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Il1r2 and Tnfrsf12a in transcranial magnetic stimulation effect of ischemic stroke via bioinformatics analysis

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Abstract

Ischemic stroke refers to ischemic necrosis or softening of localized brain tissue. Transcranial magnetic stimulation (TMS) is a painless, noninvasive and green treatment method, which acts on the central nervous system through a pulsed magnetic field to assist in the treatment of central nervous system injury diseases. However, the role of Il1r2 and Tnfrsf12a in this is unknown. The ischemic stroke datasets GSE81302 and TMS datasets GSE230148 were downloaded from Gene Expression Omnibus database. Differentially expressed genes (DEGs) were screened and weighted gene co-expression network analysis (WGCNA) was performed. The construction and analysis of protein-protein interaction (PPI) network and functional enrichment analysis were performed. Draw heat map gene expression. Through the Comparative Toxicogenomics Database (CTD) to find the most relevant and core gene diseases. TargetScan was used to screen miRNAs regulating DEGs. A total of 39 DEGs were identified. According to gene ontology (GO) analysis results, in biological process (BP) analysis, they were mainly enriched in the positive regulation of apoptosis process, inflammatory response, positive regulation of p38MAPK cascade, and regulation of cell cycle. In cellular component (CC) analysis, they were mainly enriched in the cell surface, cytoplasm, and extracellular space. In Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, they were mainly enriched in nf-κB signaling pathway, fluid shear stress and atherosclerosis, P53 signaling pathway, TNF signaling pathway, and apoptosis. Among the enrichment items of metascape, negative regulation of T cell activation, hematopoietic cell lineage, positive regulation of apoptotic process, fluid shear stress and atherosclerosis were observed in GO enrichment items. Five core genes (Socs3, Irf1, Il1r2, Ccr1, and Tnfrsf12a) were obtained, which were highly expressed in ischemic stroke samples. Il1r2 and Tnfrsf12a were lowly expressed in TMS samples. CTD analysis found that the core gene (Socs3, Irf1 and Il1r2, Ccr1, Tnfrsf12a) and ischemic stroke, atherosclerosis, hypertension, hyperlipidemia, thrombosis, stroke, myocardial ischemia, myocardial infarction, and inflammation. Il1r2 and Tnfrsf12a are highly expressed in ischemic stroke, but lowly expressed in TMS samples.

Abbreviations: BP = biological process, CC = cellular component, CTD = Comparative Toxicogenomics Database, DEGs = differentially expressed genes, GO = gene ontology, IL-1 = interleukin-1, Il1r2 = interleukin-1 receptor type 2, KEGG = Kyoto Encyclopedia of Genes and Genomes, PPI = protein-protein interaction, STRING = Search Tool for the Retrieval of Interacting Genes, TMS = transcranial magnetic stimulation, Tnfrsf12a = tumor necrosis factor receptor superfamily member 12A, USP15 = ubiquitin-specific protease 15, WGCNA = weighted gene co-expression network analysis.

Keywords: bioinformatics, differentially expressed genes, Il1r2, ischemic stroke, Tnfrsf12a, transcranial magnetic stimulation

1. Introduction

Ischemic stroke, also known as cerebral infarction, is a common cerebrovascular disease.[1] It is caused by one or more blood vessels in the brain being blocked by thrombus or embolus, resulting in the reduction or interruption of blood supply to a certain area of the brain, causing hypoxia and damage to brain tissue.[2] Ischemic stroke symptoms depends on the affected area of the brain, common symptoms include sudden facial paralysis, limb weakness, speech disorders, visual disturbances, such as headache, syncope, cerebral infarction is one of the most obvious pathological features.[3] Urgent treatment is essential for ischemic stroke, and early restoration of blood flow can minimize brain damage. Ischemic stroke risk increases with age, the incidence of women in the older section may be slightly higher than the male, also exists between different ethnic and regional differences.[4] Ischemic stroke are often sudden, symptoms will appear quickly in a short time,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the ethics committee of Beijing Rehabilitation Hospital Affiliated to Capital Medical University.

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may become apparent within a few minutes, the symptoms can be temporary, also can be persistent. Treatment including thrombolysis therapy, anticoagulation and antiplatelet drugs and surgery.[5]

Transcranial magnetic stimulation (TMS) is a noninvasive neural control technology, it is by applying Magnetic field on the scalp to stimulate the neurons in the brain activity, and does not involve direct contact with the brain tissue.[6,7] The working principle of TMS is based on the principle of electromagnetic induction and penetrates the skull and scalp without the need for surgery or incision, is a relatively safe and noninvasive method, and most patients are treated with TMS without serious side effects.[8] This technique is widely used clinically and in research to affect specific regions of the brain neural activity with high locality and can be used to treat a variety of neuropsychiatric disorders, as well as to study brain function and neural networks. TMS stimulation intensity, frequency, stimulation position and other parameters can be adjusted and controlled, so that the stimulation program can be designed and implemented according to different situations and purposes. TMS can trigger the brain neurons excitement or suppressed, it can simulate the interactions of neurons in the brain, the neurons to produce the functional sex of the temporary change.[9,10] Ischemic stroke etiology is not clear. The disease may be related to genetic factors, chromosome abnormalities, gene fusion and other factors. Therefore, it is particularly important to further study the molecular mechanism of ischemic stroke and TMS.

Bioinformatics technology is a comprehensive discipline, computer science, mathematics, statistics and biology, and other fields of knowledge and the combination of technology, used for processing and analysis of biological data, thereby helping to solve complex problems in the study of biology.[11] Bioinformatics technology in genomics, proteomics, transcription proteomics, metabolomics, etc widely used in many fields. The rapid development of bioinformatics technology has become an important part of modern biological research. It not only accelerates the speed of scientific discovery, but also provides important support for drug research and development, medical diagnosis and personalized medicine.[12,13]

However, the relationship between Il1r2, Tnfrsf12a, ischemic stroke and TMS is still unclear. Therefore, this paper intends to use bioinformatics technology to explore the core genes between ischemic stroke, TMS and normal tissues, and conduct enrichment analysis and pathway analysis. Using public datasets verify Il1r2, Tnfrsf12a in ischemic cerebral apoplexy and significant role in the TMS.

2. Methods

2.1. Ischemic stroke and transcranial magnetic stimulation data set

The ischemic stroke datasets GSE81302 and TMS data set GSE230148 were downloaded from the Gene Expression Omnibus database generated by GPL17117 and GPL22145. GSE81302 including 3 ischemic cerebral apoplexy and 3 normal brain tissue samples, GSE230148 including 26 TMS and 14 normal brain tissue samples, used to identify ischemic cerebral apoplexy and TMS of the differentially expressed genes (DEGs).

2.2. Screening of DEGs

First investigated GSE81302 data sets and GSE230148 log2 transformation, using lmFit function for multiple linear regression. Through empirical Bayesian adjustment of the standard errors to a common value, the adjusted t-statistic, the adjusted F-statistic, and the logarithmic ratio of the differential expression were calculated to finally obtain the difference significance of each gene, and the volcano plot was made. The differential genes of GSE81302 and GSE230148 were intersected to obtain DEGs.

2.3. Weighted gene co-expression network analysis (WGCNA)

The median absolute deviation of each gene was calculated using the gene expression matrices of GSE81302 and GSE230148, respectively, and the top 50% of genes with the smallest median absolute deviation were excluded. Outlier genes and samples were removed by good Samples Genes method of R package WGCNA, and WGCNA was further used to construct scale-free co-expression network. To classify genes with similar expression profiles into gene modules, average linkage hierarchical clustering was performed according to TOM-based dissimilarity measures with a minimum size (genome) of 30 for the gene dendrogram. To further analyze modules, we calculated the dissimilarity of module characteristic genes, selected a cut line for the module dendrogram, and merged some modules. Modules with distances <0.25 were also incorporated. It is worth noting that gray modules are considered to be the collection of genes that cannot be assigned to any module.

2.4. Construction and analysis of protein-protein interaction (PPI) networks

The Search Tool for the Retrieval of Interacting Genes (STRING) database (https://cn.string-db.org/) is designed to collect, score, and integrate all publicly available sources of protein-protein interaction information and to supplement these sources with computational predictions. In this study, the list of differential genes was input into the STRING database to construct a PPI network for predicting core genes. Cytoscape software provides biologists with biological network analysis and 2-dimensional (2D) visualization. In this study, Cytoscape software was used to visualize the PPI network formed by the STRING database and to predict core genes. The PPI network was imported into Cytoscape software, and the module with the best correlation was found by MCODE. The best correlation genes were calculated by 4 algorithms (MCC, MNC, DMNC, Closeness) and the intersection was taken.

2.5. Functional enrichment analysis

Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis are computational methods for assessing gene function and biological pathways. The gene list was entered into the KEGG website (https://www.kegg.jp/kegg/rest/keggapi.html), to obtain the latest KEGG annotations. Using this as background, the genes were mapped to the background set, and the R package clusterProfiler (version 3.14.3) was used for enrichment analysis to obtain the results of gene set enrichment. The GO annotation of genes in the R software package was used as the background, and the genes were mapped to the background set. The minimum gene set was 5, the maximum gene set was 5000, and P value of $< .05$ and a FDR of < 0.25 were considered to be statistically significant.

In addition, Metascape database can provide a comprehensive list of genes annotation and analysis of resources, and visualization is derived. Using Metascape database (http://metascape.org/gp/index.html) for the above differences in gene enrichment of function analysis and export list.

2.6. Heat map of gene expression

The R package heatmap was used to analyze the expression levels of core genes found in the PPI network in the gene expression

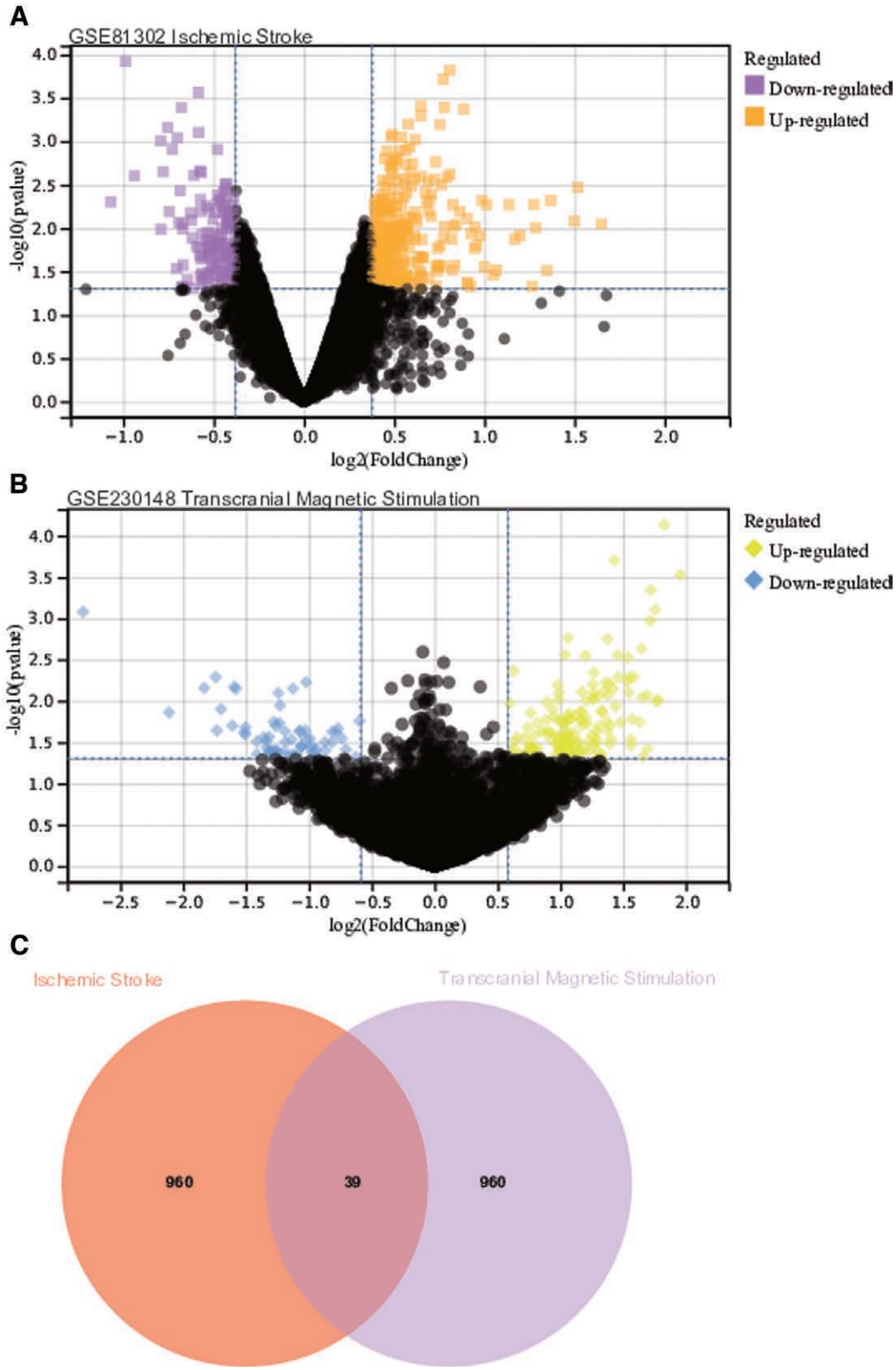

Figure 1. Differential gene analysis. (A) GSE81302. (B) GSE230148. (C) Venn diagram, 39 DEGs. BP = biological process, CC = cellular component, DEGs = differentially expressed genes.

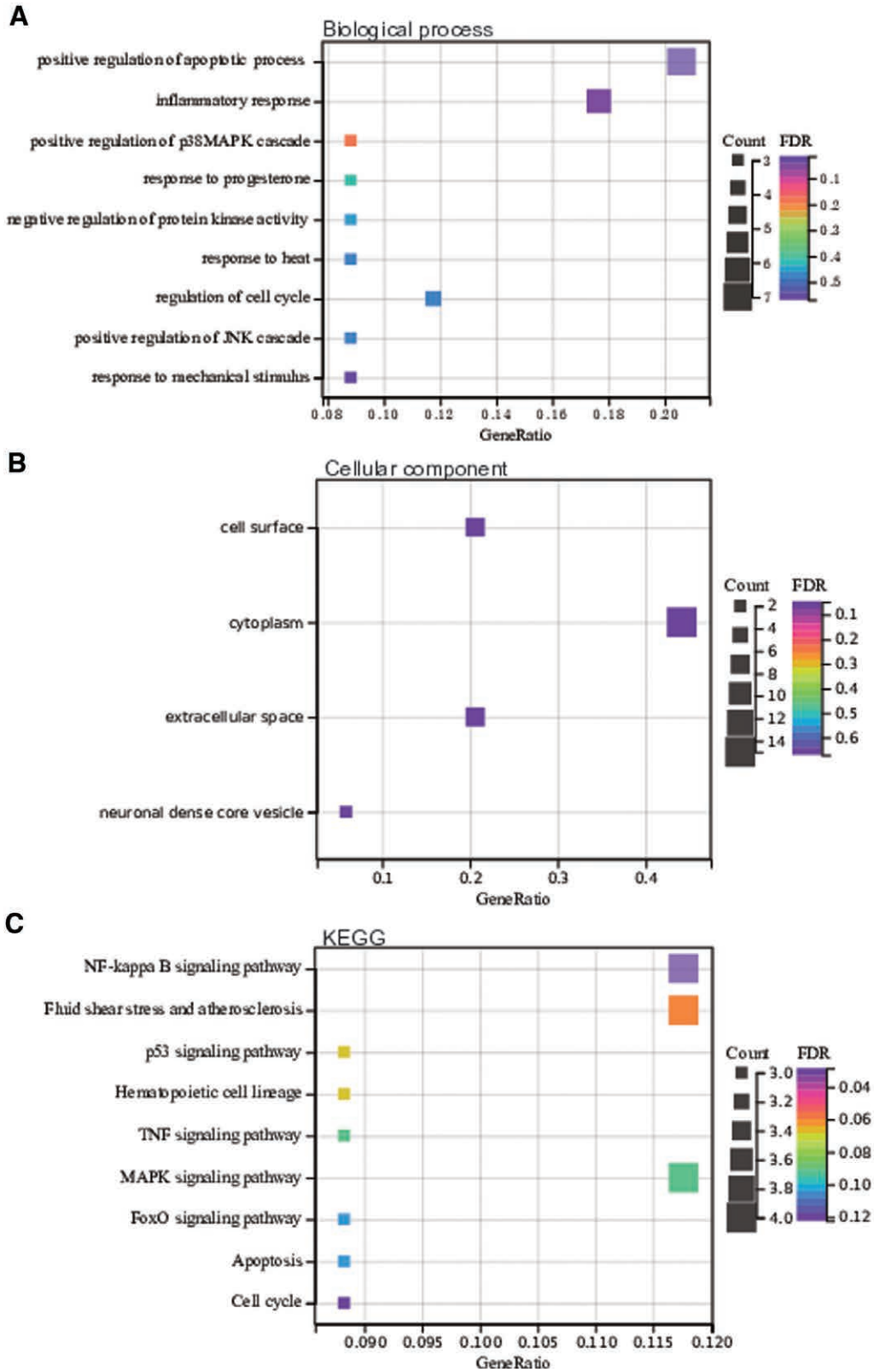

Figure 2. Functional enrichment analysis. (A) BP analysis. (B) CC analysis. (C) KEGG analysis. BP = biological process, CC = cellular component, KEGG = Kyoto Encyclopedia of Genes and Genomes.

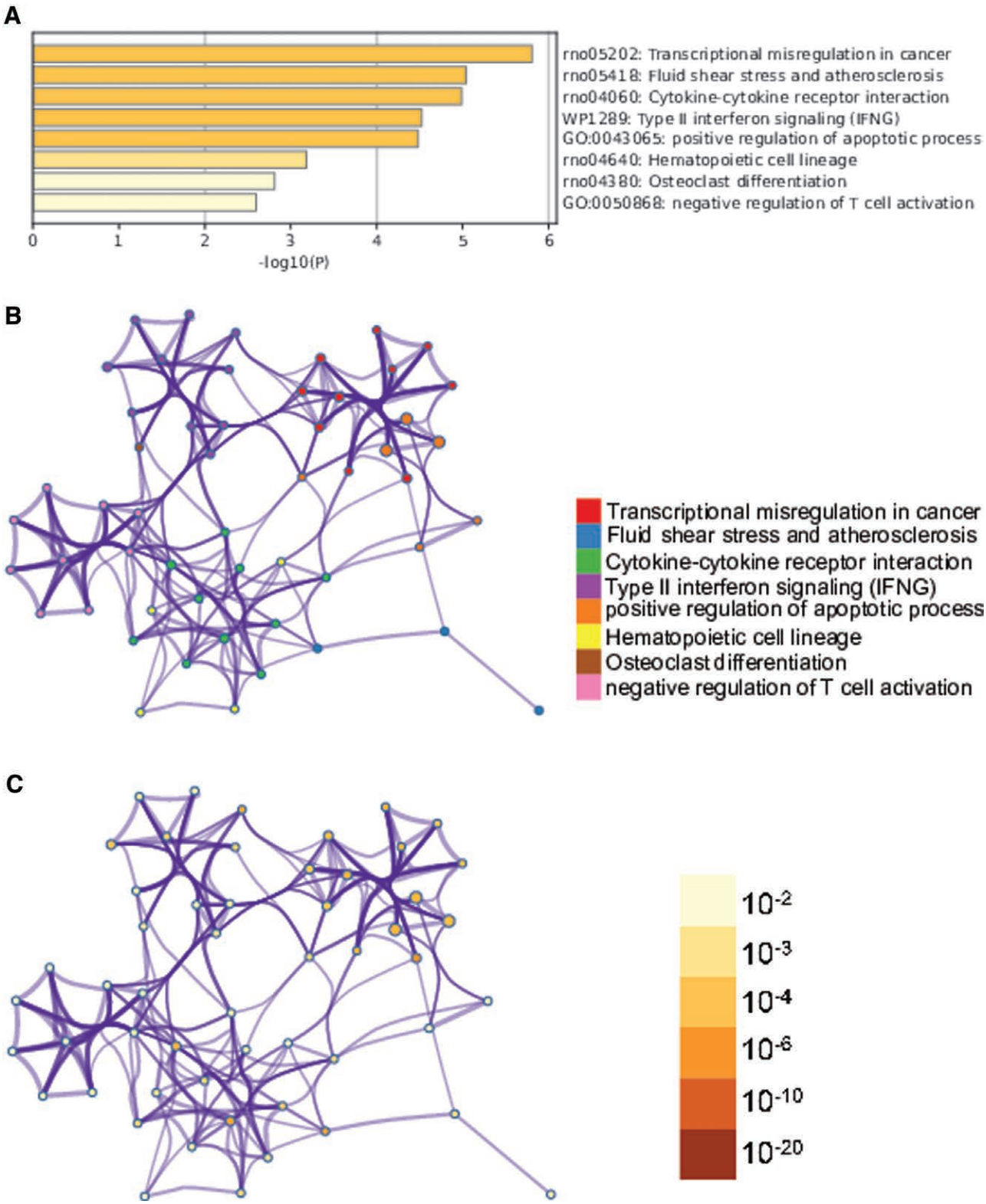

Figure 3. Metascape enrichment analysis. (A) In the enrichment program of metascape, negative regulation of T cell activation, hematopoietic cell lineage, positive regulation of apoptosis, fluid shear stress and atherosclerosis was seen in the enrichment program of GO. (B, C) The enrichment network colored by enrichment terms and *P* value. GO = gene ontology.

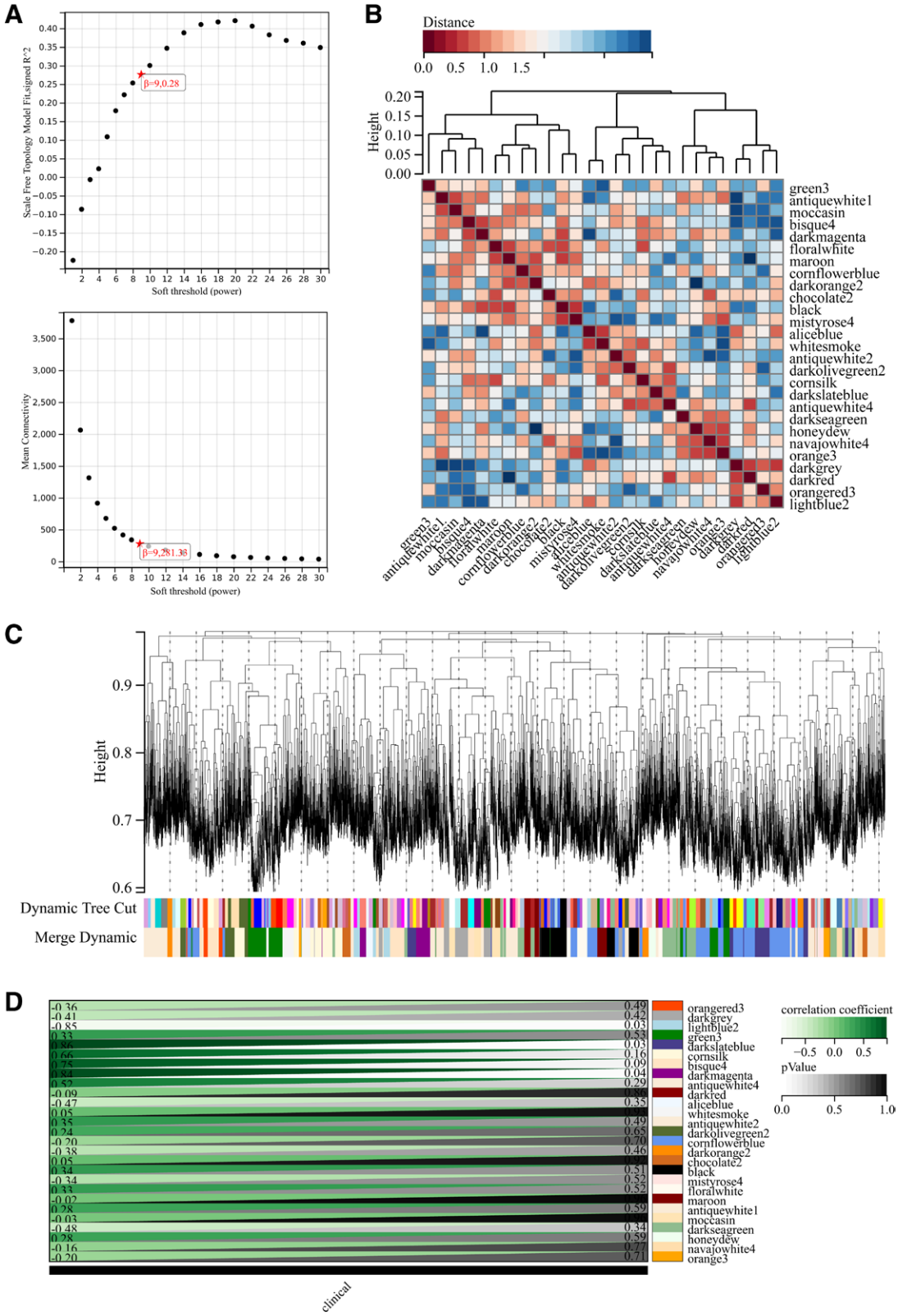

Figure 4. WGCNA of GSE81302. (A) β = 9, 0.28; β = 9, 281.33. (B) Hierarchical clustering trees of all genes were constructed and interactions between important modules. (C) 27 modules. (D) Heatmaps of module and phenotype correlations. WGCNA = weighted gene co-expression network analysis.

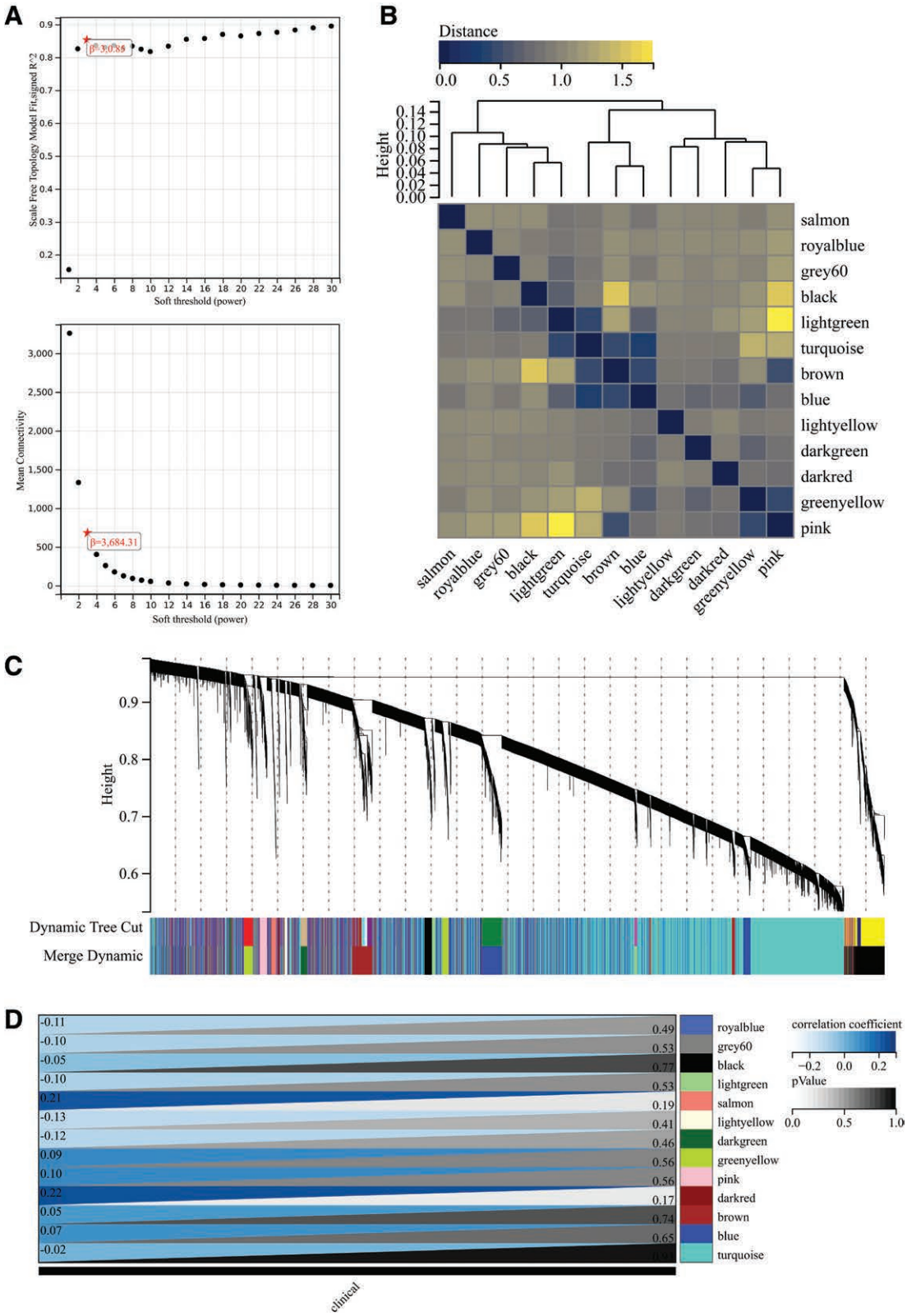

Figure 5. WGCNA of GSE230148. (A) β = 3, 0.85; β = 3, 684.31. (B) Hierarchical clustering trees of all genes were constructed and interactions between important modules. (C) 13 modules. (D) Heatmaps of module and phenotype correlations. WGCNA = weighted gene co-expression network analysis.

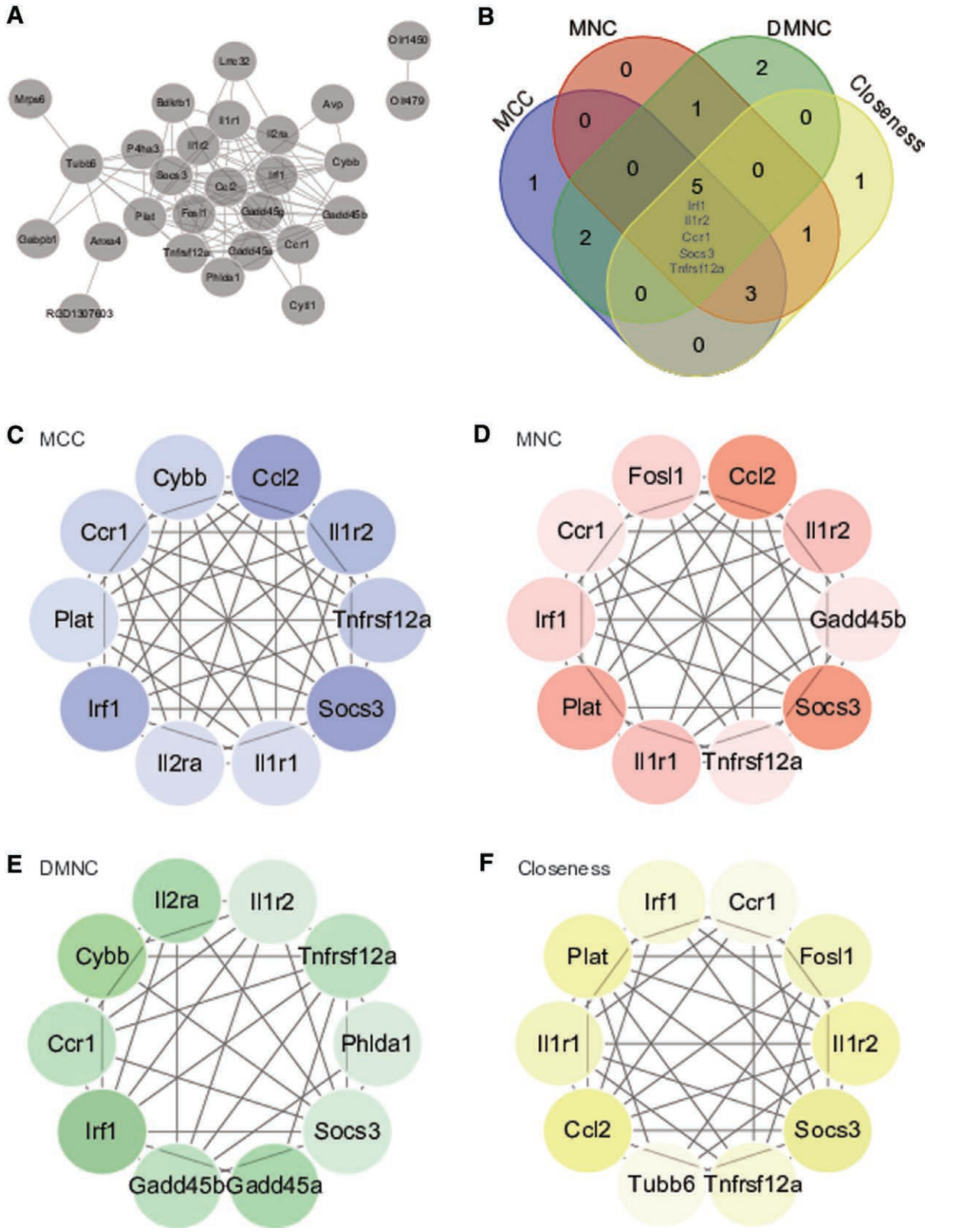

Figure 6. Construction and analysis of protein-protein interaction (PPI) network. (A) PPI network. (B) Venn diagram. (C-F) 4 algorithms (MCC, MNC, DMNC, Closeness) were used to identify the central genes.

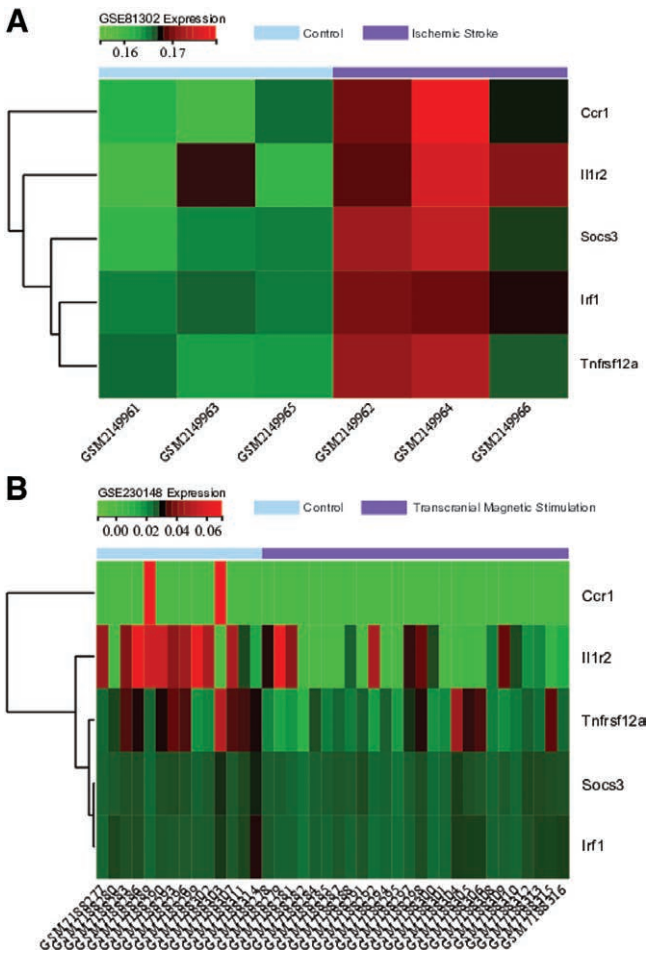

Figure 7. Heat map of gene expression. (A) Socs3, Irf1, Il1r2, Ccr1, and Tnfrsf12a were highly expressed in the ischemic stroke samples and low expressed in the normal samples. (B) Il1r2 and Tnfrsf12a in samples of transcranial magnetic stimulation for low expression, high expression in normal sample.

matrix of GSE81302 and GSE230148, and heat maps were made respectively to visualize the expression differences of core genes among ischemic stroke, TMS and normal brain tissue samples.

2.7. CTD analysis

Comparative Toxicogenomics Database (CTD) integration of a large number of chemicals, genetic, functional data, the interactions between the phenotype and disease related environmental exposure factors for disease and drug potential mechanism research provides great convenience. The core genes were entered into the CTD website, the most relevant diseases to the core genes were found, and the differential expression radar map of each gene was drawn by Excel.

2.8. The miRNA

TargetScan (www.targetscan.org) is an online database for the prediction and analysis of miRNAs and target genes. In our study, TargetScan was used to screen miRNAs regulating central DEGs.

3. Results

3.1. Differential gene analysis

In this study, according to the set cutoff value, the gene expression matrix of the ischemic stroke dataset GSE81302 (Fig. 1A) and the TMS dataset GSE230148 (Fig. 1B) were used to identify the differentially expressed genes, and then the intersection of the differentially expressed genes of the 2 datasets was taken by Venn diagram. The last received 39 DEGs (Fig. 1C).

3.2. Functional enrichment analysis

3.2.1. DEGs. These differentially expressed genes were analyzed by GO and KEGG. According to the results of GO analysis, in BP analysis, they were mainly concentrated in the positive regulation of apoptosis process, inflammatory response, positive regulation of p38MAPK cascade, and regulation of cell cycle (Fig. 2A). In CC analysis, they were mainly concentrated on the cell surface, cytoplasm, and extracellular space (Fig. 2B). In KEGG analysis, they were mainly concentrated in nf-κB signaling pathway, fluid shear stress and atherosclerosis, P53 signaling pathway, TNF signaling pathway, and apoptosis (Fig. 2C).

3.3. Metascape enrichment analysis

In the enrichment program of metascape, negative regulation of T cell activation, hematopoietic cell lineage, positive regulation of apoptosis, fluid shear stress and atherosclerosis was seen in the enrichment program of GO (Fig. 3A). At the same time, we also output enrichment networks with enrichment term coloring and *P*-value coloring (Fig. 3B and C) to visually represent the association and confidence of each enrichment item.

3.4. WGCNA

Soft threshold power selection is an important step in WGCNA analysis. For the ischemic stroke dataset GSE81302, we performed a network topology analysis to determine the soft threshold power. WGCNA of soft threshold power set to 9, 0.9 this is scale-free topology fitting index of minimum power (Fig. 4A). Hierarchical clustering trees of all genes were constructed and interactions between important modules were analyzed (Fig. 4B), which yielded 27 modules (Fig. 4C). Heatmaps of module and phenotype correlations were also generated (Fig. 4D).

For the TMS dataset GSE230148, we performed a network topology analysis to determine the soft threshold power. The soft-threshold power in the WGCNA analysis was set to 9, which was the lowest power for a scale-free topological fit index of 0.9 (Fig. 5A). Hierarchical clustering trees of all genes were constructed and interactions between important modules were analyzed (Fig. 5B), which yielded 13 modules (Fig. 5C). Heatmaps of module and phenotype correlations were also generated (Fig. 5D).

3.5. Construction and analysis of protein-protein interaction (PPI) network

The PPI network of DEGs was constructed from the STRING online database and analyzed by Cytoscape software (Fig. 6A). Four algorithms were used to identify central genes, and Venn diagram was made to obtain intersection genes (Fig. 6B). The results of 4 algorithms (MCC, MNC, DMNC, Closeness) are shown in Figure 6C, D, E, and F. Finally, 5 core genes (Socs3, Irf1, Il1r2, Ccr1, and Tnfrsf12a) were obtained.

3.6. Heat map of gene expression

The expression levels of core genes in the matrix of GSE81302 and GSE230148 of the ischemic stroke dataset and TMS dataset were visualized and heat maps were made respectively. We found that core genes (Socs3, Irf1, Il1r2, Ccr1, and

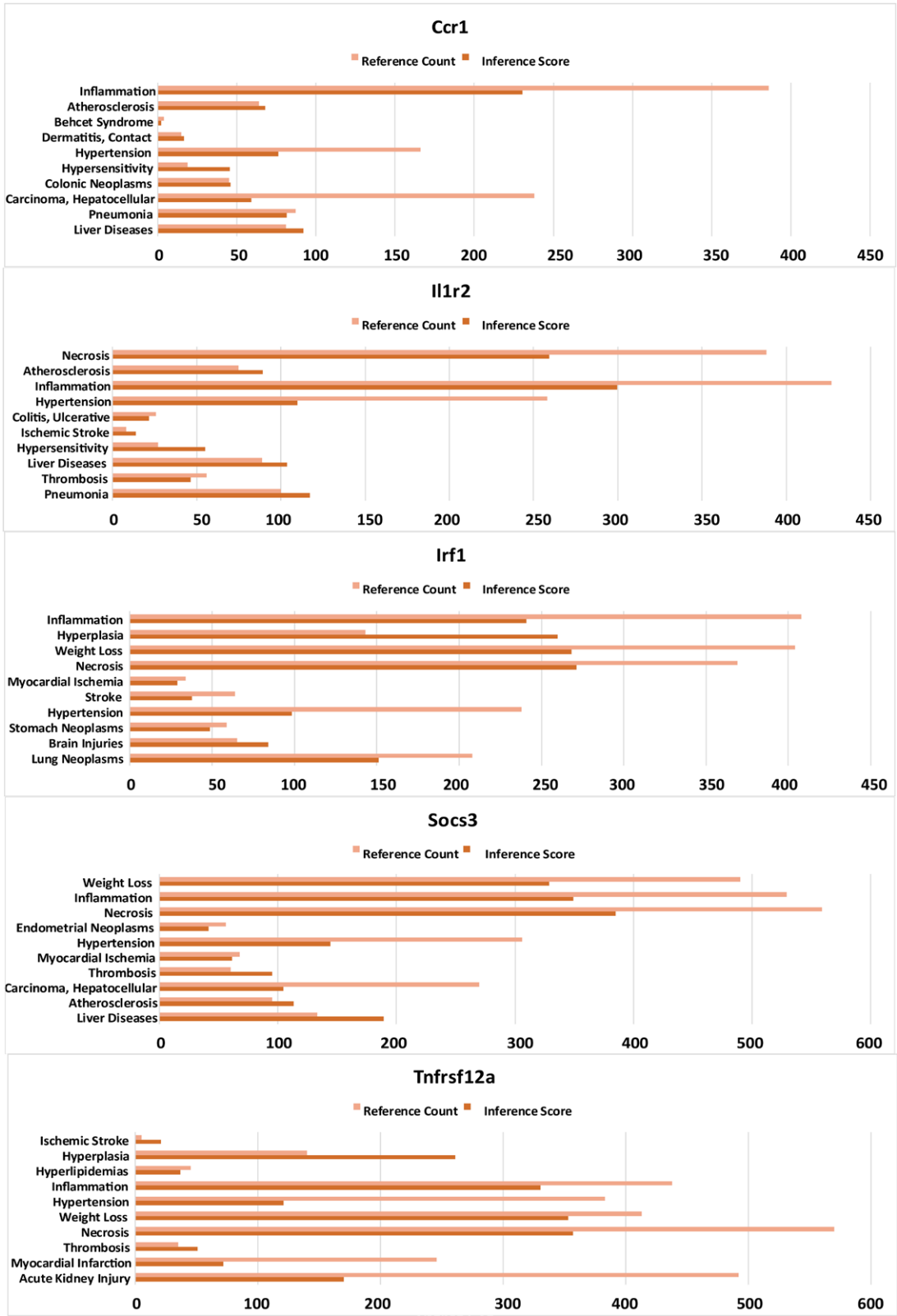

Figure 8. CTD analysis. Core genes (Socs3, Irf1, Il1r2, Ccr1, Tnfrsf12a) were associated with ischemic stroke, atherosclerosis, hypertension, hyperlipidemia, thrombosis, stroke, myocardial ischemia, myocardial infarction, and inflammation.

Table 1

A summary of miRNAs that regulate hub genes.

	Gene	MIRNA		
1	Socs3	rno-miR-455-5p	rno-miR-455-5p	
2	Irf1	rno-miR-301a-3p	rno-miR-301b-3p	rno-miR-130b-3p
3	Tnfrsf12a	rno-miR-19b-3p	rno-miR-19a-3p	
4	Il1r2	None		
5	Ccr1	None		

Tnfrsf12a) were highly expressed in the ischemic stroke samples and low expressed in the normal samples (Fig. 7A). Il1r2 and Tnfrsf12a in samples of TMS for low expression, high expression in normal sample (Fig. 7B). Speculation Il1r2, Tnfrsf12a risk for ischemic stroke and TMS has certain regulation effect.

3.7. CTD analysis

In this study, we entered the list of hub genes into the CTD website to search for diseases related to core genes, which improved the understanding of gene-disease association. Core genes (Socs3, Irf1, Il1r2, Ccr1, Tnfrsf12a) were found to be associated with ischemic stroke, atherosclerosis, hypertension, hyperlipidemia, thrombosis, stroke, myocardial ischemia, myocardial infarction, and inflammation (Fig. 8).

3.8. Prediction and functional annotation of miRNAs associated with hub genes

In this study, we input the list of hub genes into targetsacan to find relevant miRNAs and improve the understanding of gene expression regulation (Table 1). We found that Socs3 gene related miRNAs are rno-miR-455-5 p, rno-miR-455-5 p; The related miRNAs of Irf1 gene were rno-miR-301a-3p, rno-miR-301b-3p, and rno-miR-130b-3p. The related miRNAs of Tnfrsf12a gene were rno-miR-19b-3p and rno-miR-19a-3p.

4. Discussion

Ischemic stroke is a severe cerebrovascular disease, which occurs when the blood supply to the brain is interrupted or reduced, resulting in hypoxia and damage to brain tissue. It is one of the main causes of death and disability.[14,15] Ischemic stroke is highly recurrent and seriously harmful, which may lead to visual and speech disorders, brain cell damage and necrosis, lasting neurological impairment, decreased quality of life, and even fatal.[16] Explore the ischemic cerebral apoplexy and the molecular mechanism of TMS, is extremely important to the study of targeted drugs. The main results of this study were that Il1r2 and Tnfrsf12a were highly expressed in ischemic stroke, but low in TMS samples.

Interleukin-1 receptor type 2 (Il1r2) is a protein associated with immune response and inflammation. It belongs to the interleukin-1 (IL-1) receptor family.[17] IL1R2 acts as a decoy receptor for interleukin-1 and can bind to interleukin-1 without triggering a cellular response. This can be achieved by preventing interleukin 1 and other active interleukin 1 receptor interaction to help regulate by interleukin 1 mediated inflammatory signals. The balance between IL1R2 and other interleukin-1 receptors is essential to maintain an appropriate immune response and prevent excessive inflammatory responses.[18] Studies have shown that IL1R2 and eastern China the occurrence of sporadic Parkinson disease.[19] IL1R1 and IL1R2 polymorphisms associated with the risk of tuberculosis.[20] IL1R2 polymorphisms are associated with the risk of high-altitude pulmonary edema.[21]

IL1R2 as a decoy receptor located at 2 q11.2 in the human gene and is a trapping molecule for IL-1β, an important mediator of many cytokine-induced responses, and does not initiate subsequent signaling events, thereby suppressing inflammatory responses.[22] There is no single property of IL1R2, which can neutralize agonist effects by preventing IL1 from binding to signaling IL1R1, thereby limiting the biological effects of cytokines. Many studies have reported IL1R2 as a risk factor in certain diseases and IL1R2 acts as a homeostatic regulator during remission of ulcerative colitis. Another study showed that IL1R2 acts specifically on macrophages as a decoy receptor for IL-1 and is an important regulator of arthritis with an impact on RA risk in Chinese Han population.[23] IL1R2 promotes self-renewal of breast tumor initiating cells and proliferation and invasion of breast cancer cells by binding to and enhancing nuclear ubiquitin-specific protease 15 (USP15) activity.[24] IL1R2 gene polymorphisms and their interactions are associated with the susceptibility to osteoporosis in Chinese Han population.[25]

IL1R1 and IL1R2 gene encoding cytokine receptors plays a pathogenic role in inflammation and tissue destruction. IL1R2 is unable to signal upon IL-1 binding due to its lack of an intracellular TIR domain; therefore, IL1R2 inhibits inflammatory responses.[26] By competitively binding IL-1, IL1R2 can reduce the binding of IL-1 to its normal receptor, thereby inhibiting IL-1 signaling. When treating inflammatory diseases, IL1R2 can alleviate the inflammatory response and reduce the severity of the disease. IL1R2 can also reduce the excessive activation of the immune system and help to regulate the immune response. This could be potentially beneficial for the treatment of immune-related diseases.[27,28] In the process of ischemic stroke, inflammatory response plays an important role in the development of brain injury. Related studies have shown that IL-1 family of cytokine and receptors may play a role in the pathogenesis of ischemic cerebral apoplexy.[29] Therefore, Il1r2 may play an important role in ischemic stroke and TMS.

Tumor Necrosis Factor Receptor Superfamily Member 12A (Tnfrsf12a) and is also known as DR4. This is a cell membrane receptor protein involved in regulating apoptosis (programmed cell death).[30] Tnfrsf12a is a key member of the TRAIL pathway. TRAIL is a cytokine that regulates apoptosis, and it can bind to Tnfrsf12a and another receptor, Tnfrsf10b (DR5), to initiate apoptotic signaling.[31] By binding to TRAIL, these receptors can activate the apoptotic pathway, leading to cell self-destruction.[32] Apoptosis plays an important role in normal physiological processes, such as maintaining tissue balance and removing damaged cells. Tnfrsf12a and TRAIL pathways play an important role in regulating the balance between cell survival and death, and they play an important role in many physiological and pathological processes such as inflammation and immune regulation.[33]

TNFRSF12A is the smallest of TNF superfamily individuals, contains a short cytoplasmic death domain structure.[34] TNFRSF12A participation to stimulate multiple signal transduction pathways, including nuclear factor kB pathway and predominate in increasing angiogenesis. Studies have shown that QPCT, SCEL and TNFRSF12A have diagnostic value in papillary thyroid carcinoma.[35] TNFRSF12A expression may be a potential molecular markers of thyroid cancer prognosis, PPAR signaling pathways, insulin signaling pathway, mTOR signaling pathway may be TNFRSF12A control key pathways in thyroid carcinoma.[36] TNFRSF12A and CD38 lead to a vicious cycle of chronic obstructive pulmonary disease with aging pathways.[37] Inhibition of TWEAK/Tnfrsf12a axis or RIPK1-dependent apoptosis can alleviate liver injury, which provides a new potential therapeutic target for its treatment.[38] TNFRSF12A promotes bile acid-induced pyroptosis in cholestatic hepatocytes through NFκB/Caspase-1/GSDMD signaling pathway, and targeting TNFRSF12A may be a promising approach for the treatment of cholestasis.[39]

TNFRSF12A plays a key role in inflammation and cell death.[40] The activation of Tnfrsf12a can affect the inflammatory response and the activation of immune cells. In some cases, regulation of Tnfrsf12a may help to suppress excessive inflammatory responses and alleviate symptoms of immune-related diseases. Tnfrsf12a activation can promote cell growth, proliferation and invasion and increase cell viability.[41] In ischemic stroke, insufficient blood supply to the brain leads to brain cell damage or death, which may involve multiple cell death pathways, including apoptosis. Tnfrsf12a plays a role in the regulation of apoptosis, so it may play an important role in ischemic stroke and TMS.

Despite the rigorous bioinformatics analysis, there are still some shortcomings. In this study, no animal experiments with overexpression or knockdown of the gene were performed to further verify its function. Therefore, we should conduct in-depth exploration in this aspect in future research.

5. Conclusion

Il1r2 and Tnfrsf12a were highly expressed in ischemic stroke and lowly expressed in TMS samples. The Il1r2 and Tnfrsf12a genes have great potential and broad application prospects in clinical medicine. Future research directions will continue to promote the development of the field of genetic medicine, improve the treatment, prevention and diagnosis of diseases, and will help to achieve more precise medical care and more effective disease treatment. Genetic testing and molecular diagnostic techniques enable doctors to make personalized treatment plans based on the genetic information of patients, help to understand the pathogenesis of genetic diseases, so as to develop preventive measures, help to accurately diagnose and select targeted therapeutic drugs, and improve the therapeutic effect. The study of genetic markers can be used to predict the risk of disease, so as to early intervention and prevention.

Author contribution

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Formal analysis: Aixian Liu, Jiaojiao Wu.
Investigation: Jiaojiao Wu, Fang Lu.
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Supervision: Man Zhao.
Software: Jiaojiao Wu.
Validation: Linhong Mo, Fang Lu, Guiling Wan.
Visualization: Linhong Mo, Fang Lu.
Writing – original draft: Aixian Liu, Fang Lu, Guiling Wan.
Writing – review & editing: Man Zhao.

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