot.**

**Fig. 3: Principal component analysis and Heat map of DEGs. A. PCA plot shows a scatter plot with principal component 1 (x-axis) and principal component 2 (y-axis) showing total variance of ---% and ---% in ULM. ClustVis tool was used for this. B. Heat map showing the average gene expression of differentially expressed genes (DEGs) between cystic fibrosis cells under stress (CF_DMNQ) and normal cells with stress (nonCF_DMNQ). The blue to orange gradation represents the gene expression values change from small to large. ClustVis tool was used to draw heat map.**

**Fig. 4 : Protein-Protein interaction (PPI) of differentially expressed genes. A. A PPI network showing the interaction for all DEGs were constructed. B. DEGs with combined score > 0.9 were used to construct a separate network showing hub nodes based on degree and edge betweenness. C. Some of the DEGs were forming separate network from the main-network and extracted to create five sub-networks (C1, C2, C3, C4, C5). *Red Circle and Red Diamond* up-regulated genes, *Blue Circle and Blue Diamond* down-regulated genes.*Lines* the correlation between genes *Thickness of lines (edges)* is proportional to the combined score. Cytoscape v 3.2.1 was used to construct the network.**

**Fig. 5:Gene Ontology and KEGG Pathway analysis for DEGs in PPI network. Bar graph showing significant processes, function and cellular component enriched in diabetic mothers for A. up-regulated genes and B. Down-regulated genes. C. Pathway enrichment for DEGs lead to identification of 4 significant pathways. DAVID v 6.7 was used for annotation.**

**Table 1: GO enrichment for UP-regulated DEGs**

| Category | Term | P Value |
|---|---|---|
| GOTERM_BP_FAT | GO:0051351~positive regulation of ligase activity | 4.48E-07 |
| GOTERM_BP_FAT | GO:0010498~proteasomal protein catabolic process | 4.95E-07 |
| GOTERM_BP_FAT | GO:0031398~positive regulation of protein ubiquitination | 1.33E-05 |
| GOTERM_BP_FAT | GO:0045454~cell redox homeostasis | 4.03E-05 |
| GOTERM_BP_FAT | GO:0051603~proteolysis involved in cellular protein catabolic process | 6.40E-05 |
| GOTERM_BP_FAT | GO:0000278~mitotic cell cycle | 3.80E-04 |
| GOTERM_BP_FAT | GO:0032269~negative regulation of cellular protein metabolic process | 0.001063 |
| GOTERM_BP_FAT | GO:0022402~cell cycle process | 0.004747 |
| GOTERM_BP_FAT | GO:0006979~response to oxidative stress | 0.012397 |
| GOTERM_BP_FAT | GO:0007049~cell cycle | 0.025419 |

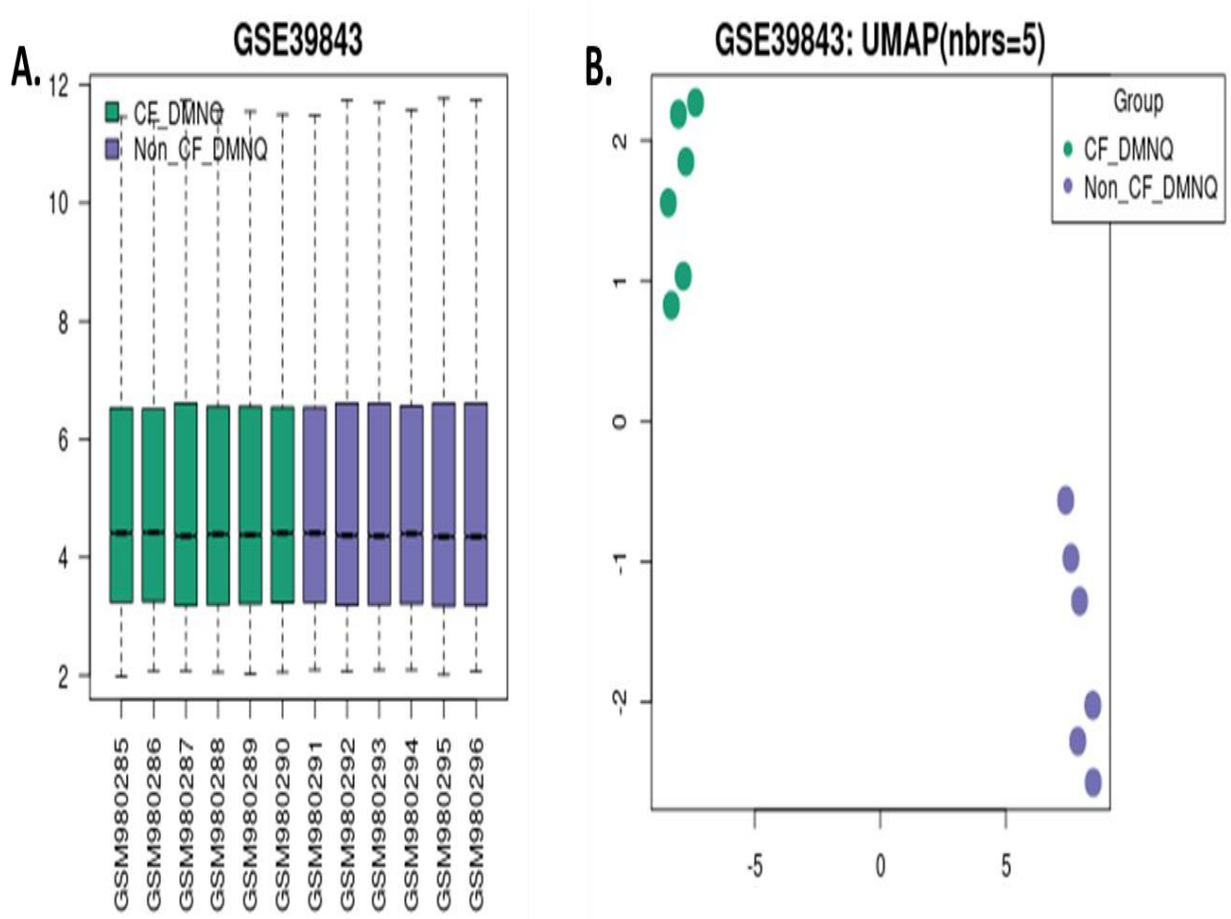
| | | |
|---|---|---|
| GOTERM_BP_FAT | GO:0006917~induction of apoptosis | 0.047836 |
| GOTERM_MF_FAT | GO:0008536~Ran GTPase binding | 8.14E-06 |
| GOTERM_MF_FAT | GO:0016667~oxidoreductase activity, acting on sulfur group of donors | 5.93E-05 |
| GOTERM_MF_FAT | GO:0016209~antioxidant activity | 2.03E-04 |
| GOTERM_MF_FAT | GO:0031072~heat shock protein binding | 6.82E-04 |
| GOTERM_MF_FAT | GO:0009055~electron carrier activity | 0.00207 |
| GOTERM_MF_FAT | GO:0015171~amino acid transmembrane transporter activity | 0.004326 |
| GOTERM_MF_FAT | GO:0001882~nucleoside binding | 0.004604 |
| GOTERM_MF_FAT | GO:0016875~ligase activity, forming carbon-oxygen bonds | 0.00745 |
| GOTERM_MF_FAT | GO:0019899~enzyme binding | 0.010651 |
| GOTERM_MF_FAT | GO:0005524~ATP binding | 0.023499 |
| GOTERM_CC_FAT | GO:0005829~cytosol | 4.14E-08 |
| GOTERM_CC_FAT | GO:0000502~proteasome complex | 1.41E-05 |
| GOTERM_CC_FAT | GO:0048770~pigment granule | 5.39E-05 |
| GOTERM_CC_FAT | GO:0005635~nuclear envelope | 0.001414 |
| GOTERM_CC_FAT | GO:0012505~endomembrane system | 0.00232 |
| GOTERM_CC_FAT | GO:0005730~nucleolus | 0.010319 |

**Table 2: GO enrichment for down-regulated DEGs**

| Category | Term | PValue |
|---|---|---|
| GOTERM_BP_FAT | GO:0016338~calcium-independent cell-cell adhesion | 2.45E-09 |
| GOTERM_BP_FAT | GO:0045216~cell-cell junction organization | 0.001137 |
| GOTERM_BP_FAT | GO:0018958~phenol metabolic process | 0.001137 |
| GOTERM_BP_FAT | GO:0016337~cell-cell adhesion | 0.001217 |
| GOTERM_BP_FAT | GO:0030155~regulation of cell adhesion | 0.001295 |
| GOTERM_BP_FAT | GO:0007162~negative regulation of cell adhesion | 0.002073 |
| GOTERM_BP_FAT | GO:0042127~regulation of cell proliferation | 0.002159 |
| GOTERM_BP_FAT | GO:0002684~positive regulation of immune system process | 0.002828 |
| GOTERM_BP_FAT | GO:0008284~positive regulation of cell proliferation | 0.003043 |
| GOTERM_BP_FAT | GO:0050671~positive regulation of lymphocyte proliferation | 0.004188 |
| GOTERM_BP_FAT | GO:0032946~positive regulation of mononuclear cell proliferation | 0.004407 |
| GOTERM_BP_FAT | GO:0070665~positive regulation of leukocyte proliferation | 0.004407 |
| GOTERM_BP_FAT | GO:0034330~cell junction organization | 0.004632 |
| GOTERM_BP_FAT | GO:0032535~regulation of cellular component size | 0.005328 |
| GOTERM_BP_FAT | GO:0009725~response to hormone stimulus | 0.005943 |
| GOTERM_BP_FAT | GO:0042417~dopamine metabolic process | 0.006124 |
| GOTERM_BP_FAT | GO:0009719~response to endogenous stimulus | 0.009967 |
| GOTERM_BP_FAT | GO:0007169~transmembrane receptor protein tyrosine kinase signaling pathway | 0.010475 |
| GOTERM_BP_FAT | GO:0030888~regulation of B cell proliferation | 0.011817 |
| GOTERM_BP_FAT | GO:0050670~regulation of lymphocyte proliferation | 0.013036 |
| GOTERM_BP_FAT | GO:0032944~regulation of mononuclear cell proliferation | 0.013462 |
| GOTERM_BP_FAT | GO:0070663~regulation of leukocyte proliferation | 0.013462 |
| GOTERM_BP_FAT | GO:0040008~regulation of growth | 0.015473 |
| GOTERM_BP_FAT | GO:0007167~enzyme linked receptor protein signaling pathway | 0.015677 |

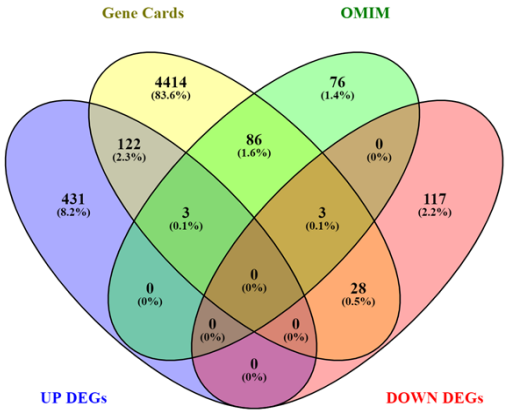
| | | |
|---|---|---|
| GOTERM_BP_FAT | GO:0010627~regulation of protein kinase cascade | 0.015944 |
| GOTERM_BP_FAT | GO:0045665~negative regulation of neuron differentiation | 0.016196 |
| GOTERM_BP_FAT | GO:0034311~diol metabolic process | 0.017142 |
| GOTERM_BP_FAT | GO:0009712~catechol metabolic process | 0.017142 |
| GOTERM_BP_FAT | GO:0006584~catecholamine metabolic process | 0.017142 |
| GOTERM_BP_FAT | GO:0010740~positive regulation of protein kinase cascade | 0.017145 |
| GOTERM_BP_FAT | GO:0030308~negative regulation of cell growth | 0.017158 |
| GOTERM_BP_FAT | GO:0033630~positive regulation of cell adhesion mediated by integrin | 0.017638 |
| GOTERM_BP_FAT | GO:0006576~biogenic amine metabolic process | 0.019727 |
| GOTERM_BP_FAT | GO:0051251~positive regulation of lymphocyte activation | 0.019727 |
| GOTERM_BP_FAT | GO:0045792~negative regulation of cell size | 0.020812 |
| GOTERM_BP_FAT | GO:0007155~cell adhesion | 0.022058 |
| GOTERM_BP_FAT | GO:0022610~biological adhesion | 0.02224 |
| GOTERM_BP_FAT | GO:0043627~response to estrogen stimulus | 0.024258 |
| GOTERM_BP_FAT | GO:0002696~positive regulation of leukocyte activation | 0.02486 |
| GOTERM_BP_FAT | GO:0048545~response to steroid hormone stimulus | 0.026971 |
| GOTERM_BP_FAT | GO:0045926~negative regulation of growth | 0.027352 |
| GOTERM_BP_FAT | GO:0001558~regulation of cell growth | 0.027876 |
| GOTERM_BP_FAT | GO:0050867~positive regulation of cell activation | 0.027994 |
| GOTERM_BP_FAT | GO:0009967~positive regulation of signal transduction | 0.030424 |
| GOTERM_BP_FAT | GO:0051046~regulation of secretion | 0.031679 |
| GOTERM_BP_FAT | GO:0008361~regulation of cell size | 0.03369 |
| GOTERM_BP_FAT | GO:0050864~regulation of B cell activation | 0.036533 |
| GOTERM_BP_FAT | GO:0034622~cellular macromolecular complex assembly | 0.04003 |
| GOTERM_BP_FAT | GO:0048103~somatic stem cell division | 0.040677 |
| GOTERM_BP_FAT | GO:0033628~regulation of cell adhesion mediated by integrin | 0.040677 |
| GOTERM_BP_FAT | GO:0043065~positive regulation of apoptosis | 0.0417 |
| GOTERM_BP_FAT | GO:0065003~macromolecular complex assembly | 0.042401 |
| GOTERM_BP_FAT | GO:0043068~positive regulation of programmed cell death | 0.042894 |
| GOTERM_BP_FAT | GO:0010942~positive regulation of cell death | 0.043701 |
| GOTERM_BP_FAT | GO:0010647~positive regulation of cell communication | 0.045211 |
| GOTERM_BP_FAT | GO:0002902~regulation of B cell apoptosis | 0.046353 |
| GOTERM_BP_FAT | GO:0045785~positive regulation of cell adhesion | 0.049027 |
| GOTERM_BP_FAT | GO:0030097~hemopoiesis | 0.051116 |
| GOTERM_BP_FAT | GO:0017145~stem cell division | 0.051996 |
| GOTERM_BP_FAT | GO:0045684~positive regulation of epidermis development | 0.051996 |
| GOTERM_BP_FAT | GO:0045321~leukocyte activation | 0.055097 |
| GOTERM_BP_FAT | GO:0042063~gliogenesis | 0.056544 |
| GOTERM_BP_FAT | GO:0051249~regulation of lymphocyte activation | 0.057315 |
| GOTERM_BP_FAT | GO:0043933~macromolecular complex subunit organization | 0.058145 |
| GOTERM_MF_FAT | GO:0042802~identical protein binding | 7.24E-04 |
| GOTERM_MF_FAT | GO:0019901~protein kinase binding | 0.014538 |
| GOTERM_MF_FAT | GO:0019900~kinase binding | 0.027655 |
| GOTERM_MF_FAT | GO:0031490~chromatin DNA binding | 0.043912 |

| | | |
|---|---|---|
| GOTERM_MF_FAT | GO:0004896~cytokine receptor activity | 0.04821 |
| GOTERM_MF_FAT | GO:0005198~structural molecule activity | 0.04926 |
| GOTERM_MF_FAT | GO:0030296~protein tyrosine kinase activator activity | 0.050027 |
| GOTERM_MF_FAT | GO:0046983~protein dimerization activity | 0.057969 |
| GOTERM_CC_FAT | GO:0070160~occluding junction | 1.90E-09 |
| GOTERM_CC_FAT | GO:0005923~tight junction | 1.90E-09 |
| GOTERM_CC_FAT | GO:0043296~apical junction complex | 2.92E-08 |
| GOTERM_CC_FAT | GO:0016327~apicolateral plasma membrane | 3.79E-08 |
| GOTERM_CC_FAT | GO:0005911~cell-cell junction | 8.48E-07 |
| GOTERM_CC_FAT | GO:0030054~cell junction | 9.99E-04 |
| GOTERM_CC_FAT | GO:0044459~plasma membrane part | 0.004143 |
| GOTERM_CC_FAT | GO:0005886~plasma membrane | 0.035738 |
| GOTERM_CC_FAT | GO:0031224~intrinsic to membrane | 0.046696 |




**(Fig. 1)**

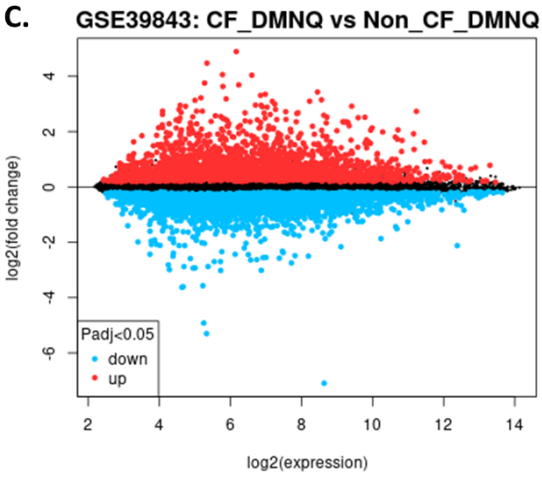
**A.**



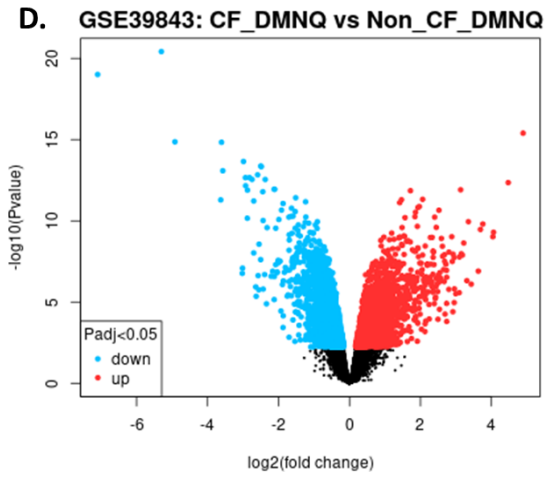

**B.**

| Genes | Number |
|---|---|
| Up-regulated DEGs | 148 |
| Down-regulated DEGs | 556 |
| Reported DEGs | 156 |
| Novel DEGs | 548 |

**C.**

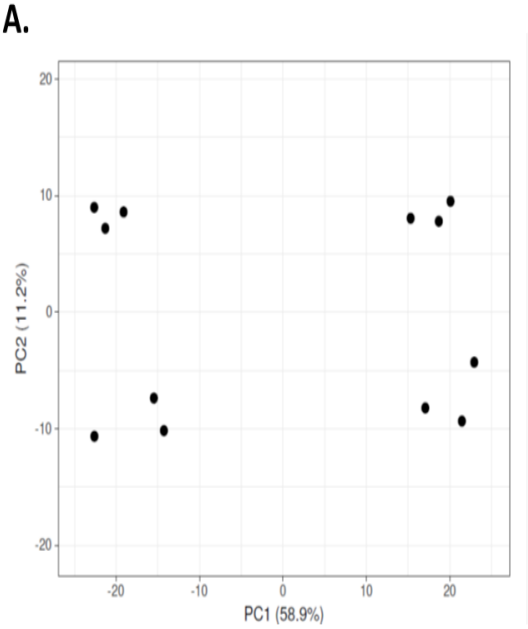



**D.**

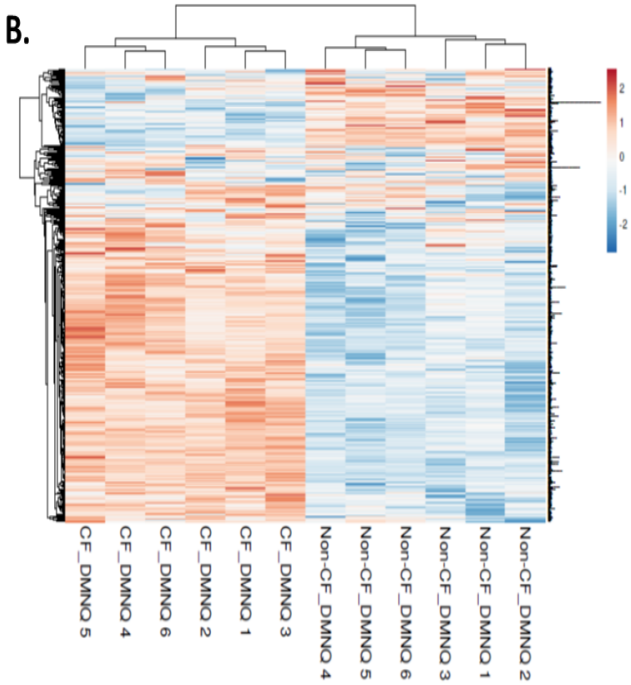



**(Fig. 2)**

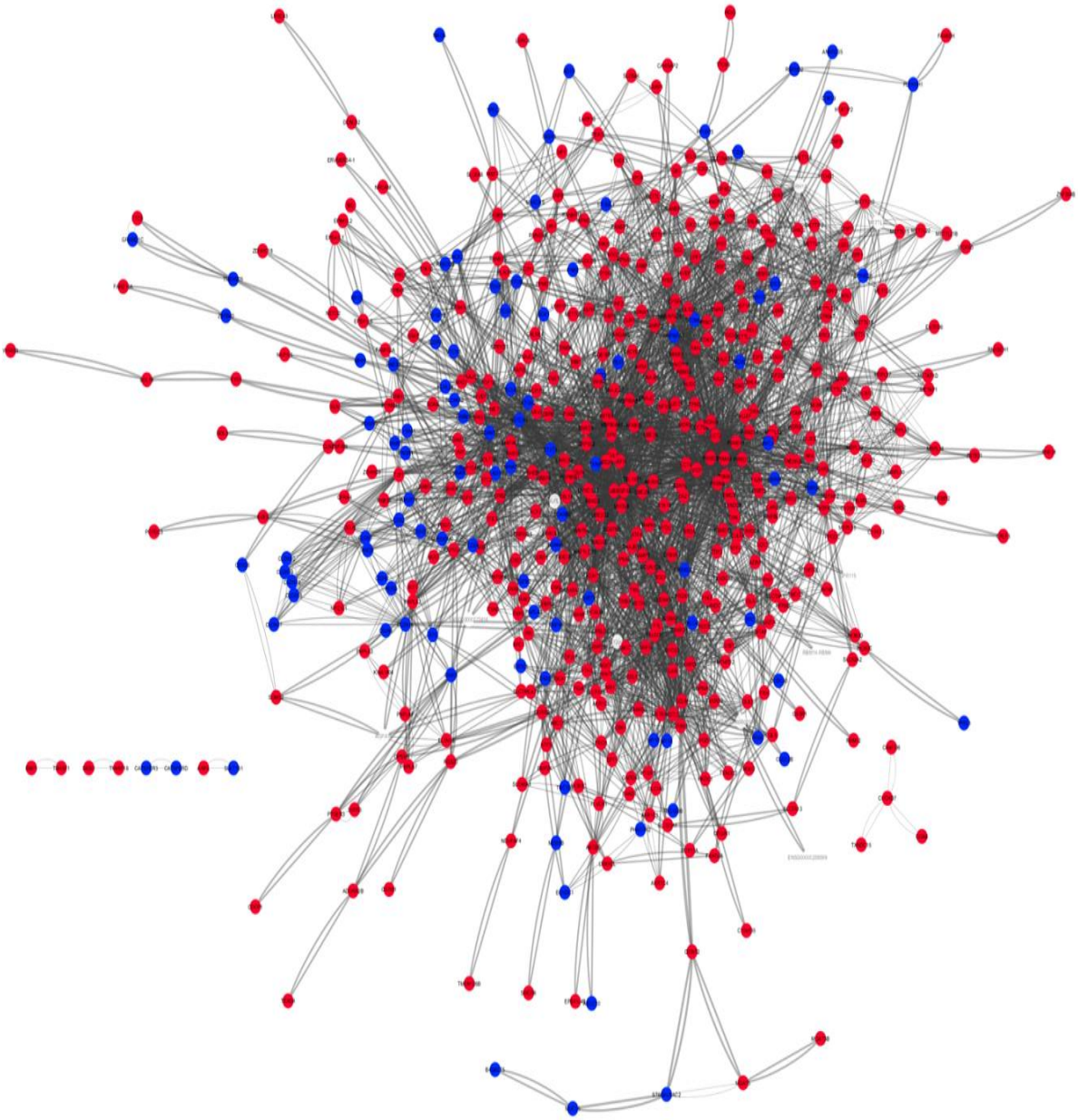
**A.**




**B.**




**(Fig. 3)**



**(Fig. 4A)**

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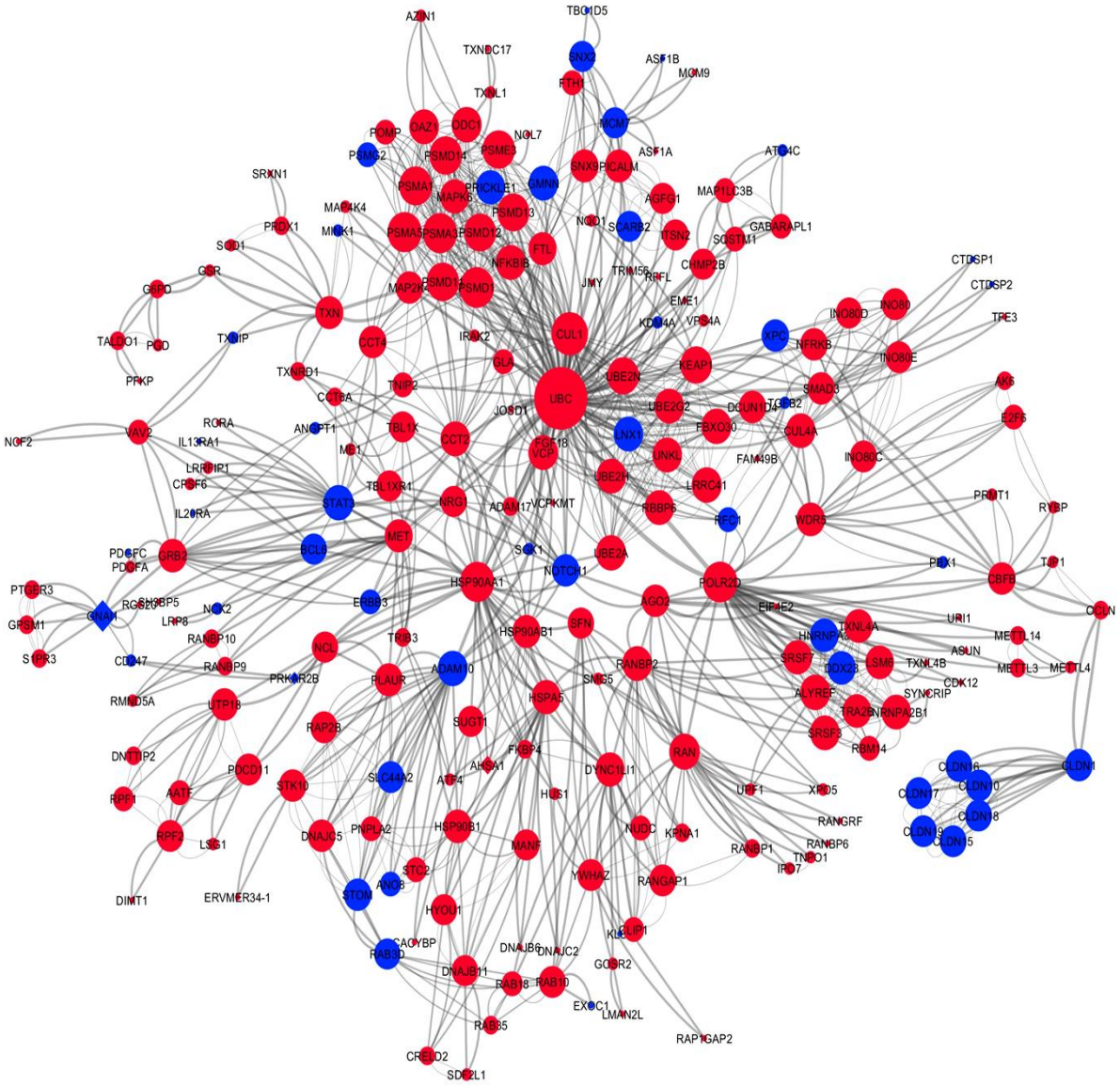
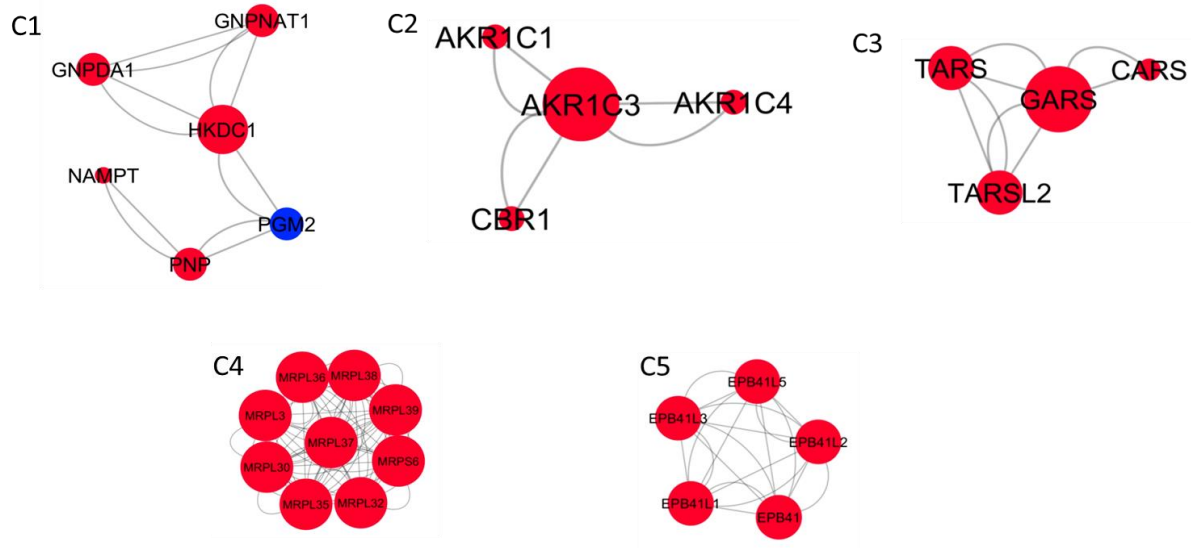



**(Fig. 4B)**






**(Fig. 4C)**

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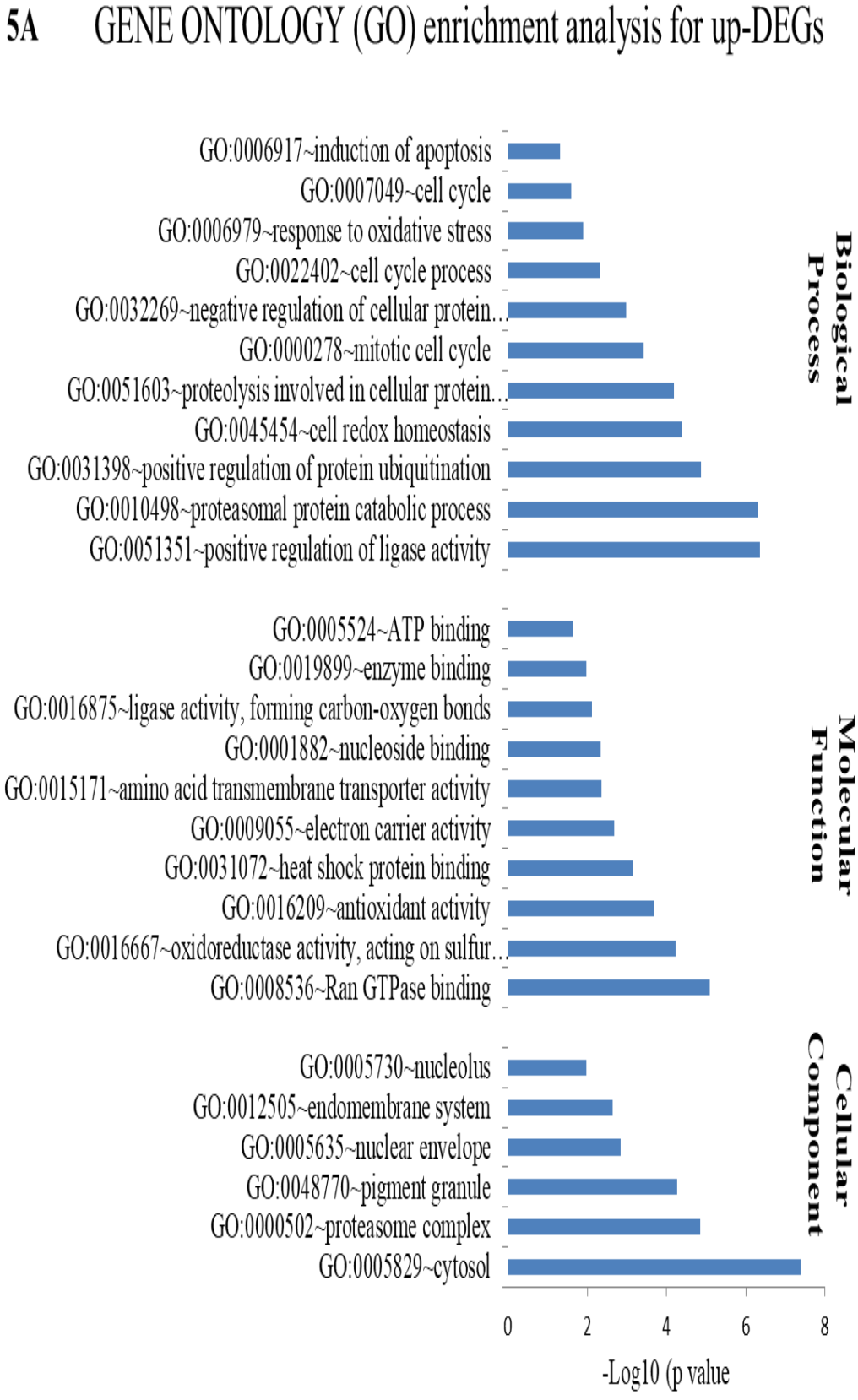


**(Fig. 5A)**

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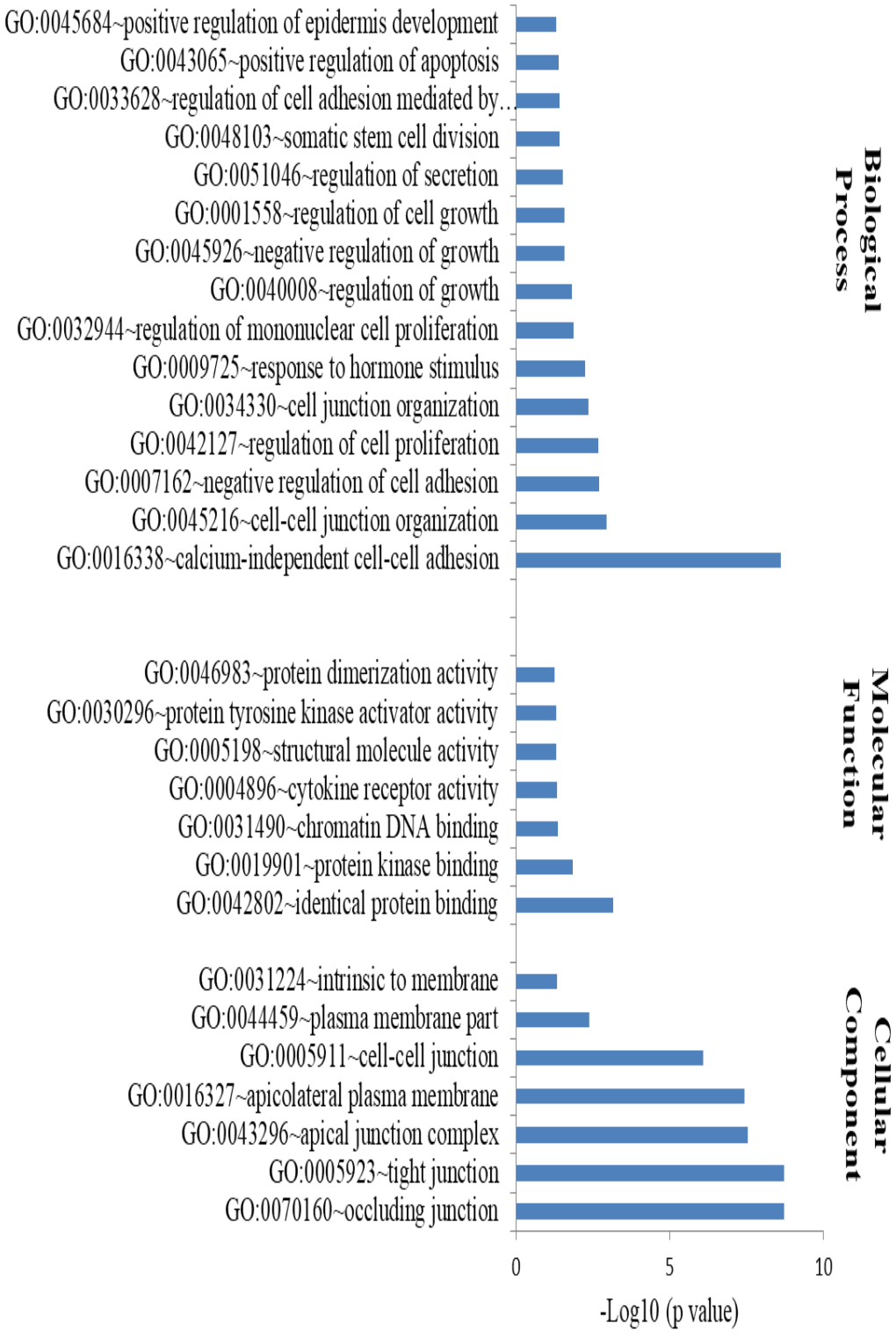
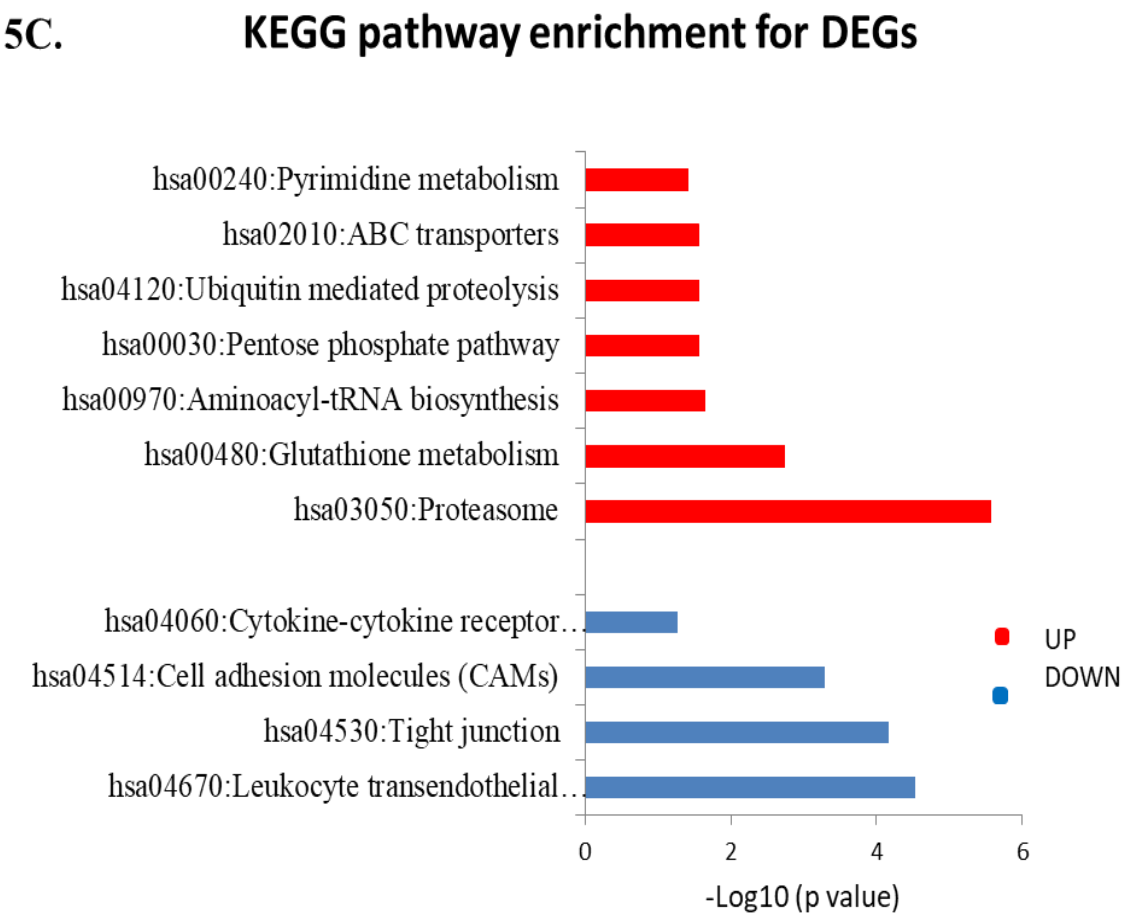
**5B.** GENE ONTOLOGY (GO) enrichment analysis for down DEGs




**(Fig. 5B)**


5C.
KEGG pathway enrichment for DEGs
hsa00240:Pyrimidine metabolism
hsa02010:ABC transporters
hsa04120:Ubiquitin mediated proteolysis
hsa00030:Pentose phosphate pathway
hsa00970:Aminoacyl-tRNA biosynthesis
hsa00480:Glutathione metabolism
hsa03050:Proteasome
hsa04060:Cytokine-cytokine receptor…
hsa04514:Cell adhesion molecules (CAMs)
hsa04530:Tight junction
hsa04670:Leukocyte transendothelial…
UP
DOWN
0
2
4
6
-Log10 (p value)

**(Fig. 5C)**