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The value of RPS15 and MRPS27 in ischemic stroke

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Abstract

Ischemic stroke is caused by insufficient blood supply to the brain. It has acute onset, often disturbance of consciousness, and high mortality and disability rate. However, relationship between ribosomal proteins (RP)-S15 and mitochondrial ribosomal proteins (MRP)-S27 and ischemic stroke remains unclear. The ischemic stroke datasets GSE22255, GSE16561, and GSE199435 were downloaded from gene expression omnibus generated by GPL6883, GPL11154, and GPL570. Differentially expressed genes (DEGs) were screened, and the construction and analysis of protein-protein interaction network, functional enrichment analysis and gene set enrichment analysis were performed. The gene expression heat map was drawn. Comparative toxicogenomics database analysis were performed to find the disease most related to core gene. TargetScan screened miRNAs that regulated central DEGs. Five hundred DEGs were identified. According to gene ontology analysis, they were mainly enriched in leukocyte activation, myoid cell activation involved in immune response, cell membrane, mitochondria, secretory vesicles, catalytic activity, enzyme binding, ribonucleic acid binding, splicing. Gene set enrichment analysis showed that the enrichment items are similar to the enrichment items of differentially expressed genes. And 20 core genes were obtained. Comparative toxicogenomics database analysis showed that 6 genes (RPS15, RPS2, RPS3, MRPS27, POLR2A, MRPS26) were found to be associated with chemical and drug-induced liver injury, necrosis, delayed prenatal exposure, nephropathy, hepatomegaly and tumor. RPS15 and MRPS27 are the core genes of ischemic stroke and play an important role in ischemic stroke.

Abbreviations: CTD = comparative toxicogenomics database, DEGs = differential epigenetic genes, GO = gene ontology, GSEA = gene set enrichment analysis, KEGG = Kyoto encyclopedia of gene and genome, MRP = mitochondrial ribosomal proteins, PPI = protein-protein interaction, RP = ribosomal proteins, STRING = search tool for the retrieval of interacting genes.

Keywords: biomarker, ischemic stroke, MRPS27, RPS15, verification

1. Introduction

Ischemic stroke refers to brain tissue necrosis caused by stenosis or occlusion of cerebral feeding arteries (carotid artery and vertebral artery) and insufficient cerebral blood supply.[1–3] Ischemic stroke is the second leading cause of death and the third leading cause of disability among adults worldwide, and global disease burden data released in 2019 show that 1/4 of people suffer from stroke in their lifetime. It is estimated that there are 96 million ischemic strokes and 4.1 million hemorrhagic strokes (including intracerebral and subarachnoid hemorrhage) worldwide each year, and the age-adjusted incidence is relatively stable in high-income countries, but it is on the rise in low-and middle-income countries. The absolute incidence is expected to increase with the aging of the population.[4,5] For stroke patients, the ability to restore work and social function is a key priority. Structured rehabilitation is accepted in most high-income countries but does not exist in many low-or middle-income areas where families are responsible for acute post-care. Ischemic stroke is one of the main causes of chronic disability worldwide. Although substantial progress has been made in the treatment of ischemic stroke in the past 5 years, there is still a lack of effective methods to improve functional recovery after stroke.[6–8] The reasons affecting ischemic stroke are not clear, which may be related to genetic factors, chromosome abnormalities, gene fusion and other factors. Therefore, in-depth study of the molecular mechanism of ischemic stroke is particularly important.

As an important part of the development of life science, bioinformatics has been at the forefront of life science and technology research. In recent years, China's biotechnology has developed by leaps and bounds, and bioinformation resources have also grown explosively. Bioinformatics reveals the biological significance represented by big data, which is a bridge between data and clinic. Represented by the analysis and reporting of gene detection data, bioinformatics plays an important role in tumor treatment.[9,10]

Ribosomal proteins (RP)-S15 encodes ribosomal protein, which is a component of 40s subunit. RPS15 has been found to

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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 Beijing Rehabilitation Hospital Affiliated to Capital Medical University.

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be activated in a variety of tumors, such as insulinoma, esophageal cancer and colon cancer. Mitochondrial ribosomal proteins (MRP)-S27 encodes mitochondrial ribosomal protein S27, which contributes to protein synthesis in mitochondria. It was also found that MRPS27 was highly expressed in several cancers. However, the relationship between it and ischemic stroke is not clear.

Therefore, this paper intends to use bioinformatics technology to mine the core genes between ischemic stroke and normal tissue, and carry out enrichment analysis and pathway analysis. The public data set was used to verify the significant role of RPS15 and MRPS27 in ischemic stroke.

2. Method

2.1. Ischemic stroke data set

In this study, the ischemic stroke dataset GSE22255, GSE16561, and GSE199435 configuration files were downloaded from the gene expression omnibus database (http://www.ncbi.nlm.nih.gov/geo/) generated by GPL6883, GPL11154, and GPL570. GSE22255 included 20 ischemic stroke and 20 normal tissue samples. GSE16561 included 39 ischemic stroke and 24 normal tissue samples. GSE199435 includes 3 ischemic stroke and 3 normal tissue samples,[11] which are used to identify differentially expressed genes (DEGs) in ischemic stroke.

2.2. Batch normalization

For the merging and batch normalization of multiple datasets, we first utilized the R package to merge the datasets GSE22255, GSE16561, and GSE199435. To merge the multiple datasets, we employed the R package inSilicoMerging [DOD:10.1186/1471-2105-13-335] to obtain a merged matrix. Furthermore, we used the "removeBatchEffect" function from the R package limma (version 3.42.2, https://bioconductor.riken.jp/packages/3.10/bioc/html/limma.html) to remove batch effects, resulting in a batch effect-free matrix for subsequent analysis.

2.3. Screening DEGs

The R package "limma" was utilized for probe summarization and background correction of the merged matrices from GSE22255, GSE16561, and GSE199435. The Benjamini-Hochberg method was employed to adjust the original p-values, and the false discovery rate was used to calculate the fold change. The cutoff criteria for DEGs were set as P value < .05, fold change > 1.5. A volcano plot was generated to visualize the DEGs.

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

The Search Tool for the Retrieval of Interacting Genes (STRING) database (https://string-db.org/) aims to collect, score, and integrate all publicly available sources of protein-protein interaction information, and to supplement these sources by calculating predictions. In this study, the list of differential genes was input into STRING database to construct a PPI network for predicting core genes (confidence > 0.4). Cytoscape software (https://cytoscape.org/) can provide biologists with biological network analysis and 2-dimensional (2D) visualization. In this study, the PPI network formed by string database is visualized and core genes are predicted by Cytoscape software. First of all, we import the PPI network into the cytoscape software, calculate the 20 genes with the best correlation by maximal clique centrality algorithm, and then visually derive the list of core genes.

2.5. Functional enrichment analysis

Functional enrichment analysis refers to the statistical analysis of various databases and analysis tools to mine the gene function categories that have significant correlation with the biological problem to be studied in the database. Gene Ontology (GO) and Kyoto Encyclopedia of Gene and Genome, Kyoto encyclopedia of genes and genomes (KEGG) analysis is a computational method for evaluating genetic functions and biological pathways, which can solve the problem of classifying genes according to their functions.

In addition, Metascape database can provide comprehensive gene list annotation and analysis resources, and can be visually exported. We used Metascape (http://metascape.org/gp/index.html) database to analyze the functional enrichment of the above differential gene list and derive it.

2.6. Gene set enrichment analysis (GSEA)

For GSEA, we obtained the GSEA software (version 3.0) from GSEA (DOI:10.1073/pnas.0506580102, http://software.broadinstitute.org/gsea/index.jsp). The samples were divided into 2

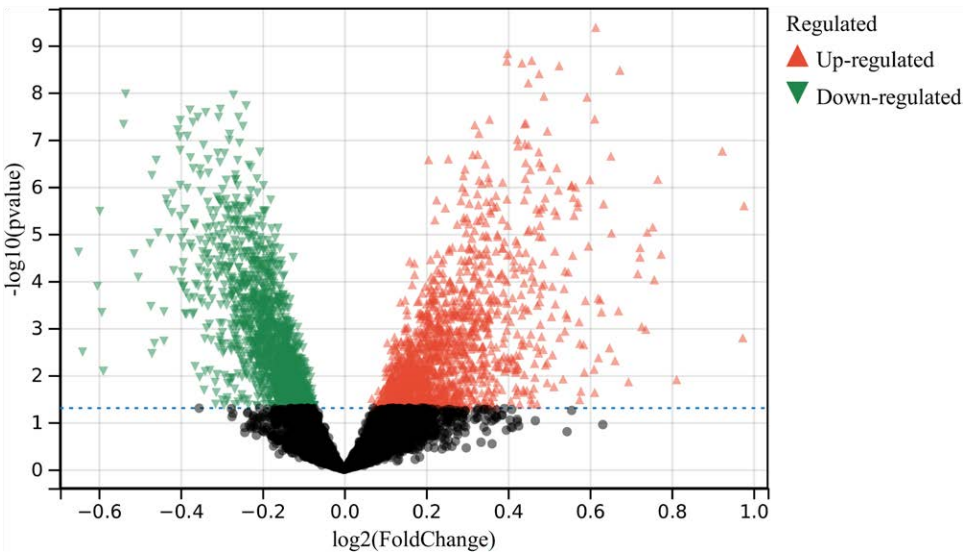

Figure 1. Functional enrichment analysis of DEGs.770 DEGs were identified. DEGs = differential epigenetic genes.

groups according to ischemic stroke and normal tissue, and from Molecular Signatures Database (DOI:10.1093/bioinformatics/btr260). In order to evaluate the related pathways and molecular mechanisms, based on gene expression profile and phenotypic grouping, the minimum gene set is 5, the maximum gene set is 5000, and a thousand resampling times, P value of < .05 and a false discovery rate of < 0.25is considered to be statistically significant.

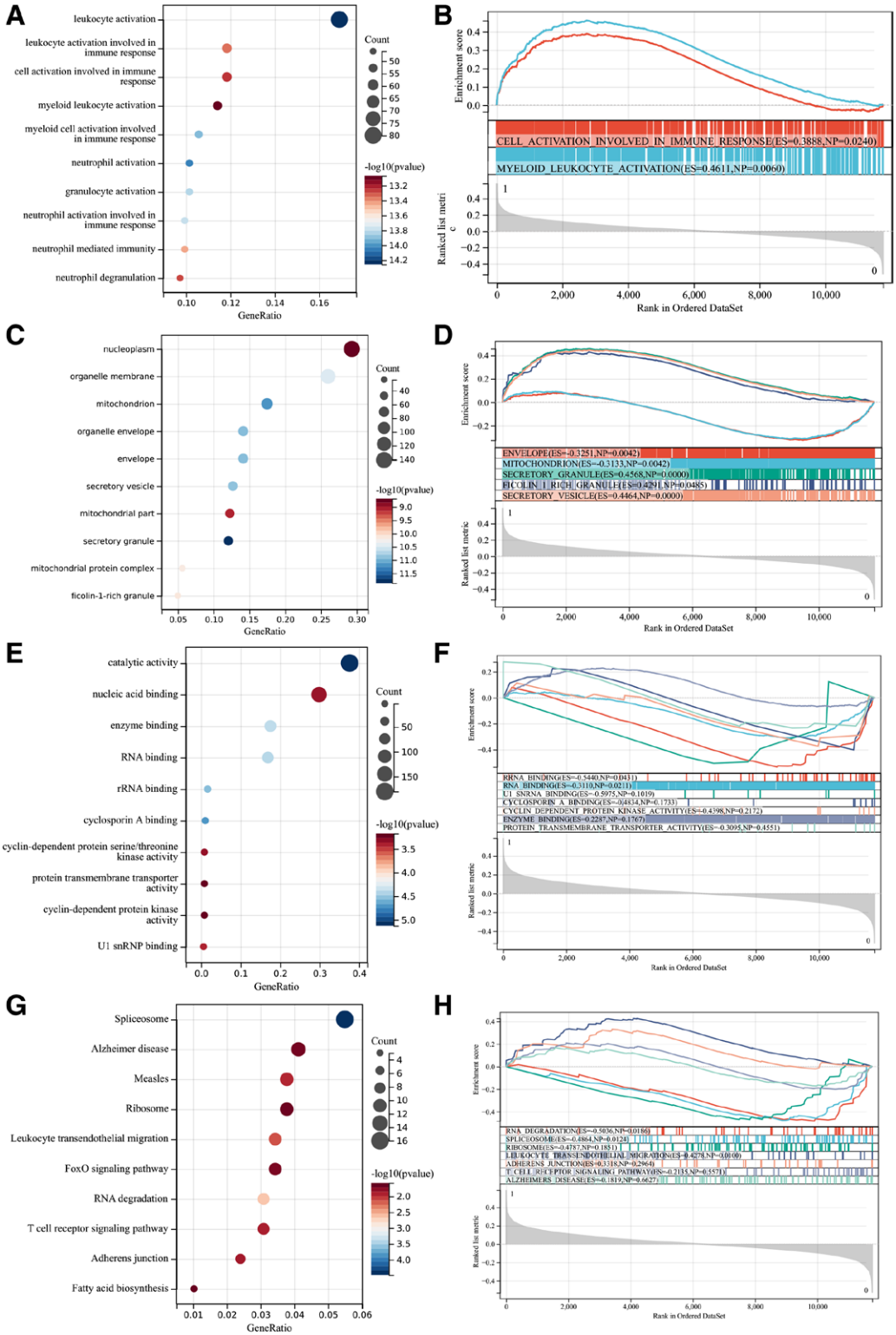

Figure 2. Functional enrichment analysis. (A, C, E, G) DEGs. (B, D, F, H) The GSEA score curve. DEGs = differential epigenetic genes, GSEA = gene set enrichment analysis.

2.7. Gene expression heat map

To visualize the differential expression of core genes obtained from the PPI network between ischemic stroke and normal tissue samples, a heatmap was generated using the R package. The heatmap represents the expression of core genes in the batch-corrected merged matrix of GSE22255, GSE16561, and GSE199435.

2.8. Comparative toxicogenomics database (CTD) analysis

CTD database integrates a large number of chemical substances, genes, functional phenotypes and disease interaction data, which provides great convenience for the study of disease-related environmental exposure factors and drug potential mechanism. We input the core gene into the CTD website, find the disease most related to the core gene, and

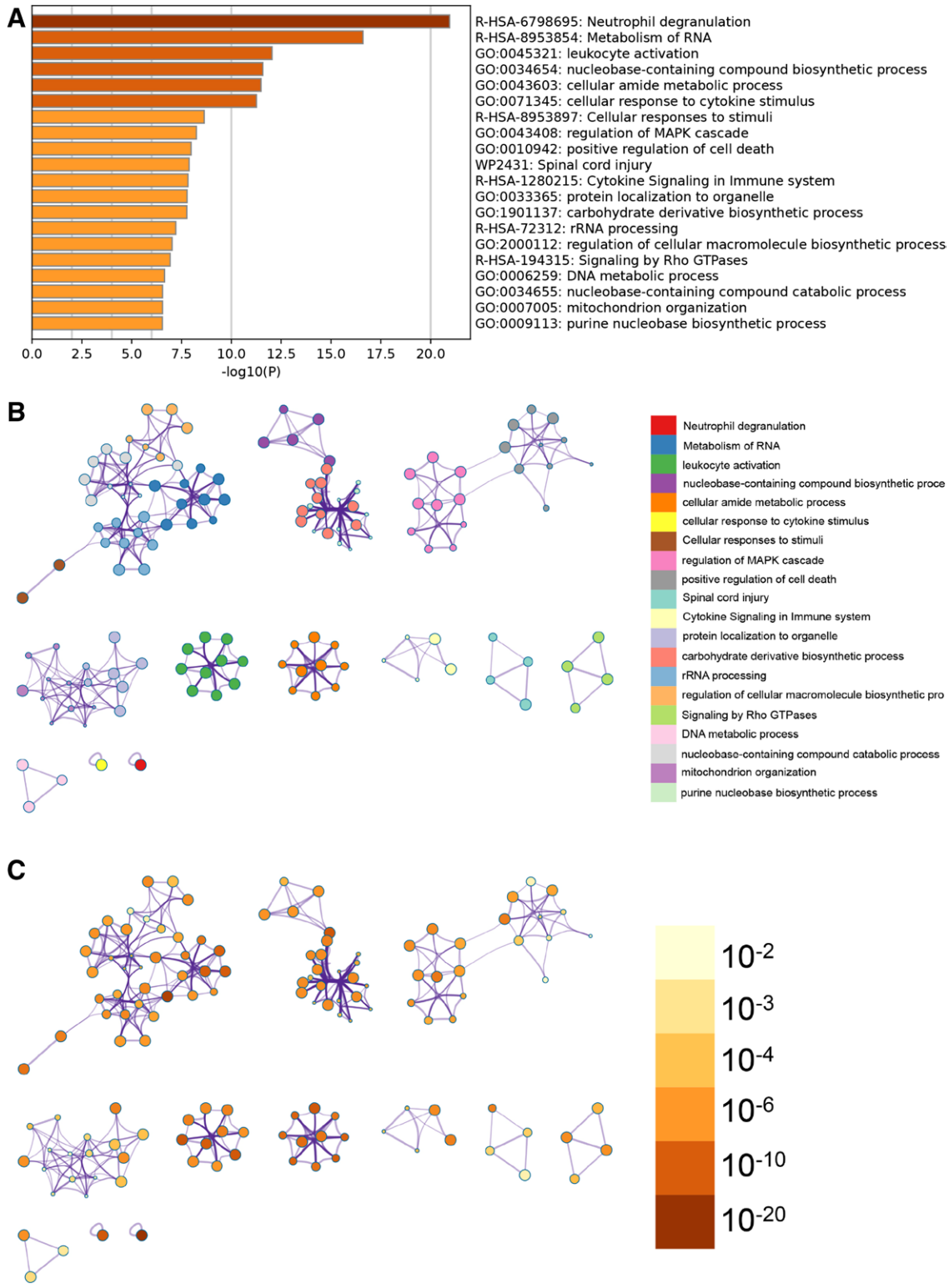

Figure 3. Metascape enrichment analysis. (A) bar graph (B) enrichment networks colored by enrichment terms (C) enrichment networks colored by p values.

use Excel to draw the radar map of the differential expression of each gene.

2.9. miRNA

TargetScan (www.targetscan.org) is an online database for predicting and analyzing miRNA and target genes. In our study, TargetScan was used to screen the miRNA that regulates central DEG.

3. Result

3.1. Functional enrichment analysis

3.1.1. DEGs. In this study, using a predetermined cutoff value, we identified DEGs in the merged matrix of the ischemic stroke datasets GSE22255, GSE16561, and GSE199435. Ultimately, a total of 500 DEGs were obtained (Fig. 1).

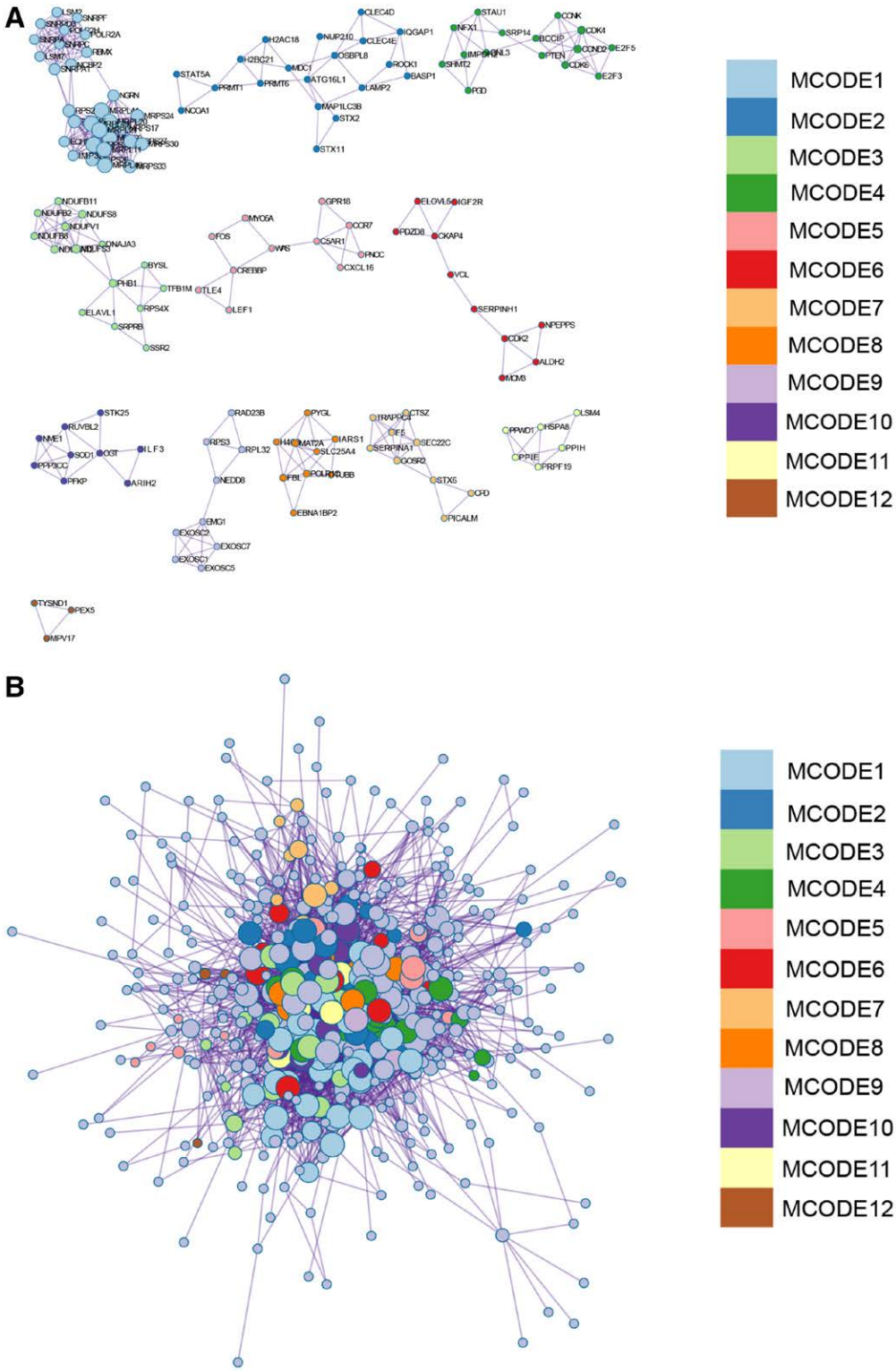

Figure 4. Metascape enrichment analysis. (A) The list of differentially expressed genes was subjected to modular analysis, resulting in 12 modules. (B) Positional relationships of the 12 modules.

Then we analyzed these differentially expressed genes by GO and KEGG. According to GO analysis, they were mainly enriched in leukocyte activation, myoid cell activation involved in immune response, cell membrane, mitochondria, secretory vesicles, catalytic activity, enzyme binding, ribonucleic acid binding, splicing. (Fig. 2A, C, E, G).

3.1.2. GSEA. In addition, we carried out GSEA enrichment analysis of the whole genome in order to find out the possible enrichment items in non-differentially expressed genes. Enrichment items for non-differentially expressed genes were similar to those for differentially expressed genes. The GSEA score curve showed that the gene set was up-regulated (Fig. 2B, D, F, H)

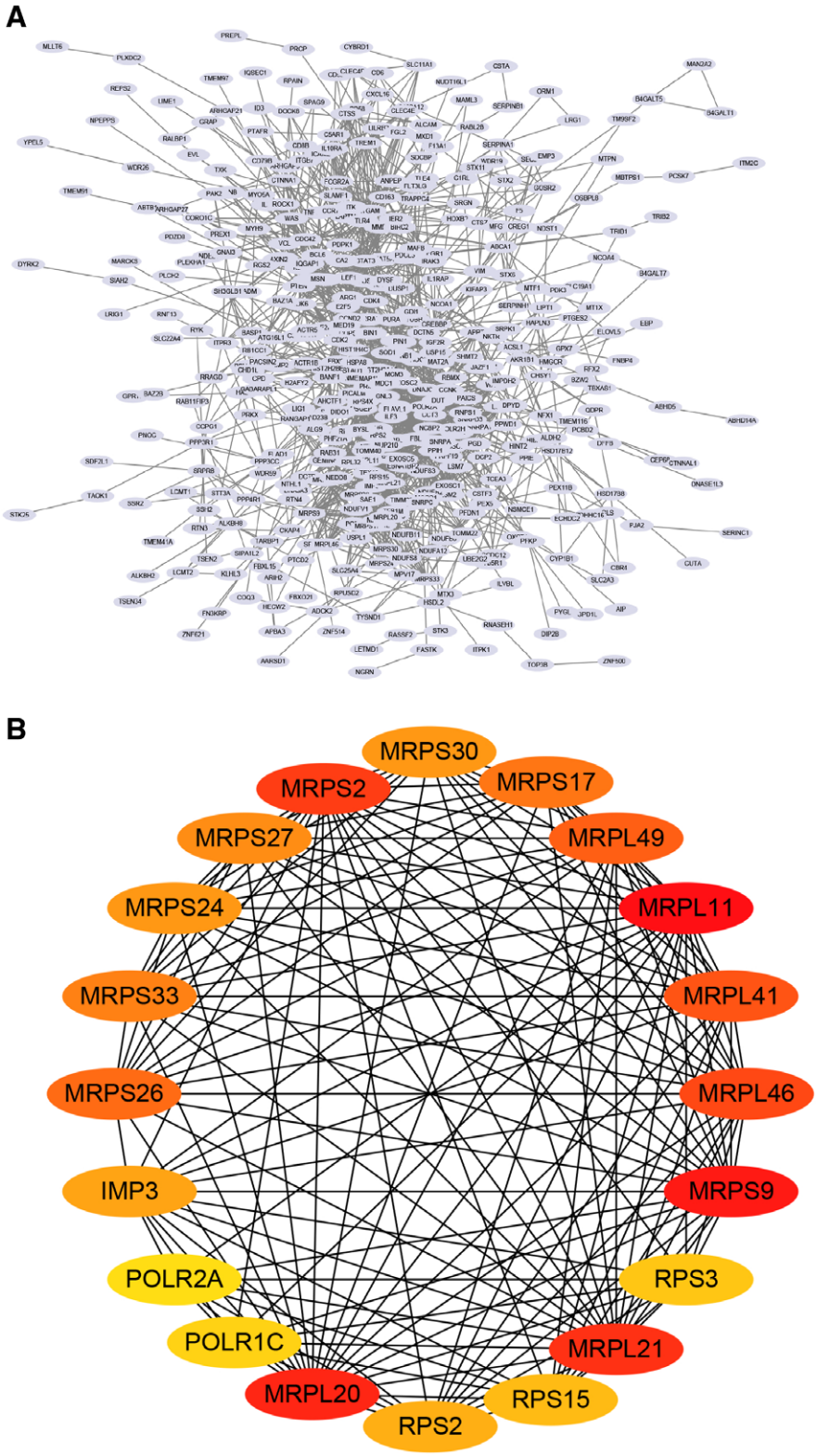

Figure 5. Construction and analysis of protein-protein interaction (PPI) Network. (A) PPI network (B) The central genes were identified by MCC algorithm. MCC = maximal clique centrality.

3.2. Metascape enrichment analysis

The content of Metascape enrichment includes GO enrichment term, and the top 20 significantly enriched terms were displayed in the form of bar graph (Fig. 3A). The enriched network is colored by the enriched terms, and the relationship between the enriched terms is displayed in the form of a network graph (Fig. 3B). Enrichment network is colored by *P* value (Fig. 3C). Modular analysis of the list of differentially expressed genes resulted in 12 modules and their positional relationships (Fig. 4).

3.3. Construction and analysis of PPI network

DEGs's PPI network is built by the STRING online database and analyzed by the Cytoscape software (Fig. 5A). The central genes were identified by maximal clique centrality algorithm (Fig. 5B), and 20 core genes were obtained.

3.4. Gene expression heat map

The difference in the expression of core genes between ischemic stroke and normal tissue samples is shown in the heat map (Fig. 6).

3.5. CTD analysis

In this study, we entered the core gene list into the CTD website to find diseases related to core genes, improving the understanding of the association between genes and diseases. Six genes (RPS15, RPS2, RPS3, MRPS27, POLR2A, MRPS26) were found to be associated with chemical and drug-induced liver injury, necrosis, delayed prenatal exposure, nephropathy, hepatomegaly and tumor. (Fig. 7)

3.6. miRNA prediction and functional annotation related to core gene

In this study, we input the core gene list into targetscan to find the relevant miRNA to improve the understanding of gene expression regulation (Table 1). We found that the related miRNA of RPS15 gene is hsa-miR-196a-5p, the related miRNA of hsa-miR-196b-5p; RPS2 gene is related to hsa-miR-193a-5p; RPS3 gene, and the miRNA related miRNA of hsa-miR-22-3pwitMRPS27 gene is hsa-miR6884-5p and hsa-miR-485-5p.

4. Discussion

Ischemic stroke, which occurs due to insufficient blood supply to the brain, is a serious and life-threatening disease, especially 1 caused by macrovascular occlusion.[12,13] Ischemic stroke is not only one of the main causes of permanent disability in the world, but also one of the main causes of death. Every year, about 60,000 people worldwide suffer from stroke for the first time, and about 50,000 people suffer from long-term disabilities. Although the acute treatment of ischemic stroke has been improved in recent years, follow-up rehabilitation is also necessary for stroke patients. Early rehabilitation

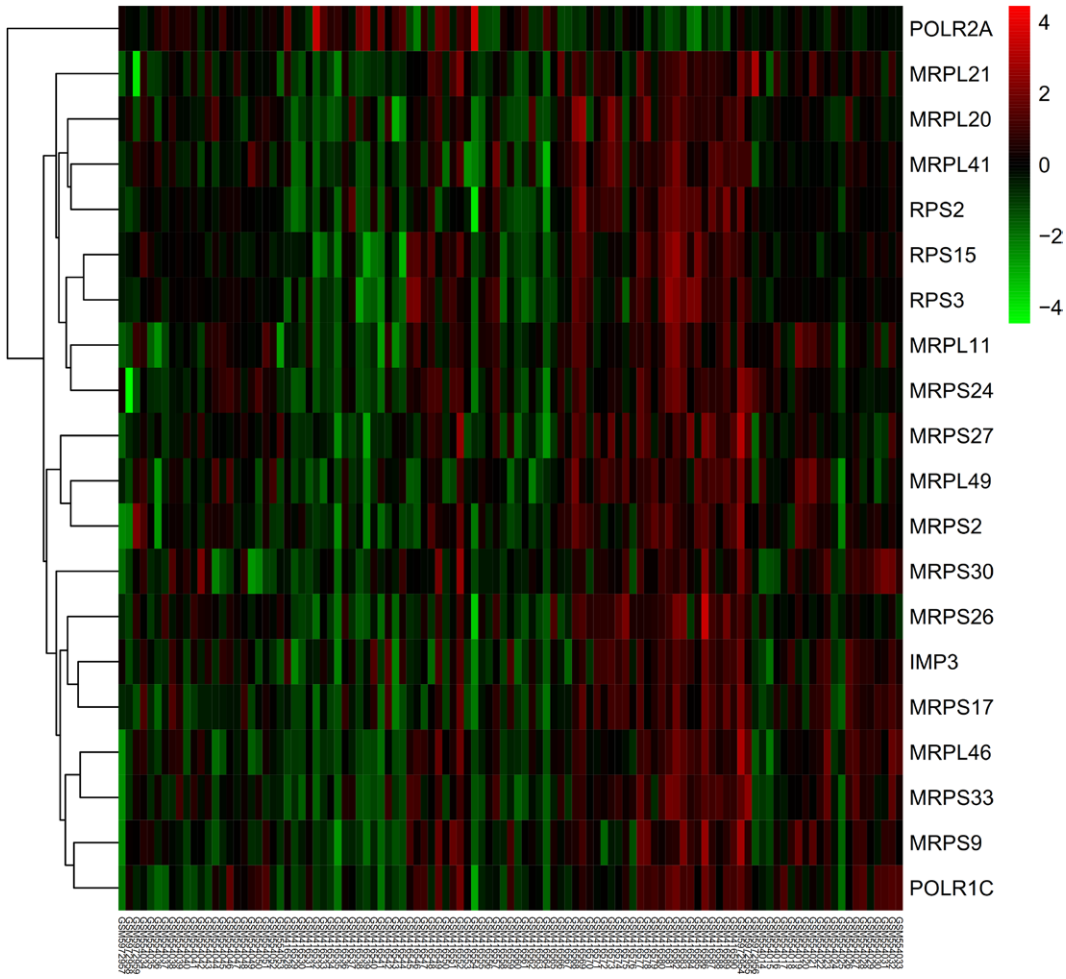

Figure 6. Gene expression heat map.

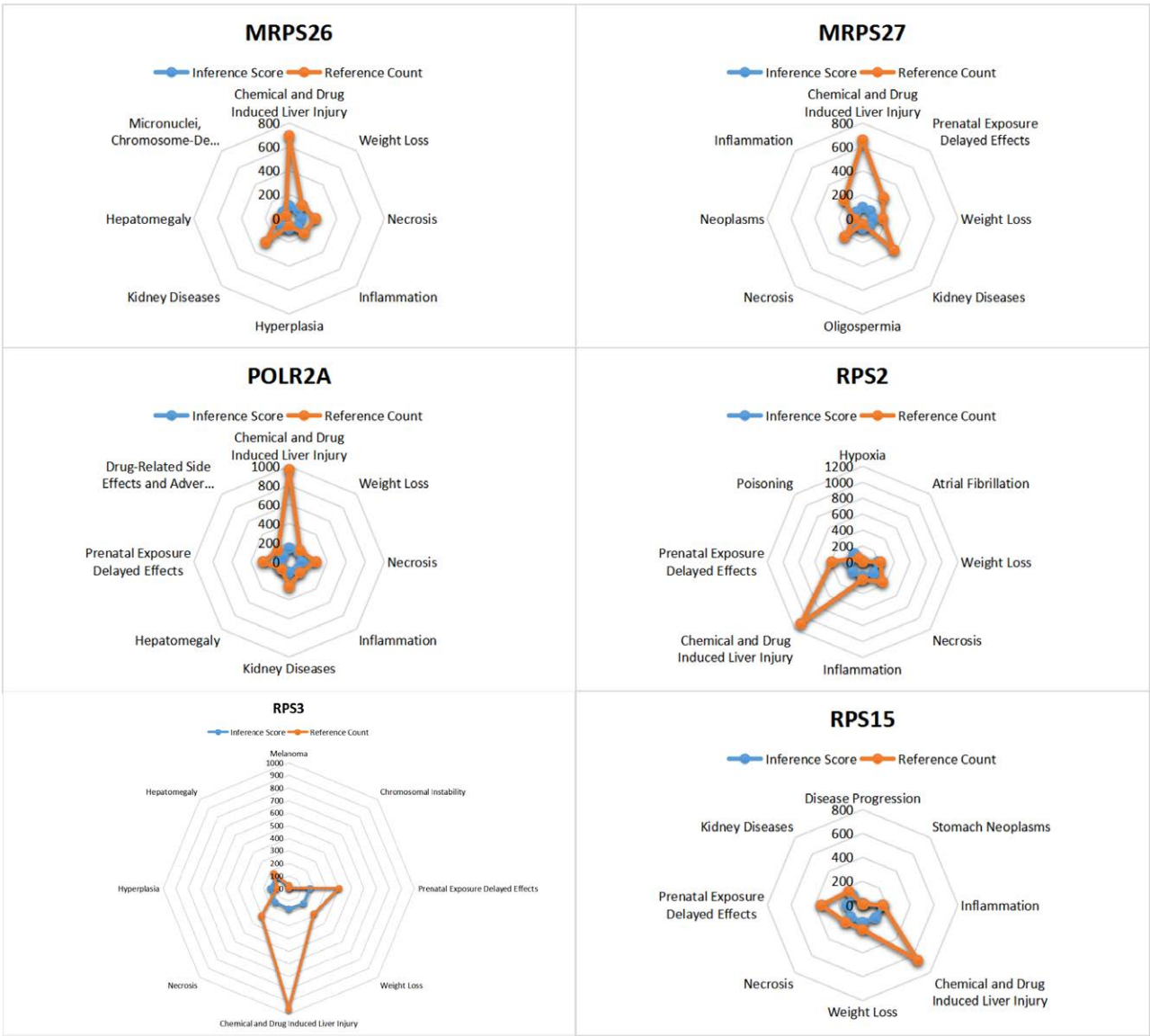

Figure 7. CTD analysis. Six genes (RPS15, RPS2, RPS3, MRPS27, POLR2A, MRPS26) were found to be associated with chemical and drug-induced liver injury, necrosis, delayed prenatal exposure, nephropathy, hepatomegaly and tumor. CTD = comparative toxicogenomics database, MRP = mitochondrial ribosomal proteins, RP = ribosomal proteins.

Table 1

A summary of miRNAs that regulate hub genes.

	Gene	MIRNA	
1	RPS15	HSA-miR-196a-5p	HSA-miR-196b-5p
2	RPS2	HSA-miR-193a-5p	
3	RPS3	HSA-miR-22-3p	
4	MRPS27	HSA-miR-6884-5p	HSA-miR-485-5p
5	POLR2A	None	
6	MRPS26	None	

MRP = mitochondrial ribosomal proteins, RP = ribosomal proteins.

treatment of stroke can minimize the impact of disability on normal life, and rehabilitation treatment should be based on the condition as soon as possible.[14,15] In-depth exploration of the molecular mechanism of ischemic stroke is very important for the study of targeted drugs. The main result of this study is that RPS15 and MRPS27 are the core genes of ischemic stroke. Then we analyzed these differentially expressed genes by GO and KEGG. According to GO analysis, they were mainly enriched in leukocyte activation, myoid cell activation involved in immune response, cell membrane, mitochondria, secretory vesicles, catalytic activity, enzyme binding, ribonucleic acid binding, splicing.

Ribosome biogenesis and protein synthesis are the basic rate-limiting steps for cell growth and proliferation. RP, which contain ribosomal structural parts, are essential for ribosome assembly and function. Multiple RP not only have typical ribosomal functions, but also have ribosomal functions, including activating p53-dependent or p53-independent pathways in stress response, leading to cell cycle arrest and apoptosis. Ribosomal biogenesis, translation, and defects in the function of a single RP (including mutations in RP) have been associated with a variety of human congenital diseases called ribosomal diseases.[16–18] Studies have shown that ribosomal protein families regulate the expression of oncogenes and tumor suppressor genes, regulate cell cycle and apoptosis, promote angiogenesis, cooperate with chromosome genes to play a more extensive role, and regulate tumor proliferation, infiltration, metastasis and other malignant biological behaviors.[19]

Small ribosomal subunit protein RPS15 is involved in early ribosomal biogenesis and subsequent export of 40s pre-granule nucleus to the cytoplasm. In addition, the C-terminal tail of RPS15 is thought to play a role in mature ribosomes, that is, in the process of translation elongation.[20] Recent studies have found that RPS15 not only plays a role in ribosome assembly, but also before cytoplasmic 40 seconds maturation. Changes in nucleoli (ribosome production site) have long been associated with cancer, and mutations in several RP are associated with an increased risk of cancer in human diseases.[21] Many RP have been shown to bind to MDM2 and inhibit MDM2E3 ligase activity, resulting in p53 stability and cell cycle arrest, thus revealing the importance of RP-Mdm2-p53 signaling pathway for ribosomal biogenesis monitoring.[22,23] Recent studies on chronic lymphoblastic leukemia have shown that RPS15 mutated primary chronic lymphoblastic leukemia cells show changes in translation efficiency of other ribosomal proteins and regulatory elements that affect key cellular processes, such as translation mechanisms and immune signal transduction.[24] In the study of Wu et al[25], RPS15 was listed as one of the first 3 proteins most likely to be a key regulator of ischemic stroke. RPS15 is a ribosomal protein. Interestingly, GO and KEGG analysis as well as GSEA and GSVA show that the ribosomal pathway is closely related to the increased incidence of ischemic stroke. This suggests that the gene encoding ribosomal protein may be a potential target and treatment for early diagnosis and treatment of ischemic stroke. Similarly, in our study, the core gene of RPS15 ischemic stroke. The above literature review is consistent with our results, so it is speculated that RPS15 may play an important role in the growth and development of ischemic stroke.

MRPS27 is a component of mitochondrial ribosomal small subunits. MRPS27 is related to 12SrRNA and tRNA, but does not regulate the level of mitochondrial RNA. Studies have shown that the decrease of MRPS27 leads to a decrease in the translation of polypeptides encoded by mitochondria, resulting in a decrease in the activities of respiratory complexes and cytochrome c oxidase in mitochondria.[26] Mitochondria are biological energy, biosynthesis and signal organelles involved in adapting to environmental changes. Mitochondria are the main energy and energy center in cells, producing nearly 90% of cell energy. Recently, it has been found that mitochondria are not only involved in energy metabolism, but also in many other important functions, including apoptosis, autophagy and cell death. Mitochondria are also important mediators of tumorigenesis, and many studies have focused on the relationship between mitochondria and tumorigenesis. A group of proteins called MRP are encoded entirely by nuclear genes, but mainly assist in the process of mitochondrial protein translation. In addition, MRP may have other functions in tumorigenesis.[27–29] Early studies have found that MRPS27 is overexpressed in breast cancer and cervical cancer, and suggests that MRPS27 overexpression may be a driving factor for the proliferation of luminal subtypes of human breast cancer. In addition, overexpressed MRPS27 is a molecular marker of advanced cervical cancer, which is closely related to rapid proliferation, oxidative phosphorylation, invasiveness and tumor size.[30,31] However, few studies have investigated the role of MRPS27 in stroke. Our research shows that MRPS27 is the core gene of ischemic stroke. Therefore, it is speculated that MRPS27 may play an important role in the growth and development of ischemic stroke.

Although this paper has carried out rigorous bioinformatics analysis, there are still some shortcomings. In this study, no animal experiments of gene overexpression or knockout were carried out to further verify its function. Therefore, in the future research, we should make an in-depth exploration in this aspect.

To sum up, RPS15 and MRPS27 are the core genes of ischemic stroke, and may play a significant role in the development of ischemic stroke through many ways. RPS15 and MRPS27 may be molecular targets for accurate treatment of ischemic stroke and provide a basis for the study of the mechanism of ischemic stroke.

Author contributions

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Methodology: Linhong Mo, Guiling Wan, Fang Lu.
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Visualization: Man Zhao, Linhong Mo.
Writing – original draft: Aixian Liu, Guiling Wan, Fang Lu.
Writing – review & editing: Man Zhao.

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