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Significance of hub genes and immune cells infiltration identified by bioinformatics analysis in pelvic organ prolapse

Ying Zhao [1], **Zhijun Xia** [Corresp., 2], **Te Lin** [3], **Yitong Yin** [1]

[1] Department of Obstetrics and Gynecology, Pelvic Floor Disease Diagnosis and Treatment Center, Shengjing Hospital of China Medical University, Shenyang, China

[2] Department of Obstetrics and Gynecology, Pelvic Floor Disease Diagnosis and Treatment Center, Shengjing Hospital of China Medical University, Shenyang, □□

[3] Department of Obstetrics and Gynecology, Pelvic Floor Disease Diagnosis and Treatment Center, Shengjing Hospital of China Medical University, Shenyang, china

Corresponding Author: Zhijun Xia
Email address: xzj18270916865@163.com

Objective Pelvic organ prolapse (POP) refers to the decline of pelvic organ position and dysfunction caused by weak pelvic floor support. The aim of this study is to screen the hub genes and immune cells infiltration related to POP disease. **Methods** Microarray data of 34 POP tissues in gene expression dataset GSE12852 were used as research objects. Weighted Gene co-expression network Analysis (WGCNA) was constructed to find the hub module and hub genes related to POP occurs. Gene function annotation was performed with the DAVID functional annotation tool. Differential analysis based on dataset GSE12852 was performed to explore the expression of the selected hub genes in POP and non-POP tissues, and RT-qPCR was used to validate the results. The differential immune cells infiltration between POP tissues and non-POP tissues was investigated by the CIBERSORT algorithm. **Results** WGCNA revealed that blue module has the highest correlation with POP occurs. Functional annotation displayed that the genes in blue module mainly involved in immunity. ZNF331, THBS1, IFRD1, FLJ20533, CXCR4, GEM, SOD2 and SAT in the blue module were identified as the hub genes. Differential analysis and RT-qPCR all indicated that the selected hub genes were overexpression in POP tissues compared with non-POP tissues. CIBERSORT algorithm was performed to calculate the 22 immune cells infiltration in POP tissues and non-POP tissues. We found that Mast cells activated and Neutrophils were higher infiltration in POP tissues than non-POP tissues, while Mast cells resting were lower infiltration in POP tissues. Then, we investigated the relationship between the differential immune cells and hub genes through Pearson correlation analysis. The results indicated that Mast cells activated and Neutrophils have positive correlation with the hub genes, while Mast cells resting have negative correlation with the hub genes. **Conclusions** In conclusion, our research identified 8 hub genes and 3 immune cells infiltration related to POP. These hub genes may participate in the pathogenesis of POP

through innate immune and inflammatory response, which has certain diagnostic and therapeutic value for POP.

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Ying Zhao[1], Zhijun Xia*[1] , Te Lin[1], Yitong Yin[1]

[1]Department of Obstetrics and Gynecology, Pelvic Floor Disease Diagnosis and Treatment Center, Shengjing Hospital of China Medical University, Shenyang, China, 110004.

***Correspondence:**

Corresponding Author: Zhijun Xia, Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang, China, 110004

Email: xzj18270916865@163.com, xiazj@sj-hospital.org

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Abstract

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Methods Microarray data of 34 POP tissues in gene expression dataset GSE12852 were used as research objects. Weighted Gene co-expression network Analysis (WGCNA) was constructed to find the hub module and hub genes related to POP occurs. Gene function annotation was performed with the DAVID functional annotation tool. Differential analysis based on dataset GSE12852 was performed to explore the expression of the selected hub genes in POP and non-POP tissues, and RT-qPCR was used to validate the results. The differential immune cells infiltration between POP tissues and non-POP tissues was investigated by the CIBERSORT algorithm.

Results WGCNA revealed that blue module has the highest correlation with POP occurs. Functional annotation displayed that the genes in blue module mainly involved in immunity. ZNF331, THBS1, IFRD1, FLJ20533, CXCR4, GEM, SOD2 and SAT in the blue module were

identified as the hub genes. Differential analysis and RT-qPCR all indicated that the selected hub genes were overexpression in POP tissues compared with non-POP tissues. CIBERSORT algorithm was performed to calculate the 22 immune cells infiltration in POP tissues and non-POP tissues. We found that Mast cells activated and Neutrophils were higher infiltration in POP tissues than non-POP tissues, while Mast cells resting were lower infiltration in POP tissues. Then, we investigated the relationship between the differential immune cells and hub genes through Pearson correlation analysis. The results indicated that Mast cells activated and Neutrophils have positive correlation with the hub genes, while Mast cells resting have negative correlation with the hub genes.

Conclusions In conclusion, our research identified 8 hub genes and 3 immune cells infiltration related to POP occur. These hub genes may participate in the pathogenesis of POP through immunity, which has certain diagnostic and therapeutic value for POP.

Keywords: Pelvic organ prolapse, WGCNA, CIBERSORT, immune cells infiltration, GEO

1 Introduction

Pelvic organ prolapse (POP) is caused by the dysfunction of pelvic floor supporting structure, which causes the position of normal pelvic organs (vagina wall, uterus, bladder, rectum, etc.) to move down, seriously affecting people's health and quality of life(Nygaard et al. 2014). According to a study, the incidence of the POP will be as high as 46% in 2050(Wu et al. 2009). In the United States, about 200, 000 POP patients receive surgical treatment every year, 30% of them recur after surgery and need to be operated again, which costs more than $1 billion every year(Subak et al. 20[illegible] POP is a complex multifaceted disease caused by the interaction of environmental and genetic factors. Pregnancy, vaginal pull-up, time of delivery, age and obesity are identified risk factors(Hendrix et al. 2002). However, the molecular mechanism of POP is still unclear, and there is a lack of ideal prevention and treatment measures in clinical practice. Therefore, further study on the pathogenesis of POP and effective prevention or treatment from the level of etiology is of

great economic and clinical value.

In recent years, with the rapid development of biotechnology, especially the development of gene chip and the new generation of sequencing technology, the biological data are growing at an explosive rate, so that the traditional data analysis methods cannot meet the analysis needs. The emergence and development of high-throughput sequencing technology has brought about a great revolution in biological research, and the biological network analysis method based on the complex network theory of high-throughput data emerges as the Times require, which can systematically describe and analyze these high-throughput data(Carrieri et al. 2015; Liu et al. 2014). At present, common biological networks include signaling network, metabolic network, protein network and gene co-expression network. Gene co-expression network plays an important role in the field of biological research. The most representative is the weighted gene co-expression network analysis(WGCNA)(Arisi et al. 2011). The network can be used to find clusters of highly correlated genes, identify gene module characteristics and hub genes to establish the relationship between gene module and external sample characteristics. These methods can be used to screen candidate biomarkers or potential therapeutic targets and have been successfully applied in a variety of biological fields, such as cancer, mouse genetics, yeast genetics and brain imaging data analysis(Langfelder & Horvath 2008; Liu et al. 2017). CIBERSORT algorithm can be performed to calculate the immune cells infiltration in tissues based on gene expression datasets. Recently, increasing number of researches used the CIBERSORT algorithm to investigate the role of immune cells infiltration in various tissues, such as clear cell renal cell carcinoma(Lin et al. 2020), breast ductal and lobular carcinoma(Zhang et al. 2019), osteoarthritis(Cai et al. 2020), high-grade serous ovarian cancer(Liu et al. 2020), etc. In this study, we found hub genes and immune cells infiltration highly related to POP occurs by using WGCNA and CIBERSORT algorithm to analyze POP expression spectrum data in public databases, which provide new ideas and methods for the treatment of POP. Then, the differential immune cells infiltration between POP tissues and non-POP tissues was investigated.

2 Materials and methods

Obtain the specimen of POP

From 2017 to 2018, 12 POP patients were selected from the Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University. Tissues of prolapse were selected as the experimental group and those of non-prolapse as the control group. All the patients were married, without estrogen related diseases, and had no hormone treatment within 3 months. The Ethics Committee of Shengjing Hospital of China Medical University approved the study protocol, in accordance with the guidelines of the Helsinki Declaration (No. 2018Ps68K).

Obtain POP data from GEO database

Gene expression data from POP GSE12852 was obtained from Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE12852) in NCBI(Brizzolara et al. 2009). GSE12852 dataset contain 16 POP patients and 18 non-POP patients. Meanwhile, the clinical information including age, menopausal status, race and prolapse stage was downloaded. Then, log scale robust multi-array analysis was used to perform background correction and normalization of the dataset.

Co-expression network construction

Firstly, POP samples and normal samples were analyzed by hierarchical cluster analysis and the correlation coefficient of expression level was calculated. The outlier samples were removed, and the other samples were used to construct gene co-expression network. The correlation matrix of gene co-expression consists of the absolute value of correlation coefficient between two genes. Common correlation coefficients include Pearson correlation coefficient and Spearman correlation coefficient. Then, we use the formula amn = |cmn|$^{\beta}$ to transform correlation matrix into adjacency matrix (amn represents Pearson's correlation coefficient between gene m and gene n; amn represents the connection coefficient between gene m and gene n; β is a soft threshold, which can strengthen the strong link between genes and weaken the weak link). Finally, we transformed the adjacency matrix into the topological overlap matrix, and divided the genes with high correlation into the same module.

Identification of hub gene module and hub genes

The main purpose of our research is to combine external information with Modular genes for analysis with Gene significance (GS) and Modular membership (MM) after obtaining Gene modules. MM is defined as the correlation between gene expression profile level and Module eigengene (ME). GS represents the degree of correlation between gene expression profiles and external information. The average value of all gene GS in the module represents the Module significance (MS). We defined the correlation between gene and disease as GS, and obtained the correlation between this module and disease as MS. The hub gene characterized by high MM and high GS was described as having the closest relationship with disease.

Functional enrichment analysis

In this study, we used the online GO enrichment analysis tool and KEGG pathway analysis tool of DAVID 6.8 website (https://david.ncifcrf.gov/) to annotate the genes in the module identified by WGCNA, in order to try to find the enrichment pathway and function in the target gene. The false discovery rate (FDR) was less than 0.01.

RNA extraction and quantitative real - time PCR

1 ml Trizol was used to isolate total RNA from POP tissues (200 mg), and reverse transcriptase of avian myeloblastoma virus and random primers were used to make complementary DNA (cDNA) according to the manufacturer's instructions. Amplification of cDNA by real-time qPCR using SYBR Pre mix Ex Taq II (Takara). According to the samples from three independent experiments, $2^{-\triangle\triangle CT}$ value was used to analyze the data. The primer of gene was displayed in Supplementary table1.

Immune infiltration in POP

CIBERSORT is a deconvolution algorithm characterized the proportion of 22 immune cells in tissues by using 547 barcode gene expression values. In this study, we performed CIBERSORT algorithm to the calculate proportion of 22 immune cells in tissues from GSE12852 dataset. The tissues with p value <0.05 were screened for further analysis(Chen et al. 2018). Pearson correlation analysis was implemented to explore the relationship between 22 immune cells. The Wilcoxon

rank-sum test and Principal component analysis (PCA) was applied to investigate the differential immune cells infiltration between POP tissues and non-POP tissues. Finally, the relationship between differential immune cells and hub genes was investigated by Pearson correlation analysis.

Statistical analyses

Graphpad prism 7.0 and R 3.6.1 were used for statistical analysis, and these two software were used for image generation. T-test is used to analyze the difference of meaning between two groups. In all the analyses, $P < 0.05$ was statistically significant.

Results

Construction of WGCNA and identification of hub modules

We use flash cluster software package provided in R, to cluster the expression gene matrix of 34 samples in the dataset GSE12852, find out 4 obvious outliers, and construct the co-expression network of other samples after their elimination (Figure 1). In order to construct scale-free network distribution better, we use picksoftthreshold to weigh the value of parameter β in POP and non-POP samples, we select 1 to 20 thresholds, and calculate the correlation coefficient, mean connectivity and average correlation degree between log (k) and log (P (k)) for each threshold. When $\beta = 7$, the square of the correlation coefficient between log (k) and log (P (k)) is greater than 0.8. At this time, the average network connectivity corresponding to the threshold is close to zero, indicating that the network connectivity is very low at this time, which is similar to the scale-free network (Figure 2). According to the corresponding steps of WGCNA to construct co-expression network, the gene co-expression network was constructed after hierarchical clustering tree. In this experiment, we use dynamic pruning tree method to identify gene modules. We set the minimum number of genes in the module as 30, and finally get 11 corresponding modules (Figure 3A). According to the thermogram of correlation between modules and traits, we can see that there is the highest correlation between blue module and sample type (Figure 3B, r=0.4, p=0.009). Therefore, the blue module is considered to be the most worthy module to be studied. Protein protein interaction (PPI) is widely involved in the process of vital movement. We use string online database (https://string-db.org/) to construct PPI interaction network for genes ($P < 0.05$) in blue

module (Figure 5E)

Functional enrichment analysis

In order to further study the biological function of genes in the blue module, GO and KEGG enrichment analysis was carried out through DAVID 6.8. GO functional enrichment analysis displayed that these genes are mainly related to immunity (Figure 4A, Supplementary table 2). KEGG enrichment analysis revealed that these genes are mainly enriched in immune-related pathways, such as IL-17 signaling pathway, TNF signaling pathway (Figure 4B, Supplementary table 3).

Identification of hub gene

According to the screening criteria | MM | > 0.8 and | GS | > 0.47, 8 genes (ZNF331,THBS1,TMEM70,CXCR4,GEM,SOD2 and SAT) in the blue module were identified as the hub genes (Figure 5A). We found that the hub genes were highly expressed in POP tissues compared with non-POP tissues by differential analysis based on dataset GSE12852 (Figure 5B). According to the heatmap, we can directly see that hub gene is overexpressed in POP tissues (Figure 5C). In addition, we also calculated the correlation coefficient between hub genes, and the results showed that there was a strong co-expression relationship between these genes (Figure 5D).

Validation of hub gene

In order to verify the accuracy of the prediction results, we used RT-qPCR to detect the expression of hub gene in 12 pairs of POP and non-POP tissues. The results showed that hub gene was overexpressed in POP tissues, which were consistent with the prediction results (Figure 6 A-H).

Immune infiltration analyses

The CIBERSORT algorithm was performed to select samples with a CIBERSORT output $p < 0.05$. 12 samples including 4 non-POP tissues and 8 POP tissues were screened out. A bar plot was generated to show the proportion of 22 immune cells infiltration of the 12 samples (Figure 7A). We found that macrophages were the most abundant immune cells infiltration in samples. Figure 7B indicated that M1 macrophages had the strongest positive correlation with Mast cells resting (r=0.78), whereas Mast cells resting had the strongest negative correlation with Mast cells

activated (r=-0.83). We found that Mast cells activated and Neutrophils were higher infiltration in POP tissues than non-POP tissues, while Mast cells resting were lower infiltration in POP tissues (Figure 8, $p<0.05$). Finally, Pearson correlation analysis was used to investigate the relationship between the differential immune cells and hub genes. The results reveled that Mast cells activated and Neutrophils have positive correlation with the hub genes, while Mast cells resting have negative correlation with the hub genes (Table 1).

3 Discussion

Pelvic organ prolapse is caused by the weak supporting structure of the pelvic floor, which causes the position of pelvic floor organs to move down and the function to be abnormal. It seriously affects the quality of life of middle-aged and old women. In recent years, with the rapid development of gene sequencing technology and bioinformation technology, further analysis and utilization of sequencing data have become possible. In order to explore the molecular mechanism related to the development of POP, we screen out 8 hub genes (ZNF331, THBS1, IFRD1, FLJ20533, CXCR4, GEM, SOD2 and SAT) related to POP based on WGCNA and explore their biological functions.

Thrombospondins (THBSs) is a group of glycoproteins that bind to collagen and tissue, and participates in the interaction between cells and matrix in the process of tissue development and repair. THBS1 gene is the first member of THBSs gene family, which plays an important role in many biological processes related to the occurrence and progression of cardiovascular diseases, such as angiogenesis, inflammation, tissue remodeling, etc(Zhao et al. 2018). In addition, THBS1 gene can also affect tumor cell adhesion, invasion, migration, proliferation, apoptosis and tumor immunity(Huang et al. 2017). Brizzolara SS & colleagues(Brizzolara et al. 2009) predicted and verified the overexpression of THBS1 in POP tissues compared with non-POP tissues, which is consistent with the results of our secondary analysis. ZNF331 is located on chromosome 19q13, a recently cloned zinc finger protein gene closely related to thyroid tumorigenesis(Babinger et al. 2007). ZNF331, as a tumor suppressor gene, has been reported to be low expression in colorectal

cancer(Wang et al. 2017), esophageal cancer(Jiang et al. 2015), gastric cancer(Yu et al. 2013), liver cancer(Wang et al. 2013), and its low expression is related to hypermethylation in the promoter region. Interferon-related developmental regulator1(IFRD1) is located on human chromosome 7q22-q31, which is related to cell differentiation and plays an important role in the development and differentiation of embryonic muscle cells(Kraus et al. 2001; Lincoln et al. 2004). Transmembrane protein 70 (TMEM70), also named FLJ20533, is a mitochondrial membrane protein, which may play a role in the biosynthesis of mitochondrial ATPase(Hejzlarova et al. 2011). At present, research on TMEM70 mainly focuses on cardiomyopathy and pulmonary hypertension. CXCR4, also known as CD184, is a highly conserved receptor for chemokine CXCL12(Kashyap et al. 2017). CXCR4 belongs to the G protein coupled receptor superfamily, which is expressed in a cortical protein dependent manner on the surface cells(Teicher & Fricker 2010). CXCR4 has been reported to be overexpressed in a variety of tumor cells and involved in tumor proliferation, invasion, metastasis, and prognosis(Ottaiano et al. 2020; Wang et al. 2020; Zhu et al. 2020). GTP binding protein overexpressed in skeletal muscle (GEM) is a GTPase originally identified in mitogen-stimulated T lymphocytes and v-abl-transformed pre-B cells, which is highly expressed in spleen, thymus, and kidney(Cohen et al. 1994; Huang et al. 2014). Mitochondrial superoxide dismutase (SOD2) is an antioxidant enzyme in mitochondria of cells, which can reduce the damage of mitochondria caused by oxidative stress and protect mitochondria(Koltai et al. 2018). Spermidine/spermine N1-acetyltransferase (SAT) is the rate limiting enzyme in polyamine catabolism, which plays a role through the acetylation of spermidine and spermidine(Pegg 2008). SAT participates in cell growth, proliferation and death by regulating polyamine metabolism(Pegg 2008; Pegg 2016). Through a detailed literature review, we have not found any report of ZNF331, IFRD1, FLJ20533, CXCR4, GEM, SOD2 and SAT in pelvic organ prolapse. To explore the expression of the selected hub genes in POP and non-POP tissues, differential analysis based on dataset GSE12852 and RT-PCR was performed. The results indicated that the selected hub genes were overexpression in POP tissues compared with non-POP tissues.

Functional annotation displayed that the hub genes in mainly involved in immunity Therefore, we investigate the immune cells infiltration in POP tissues and non-POP tissues based on CIBERSORT algorithm. We found that Mast cells activated and Neutrophils were higher infiltration in POP tissues than non-POP tissues, while Mast cells resting were lower infiltration in POP tissues. Mast cells activated and Neutrophils have positive correlation with the hub genes, while Mast cells resting have negative correlation with the hub genes. According to the research results, we have reason to believe that the hub genes may be involved in the development of POP by regulating Mast cells activated, Mast cells resting and Neutrophils. Mast cell is an important antigen-presenting cell. It can release histamine and cytokines through degranulation, and play an important role in the occurrence and development of various inflammatory diseases(Grabauskas et al. 2020; Novruzov 2008; Sajay-Asbaghi et al. 2020). Zhe Liu etc.(Qu et al. 2020) identified that THBS1 promotes the inflammatory response of CIU mast cells and the permeability of HDMECs by regulating TGF-β/SMAD pathway, and the effects can be inhibited by miR-194. Several studies have shown that CXCR4 can promote mast cell chemotaxis to inflammatory sites(Limón-Flores et al. 2009; Lv et al. 2019; Patadia et al. 2010). Several studies have shown that IFRD1 may play an important role in the treatment of targeting neutrophilic inflammation in cystic fibrosis(Blanchard et al. 2011; Gu et al. 2009; Hector et al. 2013). According to the current literature, there is no direct evidence to prove the accuracy of our prediction results, but the more or less relationship between genes and immune cells gives us reason to believe our prediction results.

Conclusions

In conclusion, our research identified 8 hub genes and 3 immune cells related to POP occurs. These hub genes can participate in the pathogenesis of POP through immunity, which has certain diagnostic and therapeutic value for POP.

Acknowledgments

We thank the authors who provided the GEO public datasets.

Ethical approval

The Ethics Committee of Shengjing Hospital of China Medical University approved the study protocol, in accordance with the guidelines of the Helsinki Declaration (No. 2018Ps68K).

Conflict of Interest Statement

The authors declare no competing interests.

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FIGURE.1. Clustering dendrogram of **34** POP samples in GSE12852.

FIGURE. 2. Determination of soft threshold and inspection of scale-free network.

(A)The correlation coefficients of log(K) and log(p(K)) corresponding to different soft-thresholding power (β). (B) The mean value of gene adjacency coefficient in the gene network corresponding to different soft-thresholding power. (C)The distribution of connectedness of each node in the network. (D) The scatter plot of log(k) and log(p(k)).

FIGURE. 3. Identification of hub module (A) Dendrogram of all expressed genes clustered based on a dissimilarity measure (1-TOM), Dynamic Tree Cut corresponds to the original module and Merged Dynamic corresponds to the final module. Since no modules need to be merged, the results are exactly the same. (B) Heatmap of the correlation between Modular significance (MS) and clinical traits of POP.

FIGURE. 4. GO functional and KEGG pathway enrichment analysis. (A) GO functional enrichment analysis. (B) KEGG Pathway enrichment analysis.

FIGURE. 5. Hub gene screening.

(A) Scatter plot for correlation between gene MM and GS in the blue module.(B) Difference analysis of hub genes in GSE12852. (C) Heatmap of hub genes in GSE12852. (D) Correlation analysis of hub genes in GSE12852.

460 **FIGURE. 6. Hub gene validation and PPI network analysis.**

461 (A-H) RT-qPCR detect the expression of hub genes in 12 pairs of POP and non-POP tissues (I)PPI
462 network analysis of genes in the blue module.

463 **FIGURE. 7. The landscape of immune cells infiltration in GSE12852 (CIBERSORT p value**
464 **<0.05).**

465 (A) The proportion of 22 immune cells in GSE12852. (B) Correlation matrix between 22 immune
466 cells.

467 **FIGURE. 8. The differential immune cells infiltration between POP tissues and non-POP**
468 **tissues.**

469 (A) Mast cells resting; (B) Mast cells activated; (C) Neutrophils. Group1: non-POP; Group2: POP.

470 **TABLE.1.** The correlation between hub genes and immune cells.

471 **SUPPLEMENTARY TABLE.1.** The primers of hub genes.

472 **SUPPLEMENTARY TABLE.2.** GO functional enrichment analysis.

473 **SUPPLEMENTARY TABLE.3.** KEGG pathway enrichment analysis.

474

Figure 1

Figure 1

FIGURE.1. Clustering dendrogram of **34** POP samples in GSE12852.

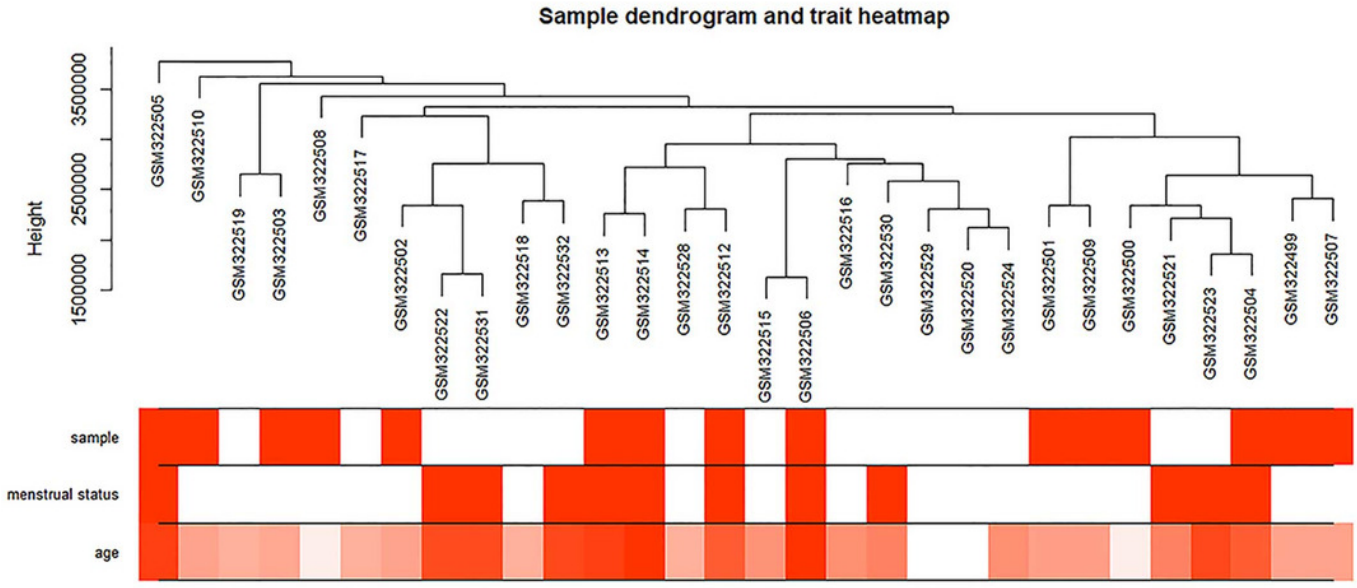

Figure 2

Figure 2

FIGURE. 2. Determination of soft threshold and inspection of scale-free network. (A)The correlation coefficients of log(K) and log(p(K)) corresponding to different soft-thresholding power (β). (B) The mean value of gene adjacency coefficient in the gene network corresponding to different soft-thresholding power. (C)The distribution of connectedness of each node in the network. (D) The scatter plot of log(k) and log(p(k)).

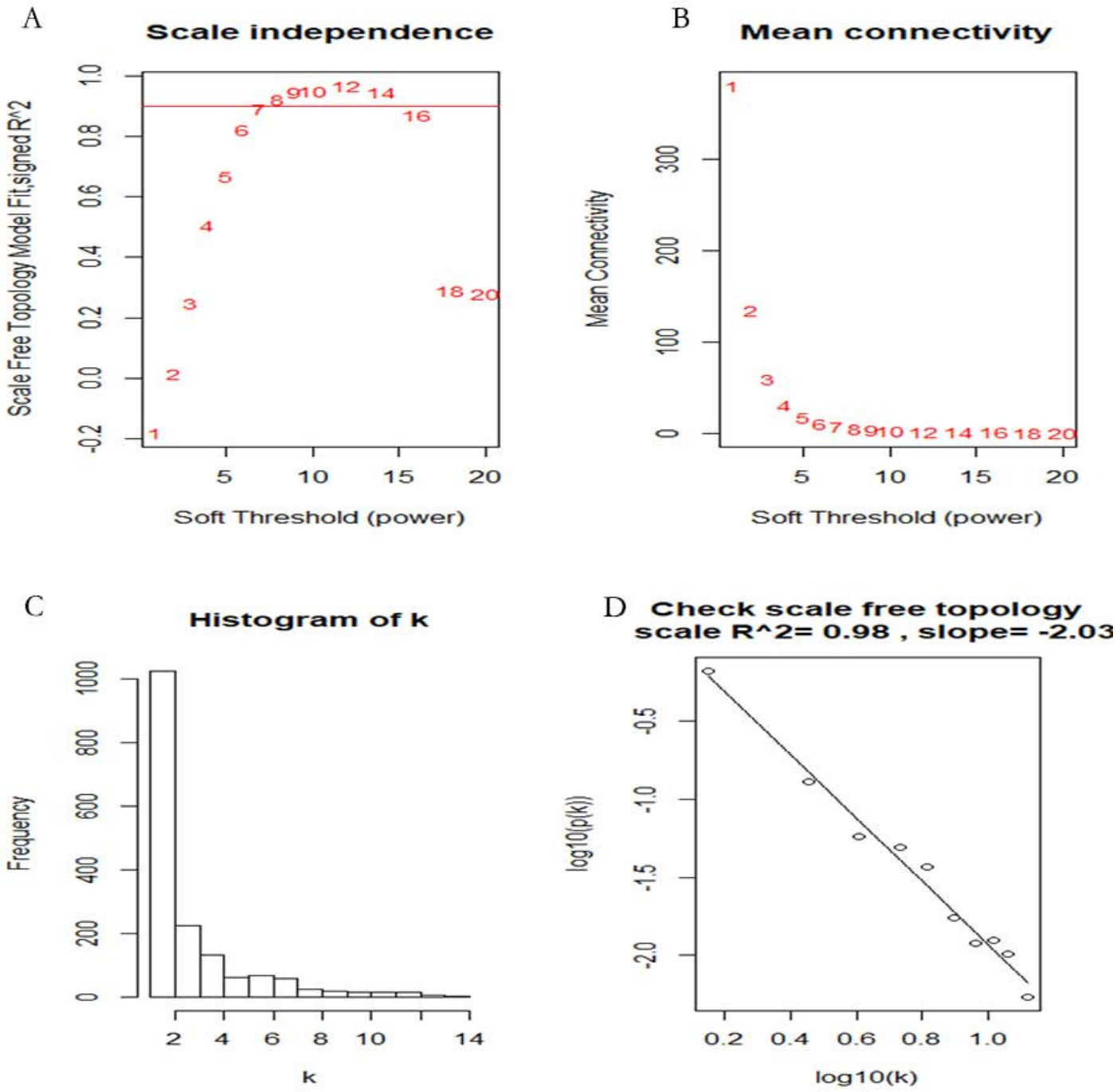
A
Scale independence
Scale Free Topology Model Fit,signed R^2
Soft Threshold (power)
B
Mean connectivity
Mean Connectivity
Soft Threshold (power)
C
Histogram of k
Frequency
k
D
Check scale free topology
scale R^2= 0.98 , slope= -2.03
log10(p(k))
log10(k)

Figure 3

Figure 3

FIGURE. 3. Identification of hub module (A) Dendrogram of all expressed genes clustered based on a dissimilarity measure (1-TOM), Dynamic Tree Cut corresponds to the original module and Merged Dynamic corresponds to the final module. Since no modules need to be merged, the results are exactly the same. (B) Heatmap of the correlation between Modular significance (MS) and clinical traits of POP.

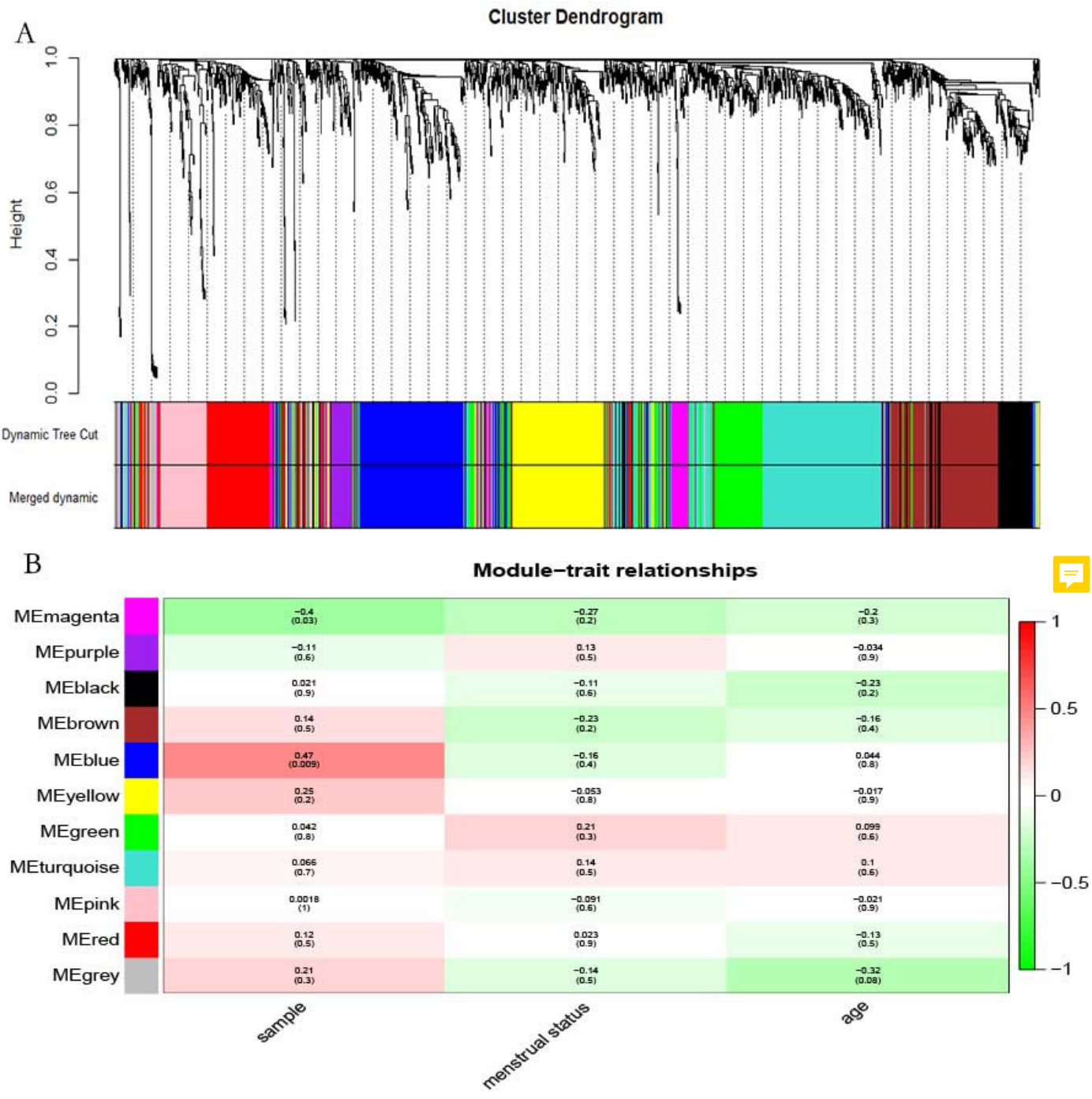
A
Cluster Dendrogram
Height
1.0
0.8
0.6
0.4
0.2
0.0
Dynamic Tree Cut
Merged dynamic
B
Module−trait relationships
MEmagenta
MEpurple
MEblack
MEbrown
MEblue
MEyellow
MEgreen
MEturquoise
MEpink
MEred
MEgrey
−0.4 (0.03)
−0.27 (0.2)
−0.2 (0.3)
−0.11 (0.6)
0.13 (0.5)
−0.034 (0.9)
0.021 (0.9)
−0.11 (0.6)
−0.23 (0.2)
0.14 (0.5)
−0.23 (0.2)
−0.16 (0.4)
0.47 (0.009)
−0.16 (0.4)
0.044 (0.8)
0.25 (0.2)
−0.053 (0.8)
−0.017 (0.9)
0.042 (0.8)
0.21 (0.3)
0.099 (0.6)
0.066 (0.7)
0.14 (0.5)
0.1 (0.6)
0.0018 (1)
−0.091 (0.6)
−0.021 (0.9)
0.12 (0.5)
0.023 (0.9)
−0.13 (0.5)
0.21 (0.3)
−0.14 (0.5)
−0.32 (0.08)
sample
menstrual status
age
1
0.5
0
−0.5
−1

Figure 4

Figure 4

FIGURE. 4. GO functional and KEGG pathway enrichment analysis. (A) GO functional enrichment analysis. (B) KEGG Pathway enrichment analysis.

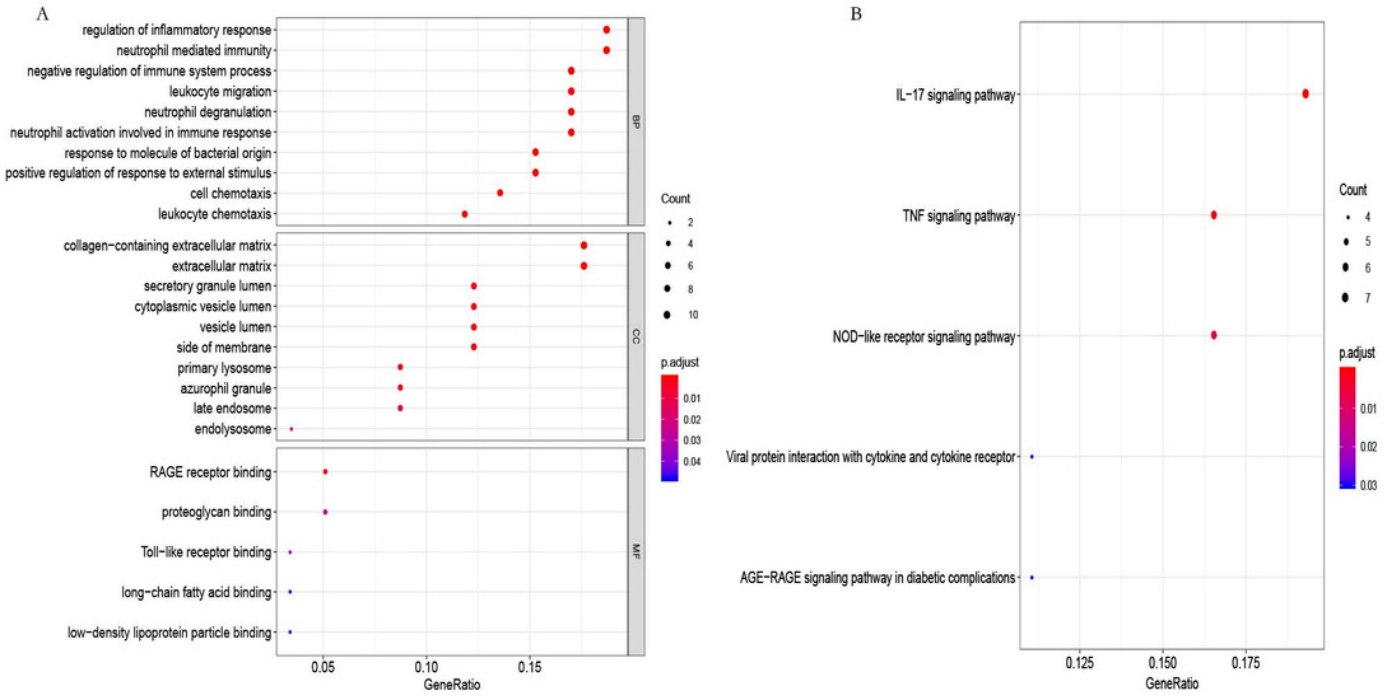

Figure 5

Figure 5

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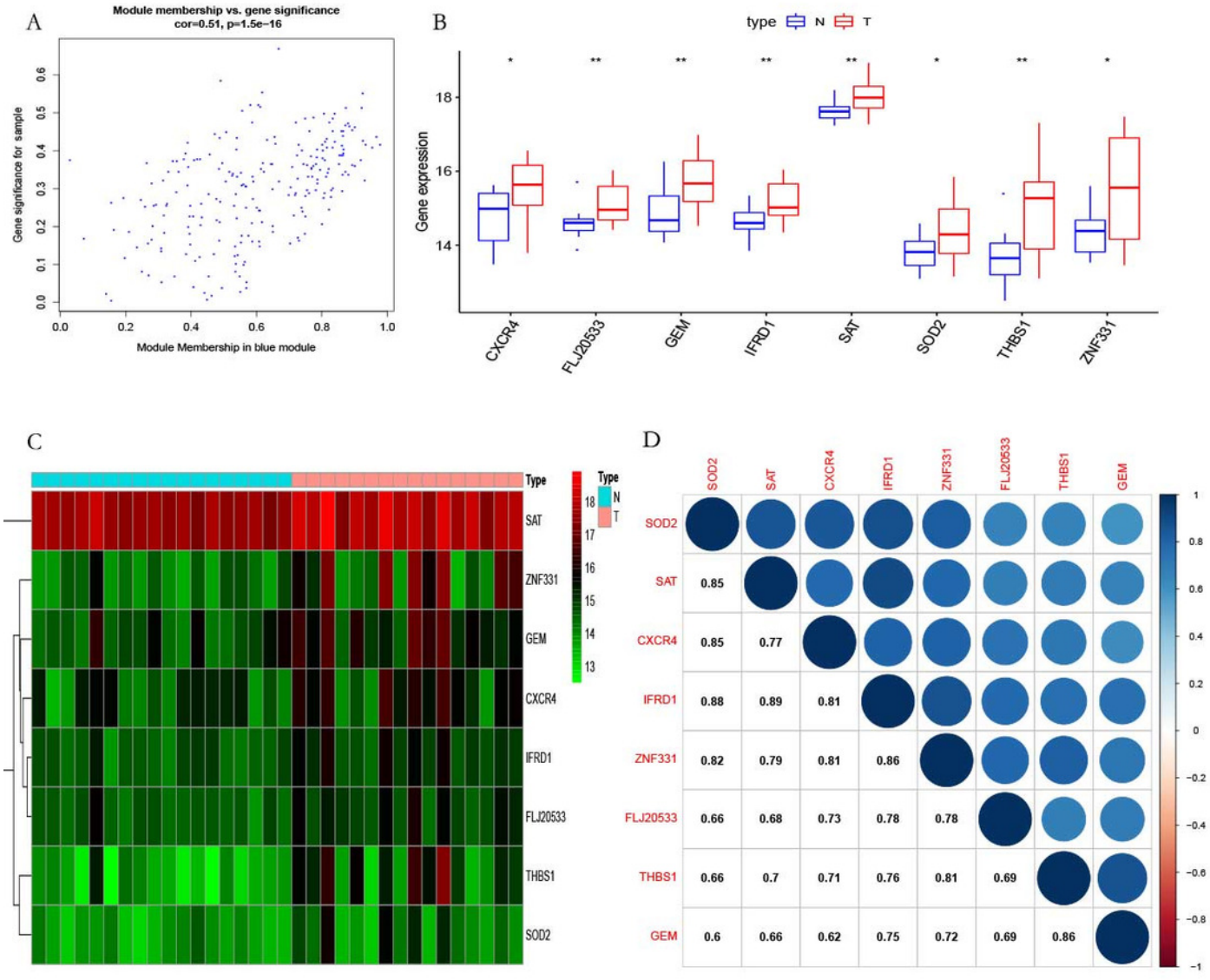

Figure 6

Figure 6

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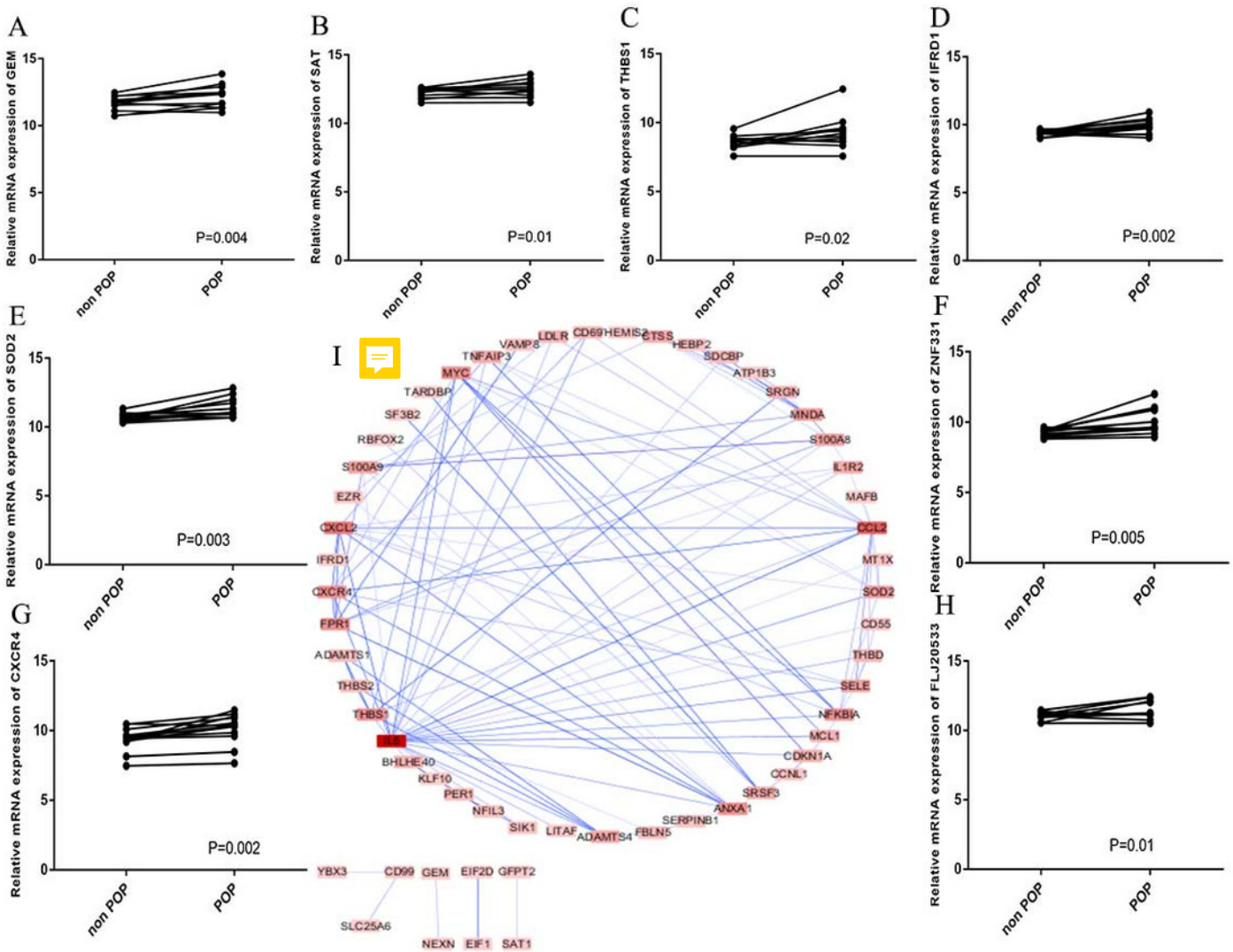

Figure 7

Figure 7

FIGURE. 7. The landscape of immune cells infiltration in GSE12852 (CIBERSORT p value <0.05). (A) The proportion of 22 immune cells in GSE12852. (B) Correlation matrix between 22 immune cells.

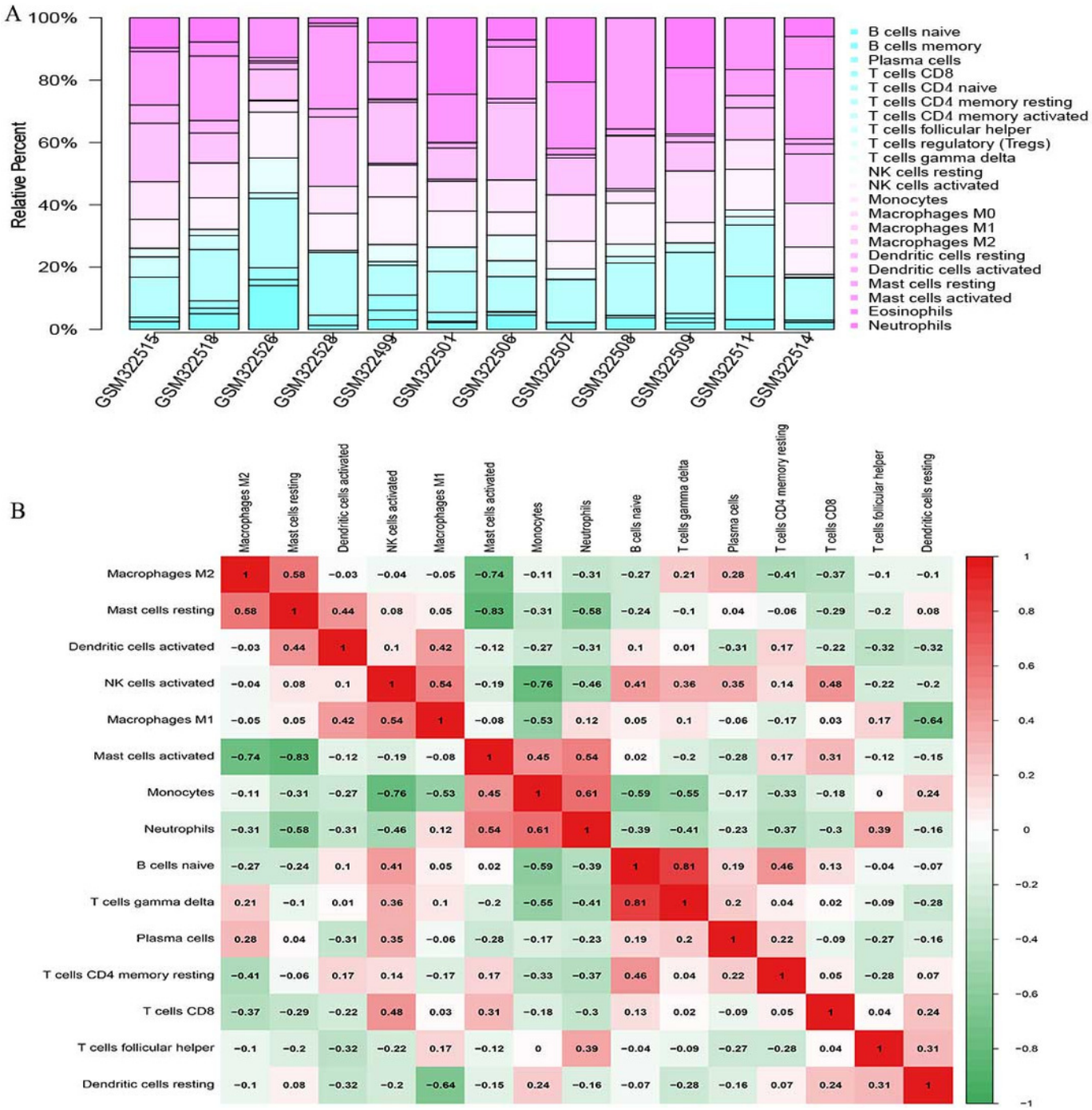
A
100%
80%
60%
40%
20%
0%
Relative Percent
GSM322515
GSM322518
GSM322526
GSM322528
GSM322499
GSM322501
GSM322506
GSM322507
GSM322508
GSM322509
GSM322511
GSM322514
B cells naive
B cells memory
Plasma cells
T cells CD8
T cells CD4 naive
T cells CD4 memory resting
T cells CD4 memory activated
T cells follicular helper
T cells regulatory (Tregs)
T cells gamma delta
NK cells resting
NK cells activated
Monocytes
Macrophages M0
Macrophages M1
Macrophages M2
Dendritic cells resting
Dendritic cells activated
Mast cells resting
Mast cells activated
Eosinophils
Neutrophils
B
Macrophages M2 1 0.58 -0.03 -0.04 -0.05 -0.74 -0.11 -0.31 -0.27 0.21 0.28 -0.41 -0.37 -0.1 -0.1
Mast cells resting 0.58 1 0.44 0.08 0.05 -0.83 -0.31 -0.58 -0.24 -0.1 0.04 -0.06 -0.29 -0.2 0.08
Dendritic cells activated -0.03 0.44 1 0.1 0.42 -0.12 -0.27 -0.31 0.1 0.01 -0.31 0.17 -0.22 -0.32 -0.32
NK cells activated -0.04 0.08 0.1 1 0.54 -0.19 -0.76 -0.46 0.41 0.36 0.35 0.14 0.48 -0.22 -0.2
Macrophages M1 -0.05 0.05 0.42 0.54 1 -0.08 -0.53 0.12 0.05 0.1 -0.06 -0.17 0.03 0.17 -0.64
Mast cells activated -0.74 -0.83 -0.12 -0.19 -0.08 1 0.45 0.54 0.02 -0.2 -0.28 0.17 0.31 -0.12 -0.15
Monocytes -0.11 -0.31 -0.27 -0.76 -0.53 0.45 1 0.61 -0.59 -0.55 -0.17 -0.33 -0.18 0 0.24
Neutrophils -0.31 -0.58 -0.31 -0.46 0.12 0.54 0.61 1 -0.39 -0.41 -0.23 -0.37 -0.3 0.39 -0.16
B cells naive -0.27 -0.24 0.1 0.41 0.05 0.02 -0.59 -0.39 1 0.81 0.19 0.46 0.13 -0.04 -0.07
T cells gamma delta 0.21 -0.1 0.01 0.36 0.1 -0.2 -0.55 -0.41 0.81 1 0.2 0.04 0.02 -0.09 -0.28
Plasma cells 0.28 0.04 -0.31 0.35 -0.06 -0.28 -0.17 -0.23 0.19 0.2 1 0.22 -0.09 -0.27 -0.16
T cells CD4 memory resting -0.41 -0.06 0.17 0.14 -0.17 0.17 -0.33 -0.37 0.46 0.04 0.22 1 0.05 -0.28 0.07
T cells CD8 -0.37 -0.29 -0.22 0.48 0.03 0.31 -0.18 -0.3 0.13 0.02 -0.09 0.05 1 0.04 0.24
T cells follicular helper -0.1 -0.2 -0.32 -0.22 0.17 -0.12 0 0.39 -0.04 -0.09 -0.27 -0.28 0.04 1 0.31
Dendritic cells resting -0.1 0.08 -0.32 -0.2 -0.64 -0.15 0.24 -0.16 -0.07 -0.28 -0.16 0.07 0.24 0.31 1
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

Figure 8

Figure 8

FIGURE. 8. The differential immune cells infiltration between POP tissues and non-POP tissues. (A) Mast cells resting; (B) Mast cells activated; (C) Neutrophils. Group1: non-POP; Group2: POP.

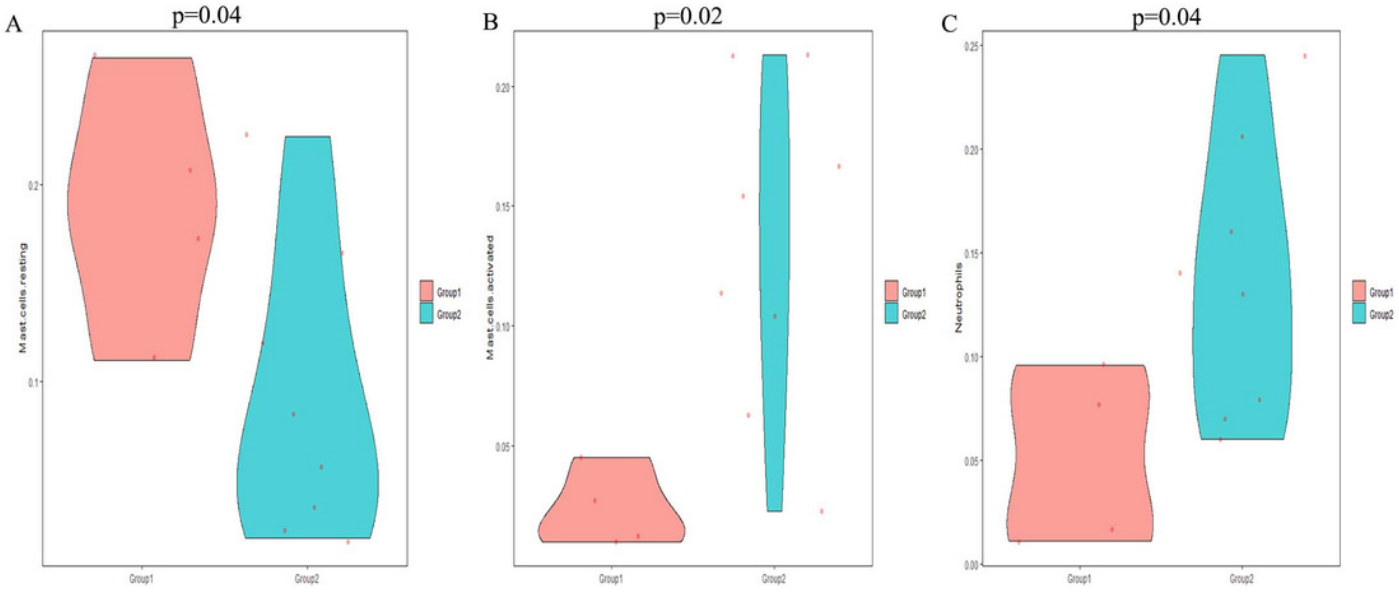

Table 1(on next page)

Table 1

TABLE.1. The correlation between hub genes and immune cells.

GENE	IIMMUNE CELL	P	R
CXCR4	Mast cells activated	0.026025009	0.636596855
FLJ20533	Mast cells activated	0.037410947	0.604312579
GEM	Mast cells activated	0.00382779	0.763874376
IFRD1	Mast cells activated	0.010102021	0.707220887
SAT	Mast cells activated	0.026678483	0.634493564
SOD2	Mast cells activated	0.019559382	0.659816924
THBS1	Mast cells activated	0.023473376	0.645196019
ZNF331	Mast cells activated	0.005806179	0.741209161
GEM	Mast cells resting	0.044390877	-0.587895781
IFRD1	Mast cells resting	0.010475671	-0.704821204
SAT	Mast cells resting	0.029213165	-0.626671202
SOD2	Mast cells resting	0.002740399	-0.780472841
CXCR4	Neutrophils	0.002884121	0.778019124
FLJ20533	Neutrophils	0.009179588	0.713441726
GEM	Neutrophils	0.030016479	0.624294555
IFRD1	Neutrophils	0.001688177	0.802313109
SAT	Neutrophils	0.001387584	0.810472605
SOD2	Neutrophils	2.12E-04	0.872716498
THBS1	Neutrophils	0.014406502	0.682777143
ZNF331	Neutrophils	0.002414909	0.786415881

1