Observational Study

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Fgf2 and Ptpn11 play a role in cerebral injury caused by sevoflurane anesthesia

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Abstract

Sevoflurane is a new inhaled anesthetic, which has better physical properties than the existing inhalational anesthetics, rapid induction, less tissue uptake, and faster recovery. Sevoflurane can directly dilators cerebral blood vessels and increase cerebral blood flow, but it also reduces cerebral oxygen metabolism rate, thereby reducing cerebral blood flow. However, the role of Fgf2 and Ptpn11 in cerebral injury caused by sevoflurane anesthesia remains unclear. The sevoflurane anesthesia brain tissue datasets GSE139220 and GSE141242 were downloaded from gene expression omnibus (GEO). Differentially expressed genes (DEGs) were screened and weighted gene co-expression network analysis (WGCNA) was performed. Construction and analysis of protein-protein interaction (PPI) Network. Gene Ontology (GO) and Kyoto Encyclopedia of Gene and Genome (KEGG), comparative toxicogenomics database (CTD) were performed. A heat map of gene expression was drawn. TargetScan was used to screen miRNAs regulating DEGs. 500 DEGs were identified. According to GO, in Biological Process analysis, they were mainly enriched in response to hypoxia, blood vessel development, inner ear development, neural tube closure, and aging. In Cellular Component (CC), they were mainly enriched in plasma membrane, integral component of membrane, and basal lamina. In Molecular Function (MF), they were mainly associated with protein binding, Wnt-activated receptor activity, and organic anion transmembrane transporter activity. In the KEGG analysis, they were mainly enriched in proteoglycans in cancer, pathways in cancer, transcriptional misregulation in cancer, basal cell carcinoma, thyroid hormone signaling pathway. In the Metascape enrichment analysis, the GO enrichment items revealed upregulated regulation of vascular endothelial cell proliferation, platelet-derived growth factor receptor signaling pathway, inner ear development, and response to hypoxia. A total of 20 modules were generated. Gene Expression Heatmap showed that the core genes (Fgf2, Pdgfra, Ptpn11, Slc2a1) were highly expressed in sevoflurane anesthesia brain tissue samples. CTD Analysis showed that the 4 core genes (Fgf2, Pdgfra, Ptpn11, Slc2a1) were associated with neurodegenerative diseases, brain injuries, memory disorders, cognitive disorders, neurotoxicity, drug-induced abnormalities, neurological disorders, developmental disorders, and intellectual disabilities. Fgf2 and Ptpn11 are highly expressed in brain tissue after sevoflurane anesthesia, higher the expression level of Fgf2 and Ptpn11, worse the prognosis.

Abbreviations: CTD = comparative toxicogenomics database, DEGs = differentially expressed genes, FGF2 = Fibroblast Growth Factor 2, GO = gene ontology, KEGG = Kyoto Encyclopedia of Gene and Genome, PPI = protein-protein interaction, PTPN11 = Protein Tyrosine Phosphatase, Non-Receptor Type 11, STRING = Search Tool for the Retrieval of Interacting Genes, WGCNA = weighted gene co-expression network analysis.

Keywords: cerebral injury caused, Fgf2, Ptpn11, sevoflurane anesthesia

1. Introduction

Cerebral injury caused by sevoflurane anesthesia refers to the occurrence of brain dysfunction, cognitive impairment, or neurological behavioral abnormalities in some individuals after receiving sevoflurane anesthesia.[1] The exact incidence of cerebral injury induced by sevoflurane anesthesia is not clear due to its transient nature and potential subtle symptoms, posing challenges in epidemiological investigations and definitive determination. Cerebral injury from sevoflurane anesthesia may also manifest as cognitive dysfunction, including memory decline and lack of concentration.[2,3] The precise pathological features of cerebral injury caused by sevoflurane anesthesia have not been fully elucidated. Research suggests that it may involve neuronal damage, synaptic injury, and alterations in neurotransmitters.[4,5] The exact cause of cerebral injury caused by sevoflurane anesthesia is unknown but may be related to multiple factors, including the underlying health status of the patient, the surgical procedure, and the depth of anesthesia.[6,7] Therefore, in-depth exploration of the molecular mechanisms underlying cerebral injury caused by sevoflurane anesthesia is of utmost importance.

The authors have no funding and conflicts of interest to disclose.

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 The Third Affiliated Hospital of Beijing University of Chinese Medicine.

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Fibroblast Growth Factor 2 (FGF2), a member of the fibroblast cytokine family, is composed of a single polypeptide with a molecular weight of 18kDa. Fgf-2 regulates immune processes by specifically targeting tyrosine kinase receptors and activating FGF/FGFR signaling pathway. FGF2 is involved in a variety of cellular processes, including cell growth, differentiation and tissue repair, and plays an important role in the development and regeneration of a variety of tissues and organs.[8] Protein Tyrosine Phosphatase, Non-Receptor Type 11 (PTPN11) is a gene located on chromosome 12 that encodes a protein that is a member of the protein tyrosine phosphatase (PTP) family.[9] Ptpn11 encodes SHP2 protein (a non-receptor protein tyrosine phosphatase), which is a member of the protein tyrosine phosphatase family and plays an important role in cell signaling and various biological processes.[10,11] PTPN11 is an important regulator of intracellular signaling and plays a role in cell growth, differentiation, and various physiological processes.[12]

The bioinformatics technology enables researchers to uncover potential biological patterns and correlations from genomic data, proteomic data, and metabolomic data, showcasing the success of big data processing.[13] The high-throughput nature of this technology allows simultaneous study of thousands of genes or proteins, making comprehensive research feasible and contributing to a comprehensive understanding of biological functions and regulatory networks.[14] Bioinformatics technology also facilitates in-depth investigation of individual genomic variations, providing a theoretical basis for personalized medicine. Through the analysis of individual genomic data, physicians can better predict disease risks and design personalized treatment plans.[15,16] Bioinformatics technology holds a crucial position and significant advantages in biological and medical research.[17]

The study aims to utilize bioinformatics technology to explore core genes involved in cerebral injury caused by sevoflurane anesthesia and compare them with normal brain tissues. Identify potential biological processes and pathways associated with the injury. Public datasets will be used to validate the significant roles of Fgf2 and Ptpn11 in cerebral injury induced by sevoflurane anesthesia. Additionally, basic cellular experiments will be conducted to further validate their functions.

2. Methods

2.1. Data collection and processing

2.1.1. Sevoflurane anesthesia brain tissue dataset. In this study, the sevoflurane anesthesia brain tissue datasets GSE139220 and GSE141242 were obtained from the gene expression omnibus, generated with the platform GPL22388. GSE139220[18] consists of 3 post-sevoflurane anesthesia brain tissue samples and 3 normal brain tissue samples, GSE141242 includes 3 post-sevoflurane anesthesia brain tissue samples and 3 normal brain tissue samples.

2.1.2. Batch correction. For the integration and batch correction of multiple datasets, merged the GSE139220 and GSE141242 using the R package "inSilicoMerging." This merging process resulted in a combined matrix. Subsequently, the batch effect is corrected using the "remove Batch Effect" function from the R package "limma" to obtain a matrix that removes the batch effect. This corrected matrix was used for subsequent analyses.

2.1.3. Differentially expressed genes (DEGs) selection. Probe aggregation and background correction were performed on the GSE139220 and GSE141242 merged matrices using the R package limma. *P* values were corrected by the Benjamini-Hochberg procedure. Fold change was calculated using the false discovery rate. The cutoff value of DEG was $P < .05$. And then draw the volcano.

2.1.4. Weighted gene co-expression network analysis (WGCNA). First of all, use de-batch and post-merge matrix of GSE139220 and GSE141242 to calculate Median Absolute Deviation of each gene.

WGCNA in the R package was used to remove outlier genes and samples to construct a scale-free co-expression network. The characteristic gene differences of the modules were calculated, the tangent lines were selected for module tree view, and some modules were merged.

2.1.5. Construction and analysis of protein-protein interaction (PPI) network. The Search Tool for Retrieval of Interacting Genes (STRING) is a system for retrieving known and predicted PPI and also includes prediction results using bioinformatics methods. The differential genes were input into STRING to construct the PPI network and predict the core genes. Cytoscape[19] software was used to visualize the PPI network. Firstly, we imported the PPI network into Cytoscape software and used the MCODE plugin to find the best modules with high relevance. Additionally, we employed 5 algorithms (MCC, MNC, Degree, BottleNeck, Closeness) to calculate genes with the best relevance for each algorithm and took their intersection. The resulting core genes were visualized and exported as a core gene list.

2.1.6. Functional enrichment analysis. Gene ontology (GO) analysis is a computational method to evaluate gene functions and biological pathways, and it is a key step to endow sequence information with practical biological significance. Kyoto Encyclopedia of Gene and Genome (KEGG) is an online database dedicated to collecting information on genomes, molecular interaction networks, enzyme catalytic pathways, and biochemical products. The genomic information and gene function were linked, and gene function was systematically analyzed. The list of differential genes screened by Wayne map was input into KEGG rest API obtained latest KEGG Pathway gene annotation. Gene set enrichment results were obtained using R package cluster Profiler.

Metascape[20] can realize cognition of gene or protein function, and can be visually exported. The Metascape database was used to perform functional enrichment analysis and derivation of the above differential gene list.

2.1.7. Gene expression heatmap. Heatmaps of core gene expression levels found in PPI networks were created using the R package "Heatmap" in the batchcorrected merging matrices GSE139220 and GSE141242. This heatmap visualizes the expression differences of the core genes between sevoflurane anesthesia brain tissues and normal brain tissues.

2.1.8. CTD analysis. Comparative toxicogenomics database (CTD) is a powerful public database, which predict gene/protein relationships with disease, are used to identify integrated chemical diseases, chemical genes, and gene disease interactions to predict new associations and generate extended networks. Core genes were entered into the CTD and the diseases most associated with the core genes were found. Excel was used to draw radar maps of DEGs.

2.1.9. The miRNA. TargetScan can predict and analyze miRNAs and their target genes. TargetScan screened mirnas that regulated central DEGs.

3. Results

3.1. Differential gene analysis

500 DEGs were identified based on batch-corrected merged matrices of GSE139220 and GSE141242 (Fig. 1A).

3.2. Functional enrichment analysis

3.2.1. DEGs. DEGs were analyzed by GO and KEGG. According to GO analysis, in Biological Process (BP) analysis, they were mainly enriched in response to hypoxia, blood vessel development, inner ear development, neural tube closure, and aging (Fig. 1B). In Cellular Component analysis, they were

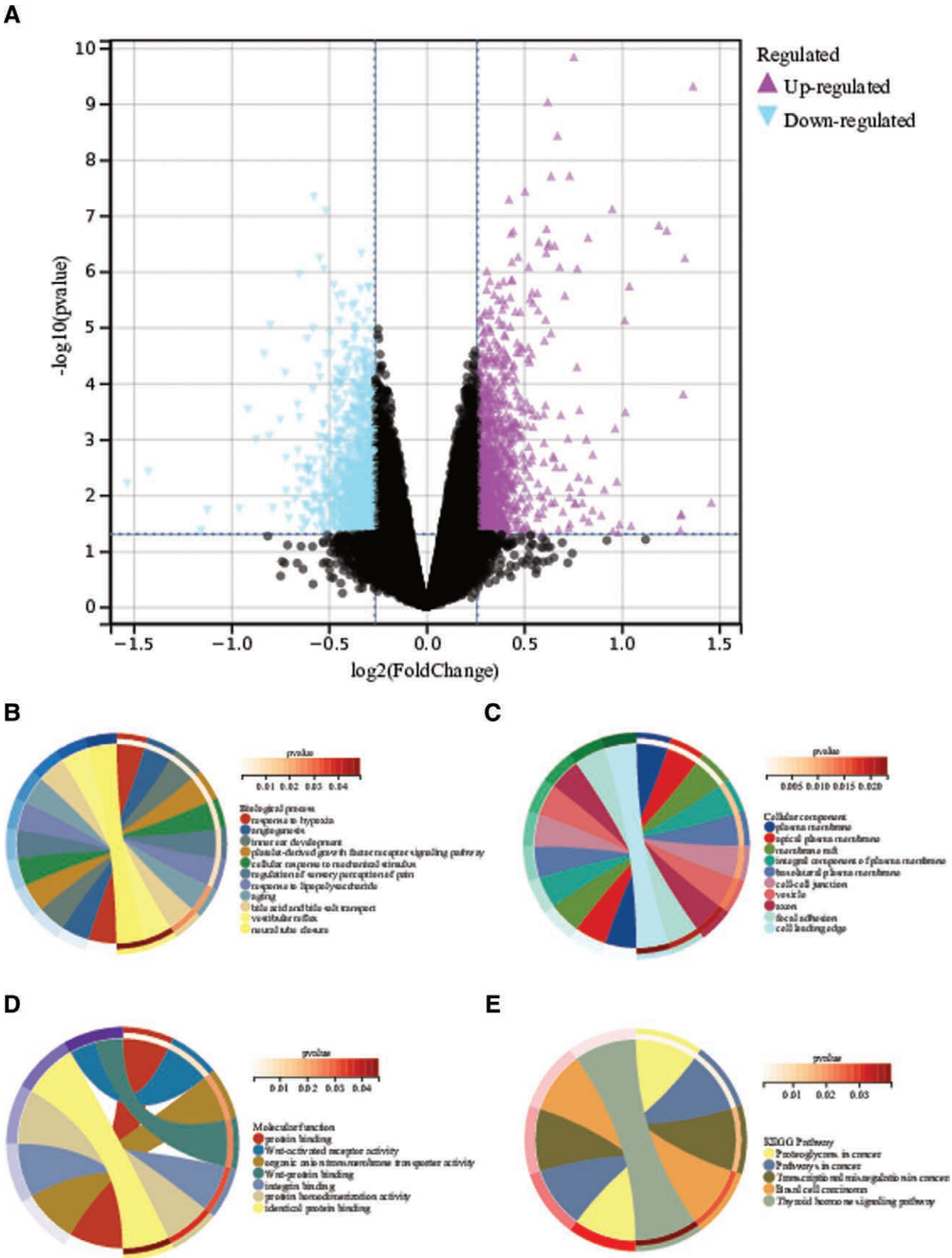

Figure 1. DEGs analysis. (A) 500 DEGs were identified (B) Biological process (C) Cellular component (D) Molecular function (E) KEGG. DEGs = differentially expressed genes, KEGG = Kyoto Encyclopedia of Gene and Genome.

mainly enriched in plasma membrane, integral component of membrane, basal lamina (Fig. 1C). In Molecular Function analysis, they were mainly associated with protein binding, Wnt-activated receptor activity, organic anion transmembrane transporter activity (Fig. 1D). In KEGG analysis, they were mainly enriched in proteoglycans in cancer, pathways in cancer, transcriptional misregulation in cancer, basal cell carcinoma, thyroid hormone signaling pathway (Fig. 1E).

3.2.2. Metascape enrichment analysis. The GO enrichment items revealed upregulated regulation of vascular endothelial cell proliferation, platelet-derived growth factor receptor signaling pathway, inner ear development, and response to hypoxia (Fig. 2A). Additionally, we generated enrichment networks with colored and *P* value colored nodes (Fig. 2B–D), visualizing associations and confidence levels of each enrichment item.

3.3. WGCNA

In WGCNA, the soft threshold efficacy was set to 9, resulting in a scale-free topological fit index of 0.9 (Fig. 3A). Hierarchical clustering trees for all genes were constructed, and important interactions between modules were analyzed (Fig. 3B). A

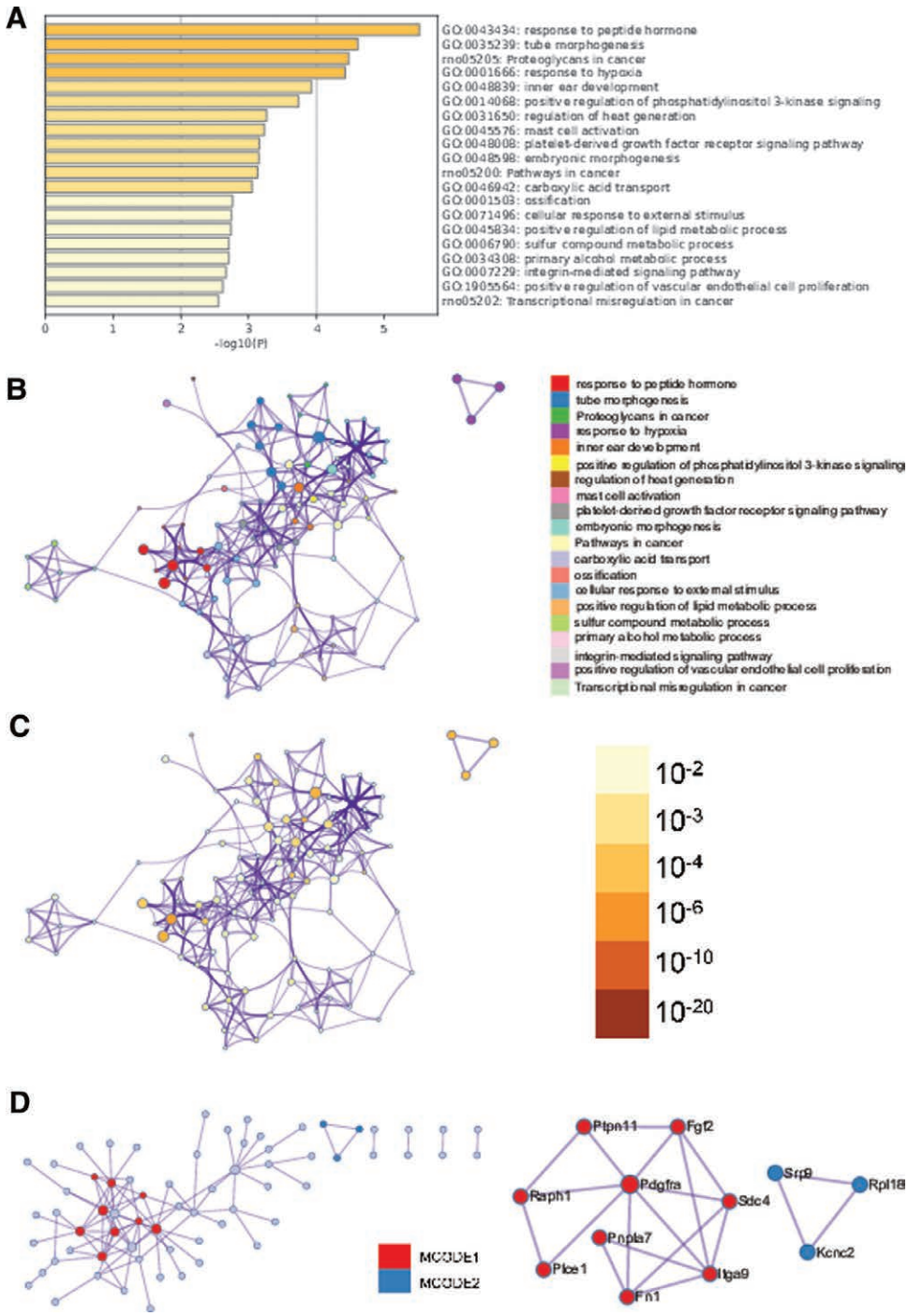

Figure 2. Metascape enrichment analysis. (A) GO enrichment items revealed upregulated regulation of vascular endothelial cell proliferation, platelet-derived growth factor receptor signaling pathway, inner ear development, and response to hypoxia (B–D) The enrichment networks colored by enrichment terms and *P* values are output, the association and confidence of each enrichment item are visualized. GO = gene ontology.

total of 20 modules were generated (Fig. 3C), and a heatmap showing the correlation between modules and phenotypes was generated (Fig. 3D). Furthermore, the correlation scatter plot between module GS and MM for hub genes was visualized (Fig. 3E).

3.4. Protein-protein interaction (PPI) network construction and analysis

The PPI network was constructed using STRING and analyzed by Cytoscape (Fig. 4A). Five different algorithms were used to identify hub genes (Fig. 4B–F), and their intersection was

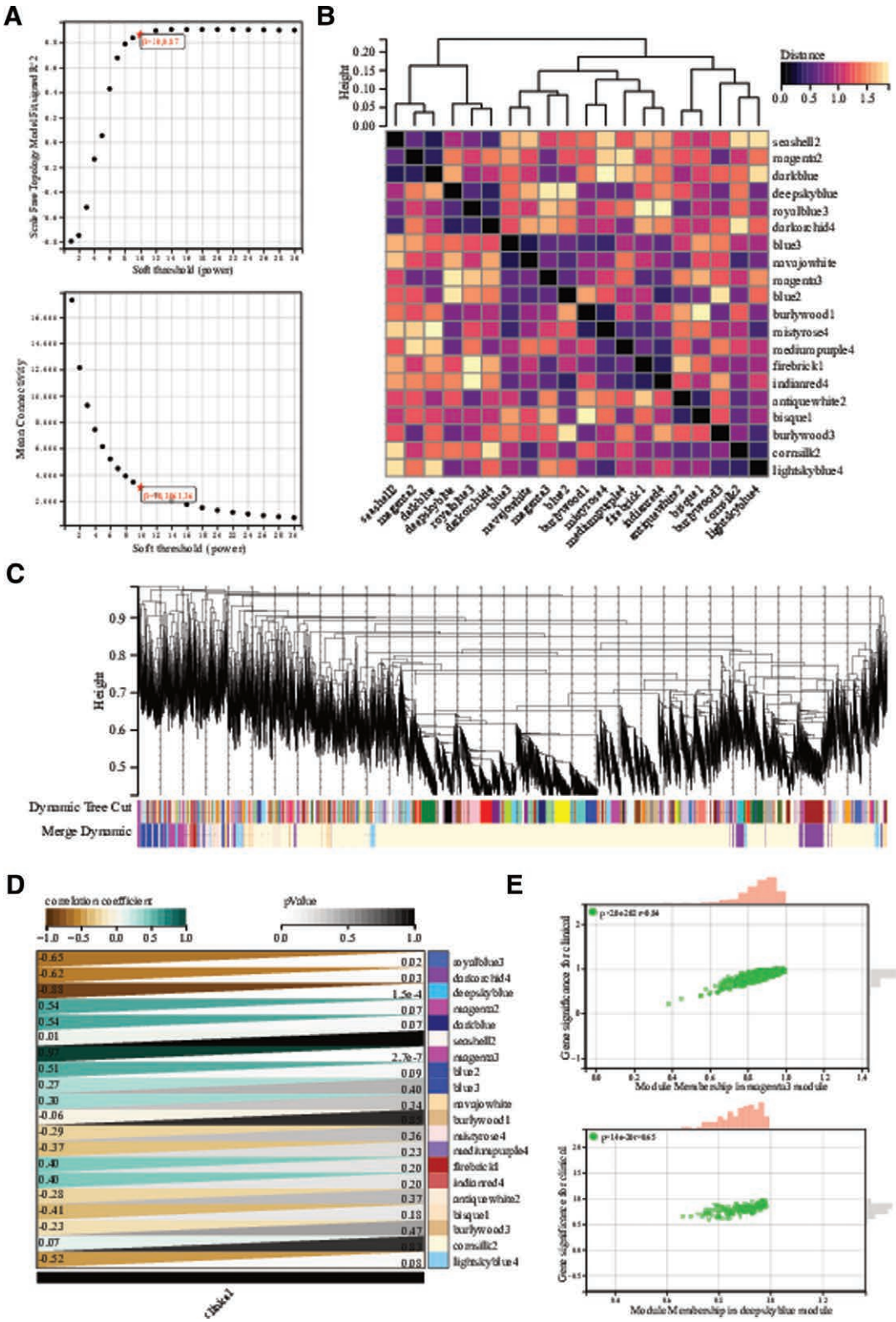

Figure 3. WGCNA. (A) β = 10,0.87. β = 10,3061.36. (B) Hierarchical clustering trees for all genes were constructed, important interactions between modules were analyzed. (C) A total of 20 modules (D) Heatmap showing the correlation between modules and phenotypes. (E) The correlation scatter plot between module eigengenes (GS) and gene significance (MM) for hub genes was visualized. WGCNA = weighted gene co-expression network analysis.

visualized in a Venn diagram (Fig. 4G), resulting in the identification of 4 core genes (Fgf2, Pdgfra, Ptpn11, Slc2a1).

3.5. Gene expression heatmap

We visualized expression levels of the core genes (Fgf2, Pdgfra, Ptpn11, Slc2a1) in the merged matrices of GSE139220 and GSE141242 and created separate heatmaps (Fig. 5A). The core genes were highly expressed in sevoflurane anesthesia brain tissue samples and lowly expressed in normal tissue samples.

3.6. CTD analysis

Four core genes (Fgf2, Pdgfra, Ptpn11, Slc2a1) were associated with neurodegenerative diseases, brain injuries, memory disorders, cognitive disorders, neurotoxicity, drug-induced

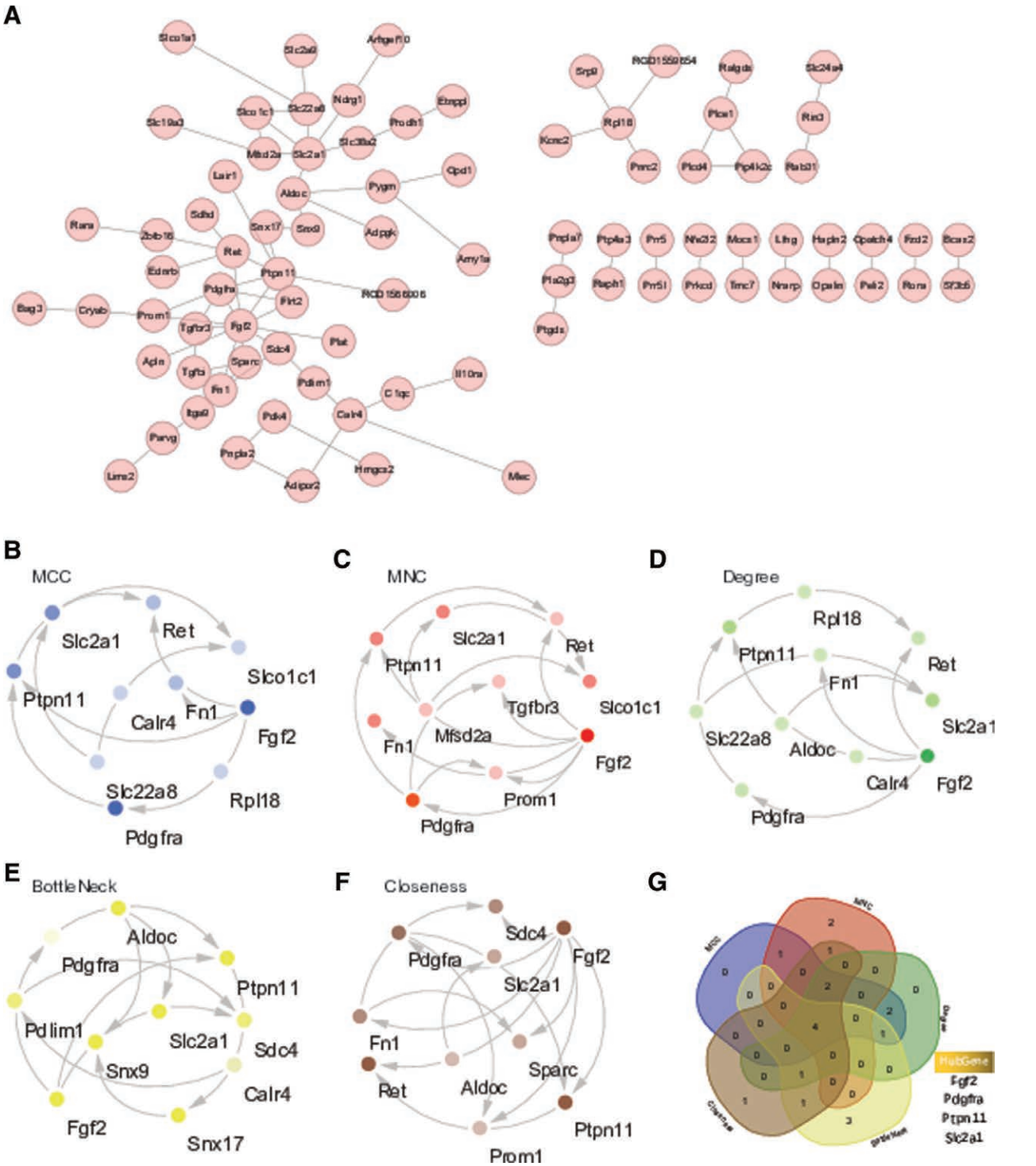

Figure 4. Protein-protein interaction (PPI) network construction and analysis. (A) The PPI network. (B–F) MCC, MCC, Degree, BottleNeck and Closeness were used to identify hub genes (G) The intersection was visualized in a Venn diagram.

abnormalities, neurological disorders, developmental disorders, and intellectual disabilities (Fig. 5B).

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

TargetScan was used to find miRNAs associated with the hub gene list and improve the understanding of gene expression regulation (Table 1). The relevant miRNAs for the Fgf2 was rno-miR-140-3p; for the Pdgfra was rno-miR-140-5p, rno-miR-140-5p; for the Ptpn11 gene was rno-miR-124-3p; and for the Slc2a1 gene was rno-miR-223-3p.

4. Discussion

Sevoflurane anesthesia-induced brain injury poses significant hazards.[21] It may lead to cognitive impairment in patients after surgery.[22] Cognitive dysfunction can further impact patients' daily life and work abilities, reducing their quality of life. The duration of brain injury is uncertain.[23] Studies have shown that sevoflurane anesthesia may cause prolonged or even permanent

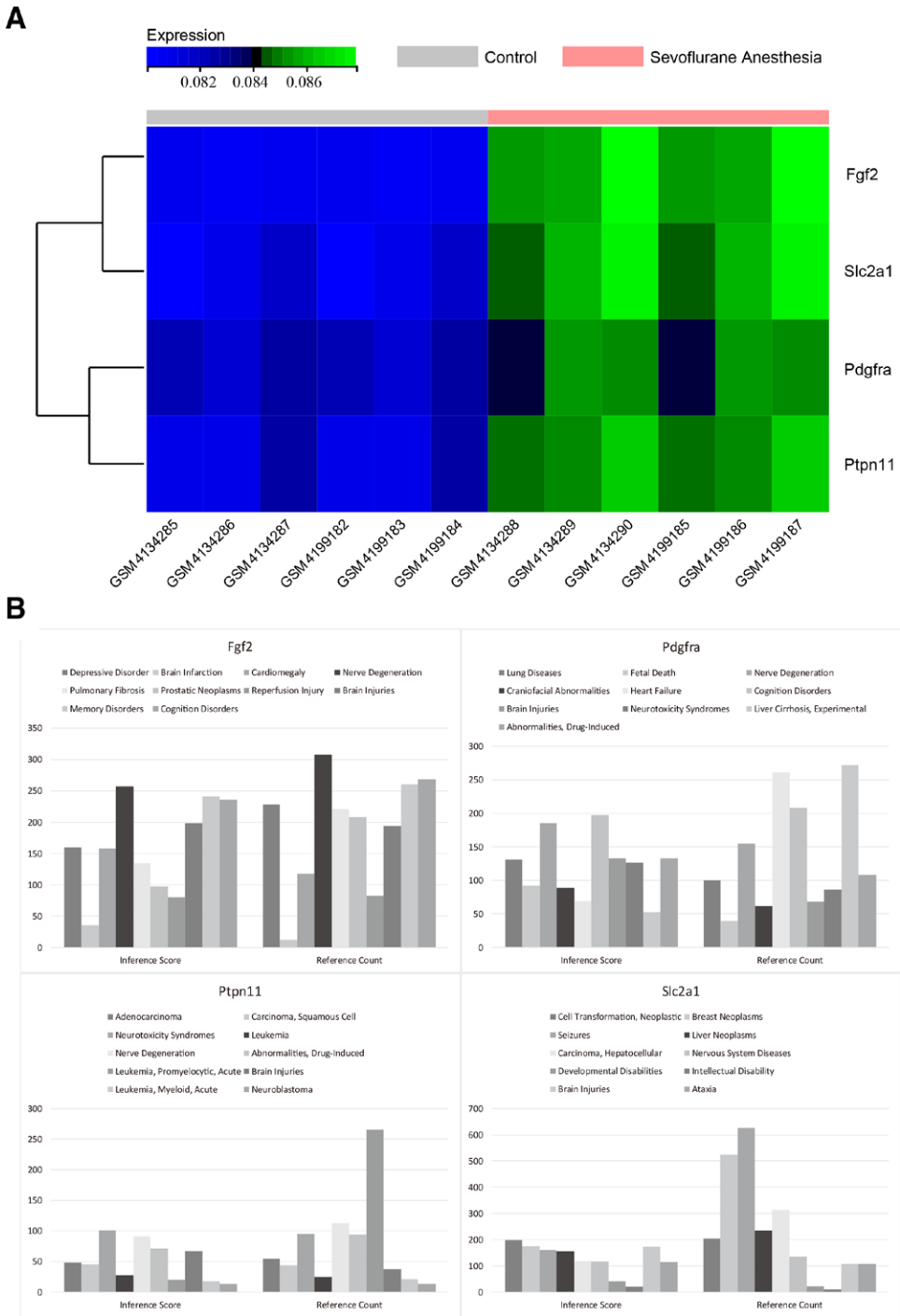

Figure 5. Gene expression heatmap and CTD analysis. (A) Created separate heatmaps. (B) The 4 core genes (Fgf2, Pdgfra, Ptpn11, Slc2a1) were associated with neurodegenerative diseases, brain injuries, memory disorders, cognitive disorders, neurotoxicity, drug-induced abnormalities, neurological disorders, developmental disorders, and intellectual disabilitie. CTD = comparative toxicogenomics database.

Table 1

A summary of miRNAs that regulate hub genes.

	Gene	MIRNA	
1	Fgf2	rno-miR-140-3p	
2	Pdgfra	rno-miR-140-5p	rno-miR-140-5p
3	Ptpn11	rno-miR-124-3p	
4	Slc2a1	rno-miR-223-3p	

brain damage, especially in patients undergoing prolonged or frequent surgeries, possibly resulting in loss of self-care abilities.[24] For patients undergoing sevoflurane anesthesia, brain injury can worsen postoperative outcomes and complicate the recovery process, affecting rehabilitation results.[25] Despite ongoing research on sevoflurane-induced brain injury, its pathogenesis remains incompletely understood. Therefore, there is still uncertainty in mitigating and preventing brain injury, which underscores the need for caution and risk assessment when using sevoflurane.

In-depth exploration of the molecular mechanisms underlying sevoflurane-induced brain injury is crucial for targeted drug research.[26] By understanding the molecular mechanisms of brain injury, we can develop targeted drugs against specific targets or pathways, which may more effectively intervene in the occurrence of brain injury, thus improving treatment outcomes.[26] Targeted drugs are designed to treat specific molecules or pathways and may be more precise and reduce off-target effects compared to broad-spectrum drugs, leading to reduced adverse effects.[27] Our study's findings show high expression levels of Fgf2 and Ptpn11 in sevoflurane-induced brain injury, which directly correlate with prognosis. In-depth exploration of their molecular mechanisms can provide new clues for future therapeutic directions and may lead to the identification of more molecular targets and drugs, offering diverse options for the treatment of sevoflurane-induced brain injury.

Fgf2 is an important growth factor that plays a significant role in neural development and repair processes.[28] It is involved in cell proliferation, migration, differentiation, as well as synaptic formation and repair. Studies suggest that during the process of sevoflurane anesthesia-induced brain injury, Fgf2 may be associated with neuronal regeneration and repair, participating in the regeneration of neurons and reconstruction of synapses after brain injury, but it may also be linked to inflammatory responses and cell apoptosis.[29,30] Ptpn11 is a phosphatase that plays a crucial role in cell signal transduction.[31] It is involved in regulation of various signaling pathways, including cell proliferation, differentiation, growth, and apoptosis.[32] Research indicates that during the process of sevoflurane anesthesia-induced brain injury, Ptpn11 may participate in the regulation of cell signaling pathways, affecting the survival and death processes of neural cells.[33,34] Numerous researchers have investigated the expression levels and regulatory mechanisms of Fgf2 and Ptpn11 in brain injury through cell culture, animal models, or clinical samples, contributing to a better understanding of their specific roles and regulatory mechanisms in brain injury.[35]

In different organ injuries, Fgf2 may be generated or produced. For instance, Man J Livingston[36] found that in cases of acute kidney injury, renal tubular cells produced FGF2 through autophagy, resulting in fibroblast activation and renal fibrosis. This finding was validated through gene knockout experiments in mice, indicating that FGF2 produced after injury had adverse effects on future recovery. Similarly, in the context of brain injury, high expression of Fgf2 may lead to excessive neuronal growth and abnormal neural connections, interfering with the normal neural network.[37] Post-brain injury, synaptic reconstruction is crucial for neural function recovery. However, elevated Fgf2 expression may result in adverse synaptic reconstruction, impacting neural conduction and information transmission.[38] Brain injury is often accompanied by neural damage, and elevated Ptpn11 expression may interfere with the processes of neural cell proliferation and differentiation, thus affecting the regeneration and repair of neural cells after brain injury.[39] Numerous research findings demonstrate the interplay between Fgf2, Ptpn11, and sevoflurane anesthesia-induced brain injury, and their expression levels have a significant impact on the prognosis.

Sevoflurane anesthesia-induced brain injury may lead to a series of adverse consequences, including cognitive, motor, neurological, and speech impairments. Furthermore, the anesthesia itself can trigger inflammation.[40] Luh[4] conducted experiments using 3 anesthetics in animal models, including sevoflurane, isoflurane, and intraperitoneal anesthesia combination (midazolam, fentanyl, and medetomidine). The study measured the results before and after brain injury and anesthesia stimulation. The experimental findings showed that Iba1-positive cells increased significantly after sevoflurane anesthesia. The use of anesthetics within several hours after injury has a neuroprotective effect.[41] On the other hand, Fgf2 and Ptpn1 genes are involved in regulating cell signaling pathways during brain injury. Overexpression of Fgf2 and Ptpn1 can inhibit the process of cell apoptosis, leading to excessive activation of the inflammatory response and increasing inflammatory damage to brain tissue. This may interfere with proliferation and differentiation of neural cells, affecting the regeneration and repair of neural cells after brain injury.[42] Thus, the combination of anesthesia effects on cerebral perfusion, excitotoxicity, inflammation, cell apoptosis, along with the high expression of Fgf2 and Ptpn1, could result in changes in the extent of neuronal injury and functional outcomes in humans or other animals, leading to a poorer prognosis.[43]

The above literature review aligns with our results. Fgf2 and Ptpn11 play a series of roles in the brain tissue after sevoflurane anesthesia by participating in cell signaling pathways, regulating cell apoptosis, and promoting the inflammatory response. The higher their expression levels, the more negative impact on the brain tissue after sevoflurane anesthesia, hindering the recovery and rehabilitation process.

Although this paper has carried out rigorous bioinformatics analysis, there are still some shortcomings. A limited sample size can lead to statistical instability and potentially reduce the statistical power of the study. Inadequate reporting of methods makes it difficult for other researchers to replicate the study. This research did not include animal experiments involving gene expression or knockdown to further validate its function. There is also a risk of overconfidently drawing broad conclusions while neglecting the limitations of the study.

5. Conclusion

In conclusion, our study findings demonstrate that Fgf2 and Ptpn11 play significant roles in the brain tissue after sevoflurane anesthesia. The higher expression levels of Fgf2 and Ptpn11 in the brain tissue after sevoflurane anesthesia are associated with poorer prognosis.

Author contribution

Conceptualization: Lin Zhang.
Data curation: Lingyan Xu.
Formal analysis: Lingyan Xu.
Methodology: Lin Zhang, Lingyan Xu.
Software: Lin Zhang.

Writing – original draft: Lin Zhang, Lingyan Xu.
Writing – review & editing: Lin Zhang, Lingyan Xu.

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