



Bioinformatic Analyses Determine the Importance of CXCL2 and CXCL8 in Atypical Meningioma Development and Reoccurrence

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ABSTRACT

AIM: To compare gene expression profiles between atypical meningiomas and normal meninges from the National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database to identify key genes and pathways.

MATERIAL and METHODS: The microarray datasets GSE43290 and GSE16581 were downloaded from Gene Expression Omnibus (GEO) database to explore the key genes involved in meningioma formation and recurrence. Additionally, the relationship between the key genes identified and clinical factors, including age, survival, and recurrence, was assessed. To investigate the biological functions of the key genes, the gene ontology (GO) and Kyoto Encyclopedia of Gene and Genomes (KEGG) pathways enrichment analyses were performed. Finally, the differences in immune infiltration between atypical meningiomas and healthy tissues were assessed.

RESULTS: A total of 286 hub genes were identified, which were enriched in leukocyte migration, collagen-containing extracellular matrix, signaling receptor activator activity, and receptor-ligand activity. The differentially expressed genes (DEGs) were mainly enriched in the IL-17 signaling pathway and focal adhesion. Among these hub genes, two overlapping genes, including CXCL8 and CXCL2, were selected as key genes which were correlated with tumor survival and recurrence. These two genes were enriched in mediating chemokine and cytokine responses, especially neutrophil and granulocyte responses, and influenced the immune cells infiltrated in the tumor tissue, thereby, influencing prognosis.

CONCLUSION: The implications of this study excavated the key genes in atypical meningiomas which could help us understand the molecular mechanisms and provide the candidate therapeutic targets.

KEYWORDS: Atypical meningioma, GEO data, WGCNA, Hub genes, Bioinformatic analyses

ABBREVIATIONS: CNS: Central nervous system, MRI: Magnetic resonance imaging, NCBI: National center of biotechnology information, GEO: Gene expression omnibus, DEG: Differentially expressed genes, WGCNA: Weighted gene co-expression network analysis, BP: Biological process, CC: Cellular component, MF: Molecular function, STRING: Search tool for the retrieval of interacting gene database, GO: Gene ontology, PPI: Protein-protein interaction, MCODE: Molecular complex detection, MCC: Maximal clique centrality, MNC: Maximum neighborhood component, EPC: Edge per collated component, KEGG: Kyoto encyclopedia of genes and genomes

■ INTRODUCTION

Meningiomas are a group of neoplasms derived from arachnoid meningeal cells that are the second most common neoplasms in the central nervous system (CNS), accounting for approximately 30% of newly diagnosed CNS tumors (40). According to 2016 WHO classification, meningiomas are classified into three types: I, II, and III, depending on their recurrence and aggressiveness. Atypical meningiomas, which belong to grade II, represent approximately 15-20% of all meningiomas (26,29,40). Frequently, meningiomas are diagnosed based on magnetic resonance imaging (MRI), which might distinguish atypical meningiomas from typical meningiomas (15). In the past, the histological classification was based on the additive criteria of three of the five following features: spontaneous necrosis, sheeting, prominent nucleoli, high cellularity, and small cells. Later on, brain invasion with a mitotic count of 4 or more has been included in these histological criterion (26). The recent advances in molecular profiling have permitted to develop a more accurate classification of meningiomas: meningiomas tumors with neurofibromatosis 2 (NF2) mutations, which tend to be atypical or anaplastic pathologies; and meningiomas without NF2 mutations, which tend to be typical pathologies, and usually present mutations in TRAF7, KLF4, SMO, AKT1, and POLR2A (13,33).

The most common treatment approach for atypical meningiomas is surgical resection, but its effectiveness is limited, as the recurrence rate is approximately 40% post-resection, and even higher as the time passes (32). Patients experiencing Simpson Grade I and/or II resection appear have a lower risk of recurrence than those with Simpson Grade III-V resection; and patients who experienced subtotal resection had a higher risk of recurrence than those undergoing surgical resection and postoperative radiotherapy (7,36). Nonetheless, radiotherapy can trigger side effects and have long-term toxicity, including effects such as inducing malignant transformation (5,31,39). Therefore, chemotherapy is nowadays the preferred approach to control the recurrence or to decrease the volume of the remaining tumor that couldn't be resected. Otsuka et al. (30) reported that the expressions levels of VEGF and VEGFR were correlated, and played a crucial role in the formation of peritumoral brain edema. Due to a restricted number of patients who accepted chemotherapy, including Gefitinib, Erlotinib, Sunitinib, there was a conflict circumstance that needs medical evidence-based support (19,28).

Hence, it is critical to investigate the molecular mechanisms of malignant behavior and discover novel potential therapeutic markers. In recent years, gene microarray technology at the genetic level has developed fast and has been widely used to identify DEGs and functional pathways dysregulated in cancer that could help to unravel the underlying oncogenic mechanism. In this study, we compared gene expression profiles between atypical meningiomas and normal meninges from the National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database to identify key genes and pathways, aiming to investigate the molecular mechanisms underlying carcinogenesis and find potential therapeutic targets.

■ MATERIAL and METHODS

Microarray Data

The GEO database (<http://www.ncbi.nlm.nih.gov/geo>) is a public functional genomics data repository containing high-throughput data on gene expression. The gene expression dataset GSE43290 (Affymetrix GPL96 platform, Affymetrix Human Genome U133A Array) was downloaded from the GEO database and used for the following analyses.

Identification of Hub Gene

The DEGs between atypical meningiomas and normal meninges were detected using GEO2R (<http://www.ncbi.nlm.nih.gov/geo/geo2r>), and the adjusted P-value and $|\text{LogFold Change (FC)}|$ were calculated. Probe sets without meaningful gene symbols and genes with more than one probe were not considered for the analyses. The genes with $|\text{LogFC}| \geq 2$ and adjusted P-value < 0.01 were considered statistically significant. Weighted gene co-expression network analysis (WGCNA) was performed to find the significant gene modules, and the genes in the most significant module were selected to further exploration (23). A Venn diagram (8) was plotted to identify the key gene of the identified DEGs and the genes in the most significant module of WGCNA analysis.

GO and KEGG Pathway Analyses

The GO and KEGG pathway enrichment analyses were performed using the clusterProfile package in R software (41). GO is a functional classification that categorizes genes according to their biological process (BP), cellular component (CC), and molecular function (MF). The KEGG pathway contains pathway maps for the molecular systems in both normal and perturbed states.

PPI Network and Module Analysis

The Search Tool for the Retrieval of Interacting Gene database (STRING; <http://string-db.org>) (37) is an online database to analyze interactions between proteins. STRING was used to evaluate the potential interactions of the proteins encoded by DEGs with a combined score > 0.9 . The protein-protein interaction (PPI) network was constructed and visualized using Cytoscape software (version 3.7.2) (34). The plugin Molecular Complex Detection (MCODE, version 1.6) (3) was used to find the more densely connected region of the network based on its topology. The most significant network was detected by MCODE using the following criteria: degree cutoff = 2, node score cutoff = 0.2, k-core = 2, max depth = 100.

Identification and Analyses of Hub Genes

The plugin CytoHubba (11), which provides 11 methods for topological analysis, was used to rank nodes of the PPI network. The top 5 genes were ranked by Cytohubba using the methods degree, the maximal clique centrality (MCC), maximum neighborhood component (MNC), and edge per collated component (EPC). The overlapping genes were considered hub genes. To explore the relationship between hub genes and clinical outcomes, including age, recurrence, and overall survival, we further downloaded and analyzed the GSE16581 dataset to find the potential key genes using

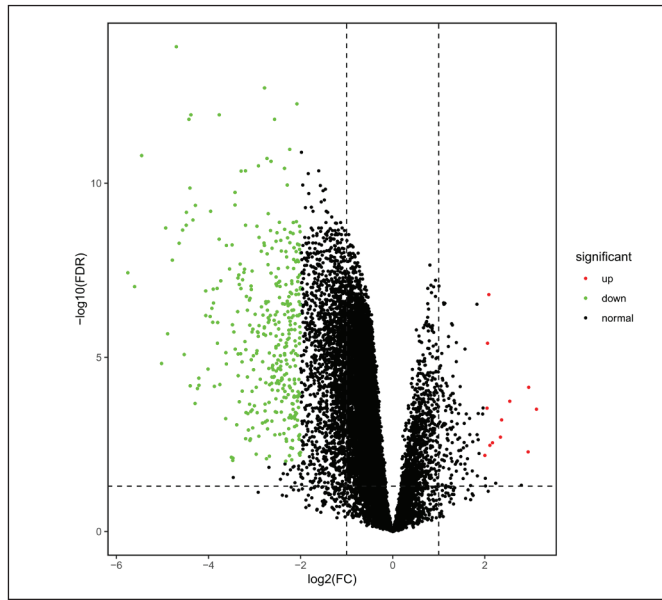


Figure 1: Differential expressions of data.
Note: The red points represent upregulated genes with $|\text{LogFC}| \geq 2$ and adjust p-value < 0.01 . The green points represent downregulated genes with $|\text{LogFC}| \geq 2$ and adjust p-value < 0.01 . The black points represent genes with no statistical significance.

R software (version 4.0.1). Additionally, we performed GO analyses and the KEGG pathway analysis (20) to determine the evaluate the function of the key genes, and compared the environment differences between normal meninges and atypical meningiomas.

RESULTS

Identification of DEGs and WGCNA

A total of 390 DEGs were identified ($|\text{LogFC}| \geq 2$ and adjusted p-value < 0.01) between normal meninges and atypical meningiomas. Of these genes, 16 were upregulated and 374 were downregulated (Figure 1). To further evaluate the relationship between the DEGs, we performed WGCNA after removing the outlier samples. An appropriate soft threshold power (soft power = 5) was selected to ensure standard scale-free networks. Modules were identified using the dynamic tree cut method by hierarchically clustering genes with a deep split value of 2 and a minimum size cutoff of 50 for the resulting dendrogram. The most significant module trait, ME_blue, and the genes included were selected to be further investigated (Figure 2-5).

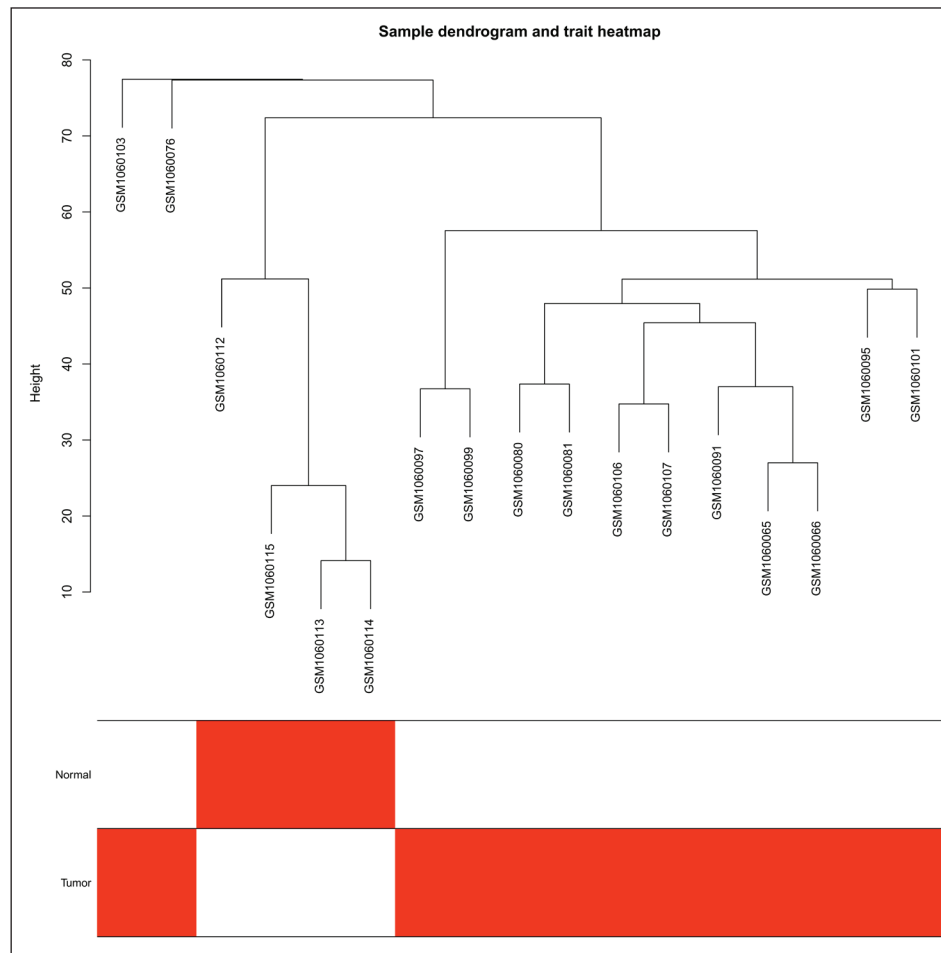


Figure 2: The clustering dendrogram of samples.

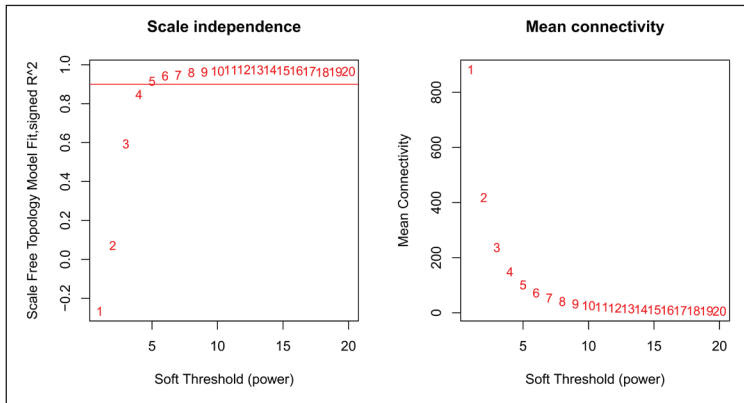


Figure 3: The scale-free fit index for various soft-thresholding powers.

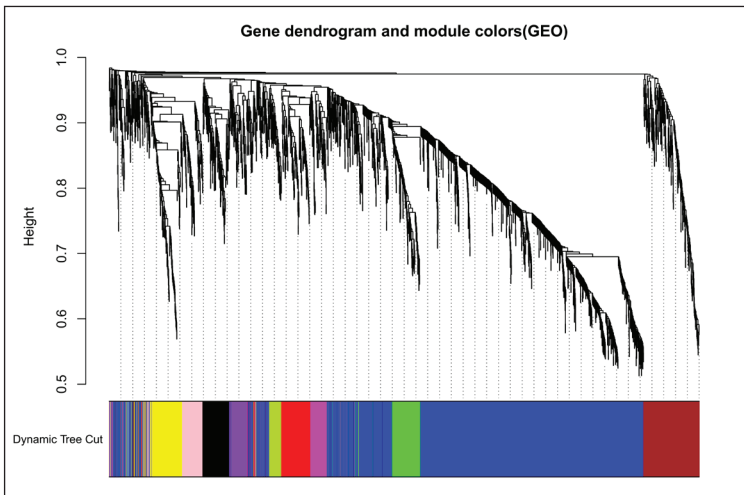


Figure 4: Gene dendrogram and merged dynamic.

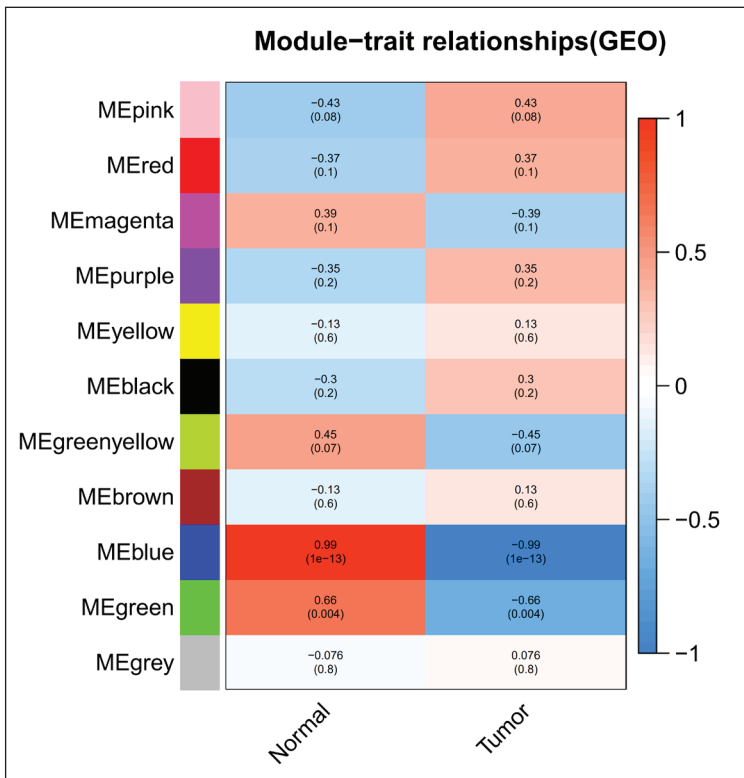


Figure 5: Module eigengenes heatmap.

Identification and Biological Enrichments of Hub Genes

A Venn diagram was drawn with the genes encoding proteins related to the stromal-immune environment and the genes that were identified as significant by WGCNA. A total of 286 overlapping genes were selected as hub genes (Figure 6). GO

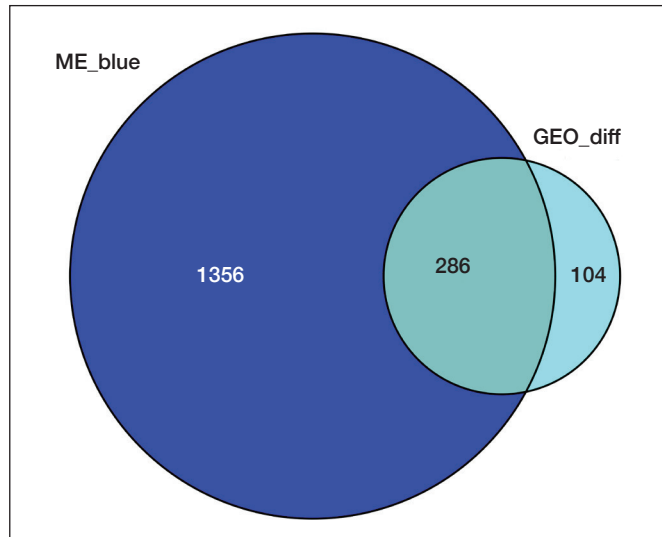


Figure 6: Hub gene selected by Venn diagram.

enrichment analysis of this set of genes showed that they were enriched functions related to leukocyte migration, collagen-containing extracellular matrix, signaling receptor activator activity, and receptor-ligand activity, and KEGG pathways enrichment analysis indicated that they were mainly enriched in the IL-17 signaling pathway and focal adhesion (Figure 7A, B).

PPI Network Construction and Module Analysis

The PPI network of the hub genes was constructed by Cytoscape. Then, the most significant module was identified by the MCODE plugin, which included 10 nodes and 45 edges (Figure 8). Then the biological functions of the significant genes were evaluated by GO and KEGG enrichment analysis, which showed that they were associated to chemokine signaling and chemotaxis (Figure 9A, B).

Key Genes Selection and Analyses

CXCL8 and CXCL2 were selected as hub genes from the overlapping genes (Table I). To explore the clinical significance of hub genes, we downloaded the GEO dataset GSE16581 and performed univariate analysis, finding that the expression levels of CXCL8 and CXCL2, and tumor grade were associated with overall survival. Additionally, CXCL8 and CXCL2 expression levels were related to age and tumor recurrence (Figure 10, 11A-D). GO analysis of the two hub genes

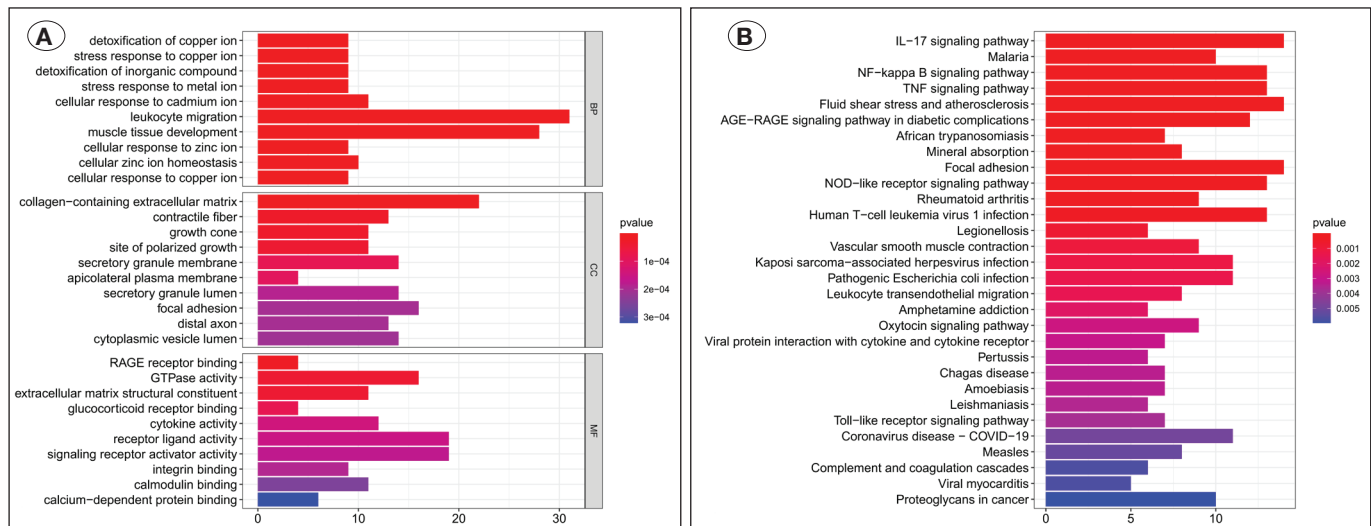


Figure 7: Significantly enriched GO and KEGG terms of hub genes.

Table I: Key Genes Ranked in the Cytohubba

	Rank Methods in Cytohubba			
	MNC	MCC	EPC	Degree
	CXCL8	CXCL8	CXCL8	JUN
Gene symbol	JUN	CXCL2	IL6	CXCL8
	IL6	CXCR4	JUN	IL6
	CXCL2	PPBP	CXCL2	PPBP
	CXCR4	ADRA2A	PPBP	CXCL2

showed were enriched in mediating chemokine and cytokine responses, especially neutrophil and granulocyte responses. KEGG pathway analysis showed that the two genes were enriched in the IL-17 signaling pathway (Figure 12A, B). Then, we compared the infiltration of the immune cells in the tumor

microenvironment to evaluate the differences between normal meninges and atypical meningiomas in GSE43290. The results showed that immune cells in atypical meningiomas, especially Macrophages M2, were significantly different from those in normal meninges (Figure 13A, B).

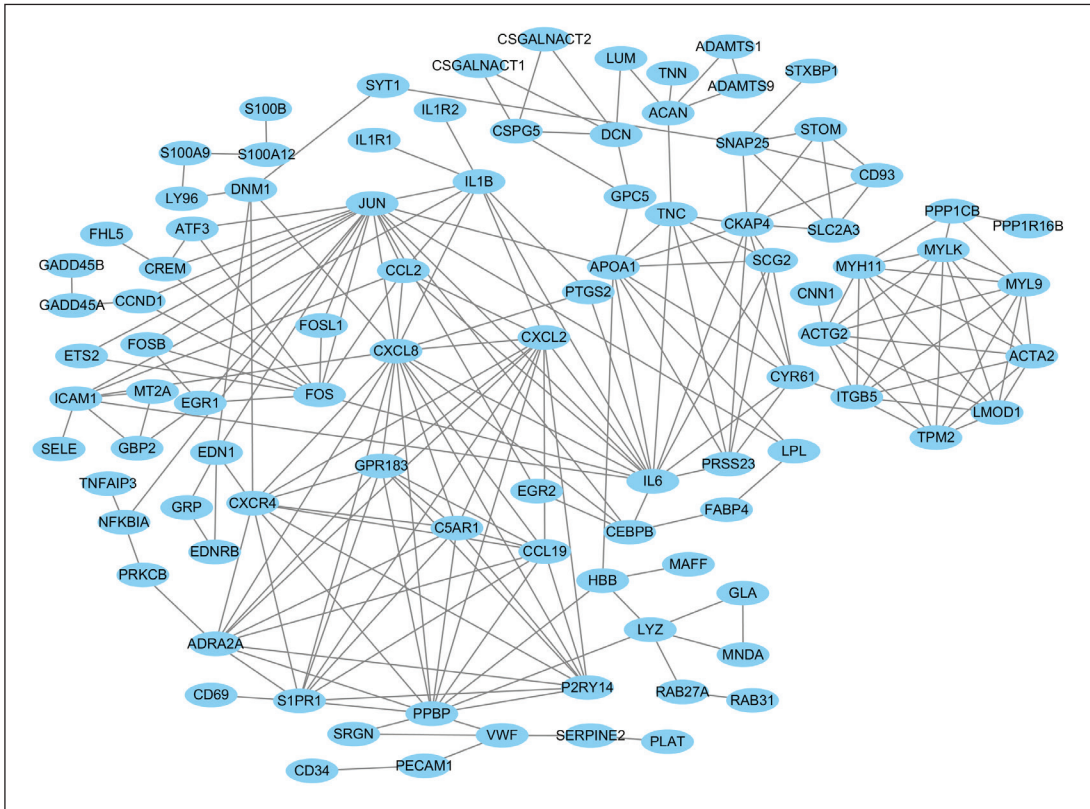


Figure 8: Protein-protein network interaction of hub gens.

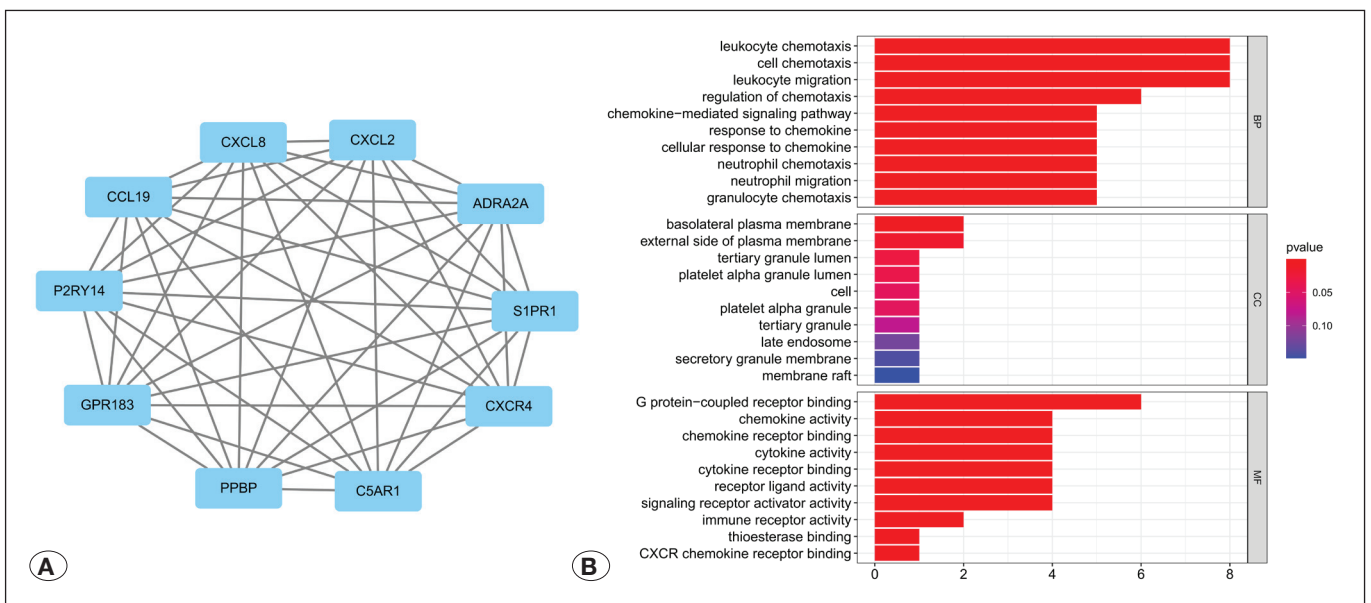


Figure 9: Module analysis using MCODE:Node Score Cutoff: 0.2, Haircut: true, Fluff: false, K-Core: 2, Max. Depth from Seed: 100.

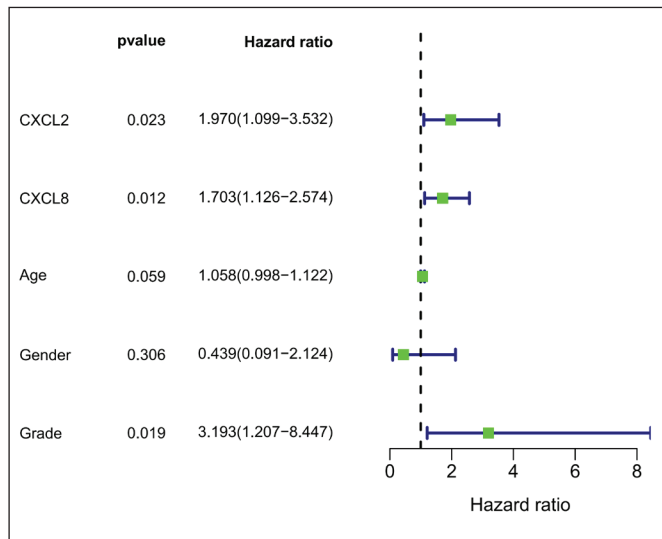


Figure 10: The Hazard ratio of overall survival performed by univariate analysis.

DISCUSSION

Atypical meningiomas have a higher recurrence rate, requiring long-term follow-up (16). Complete resection may not be applied to each sort of atypical meningiomas, and one imperative reason was that tumor location was emphatically associated with the extent of the Simpson grade resection. There might be much more serious functional impairments, such as vascular insults or the 9th to 12th nerve deficit in ventral foramen magnum meningiomas (2,9,38). Given that it is not possible to apply complete resections to all meningiomas due to tumor location, treatment of this disease is often accompanied by radiotherapy or chemotherapy. However, radiotherapy should be applied tactfully, as it entails a risk of potentiating the of malignant transformation of the remaining tumor cells (18,31). Because of lacking potential therapeutic targets, we might utilize constrained ways to control atypical meningiomas. Thus, it is necessary to explore the molecular mechanisms of atypical meningioma progression to find potential chemotherapeutic targets.

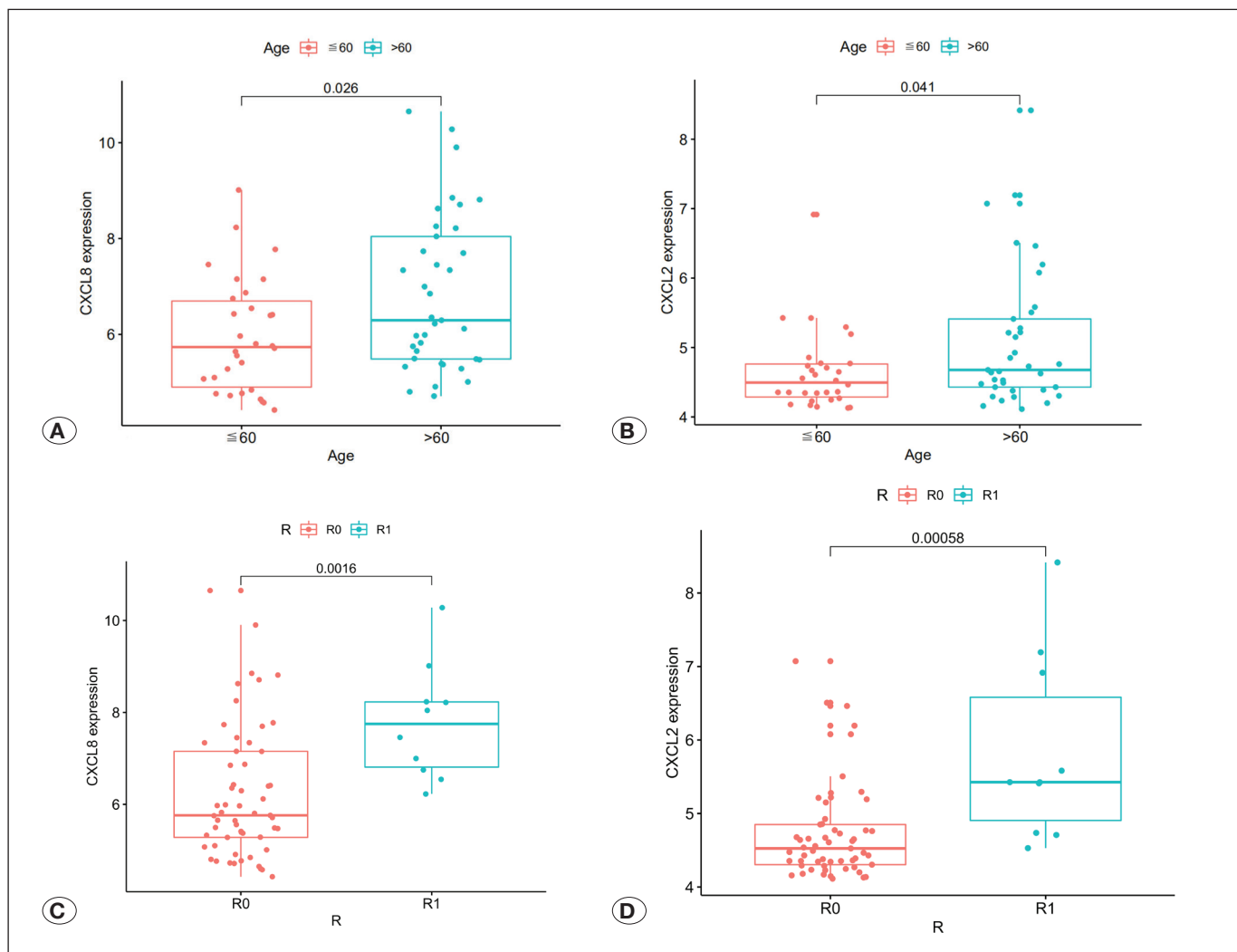


Figure 11: The relationship between key genes and age, recurrence. **Note:** R0 represents none recurrence. R1 represents recurrence.

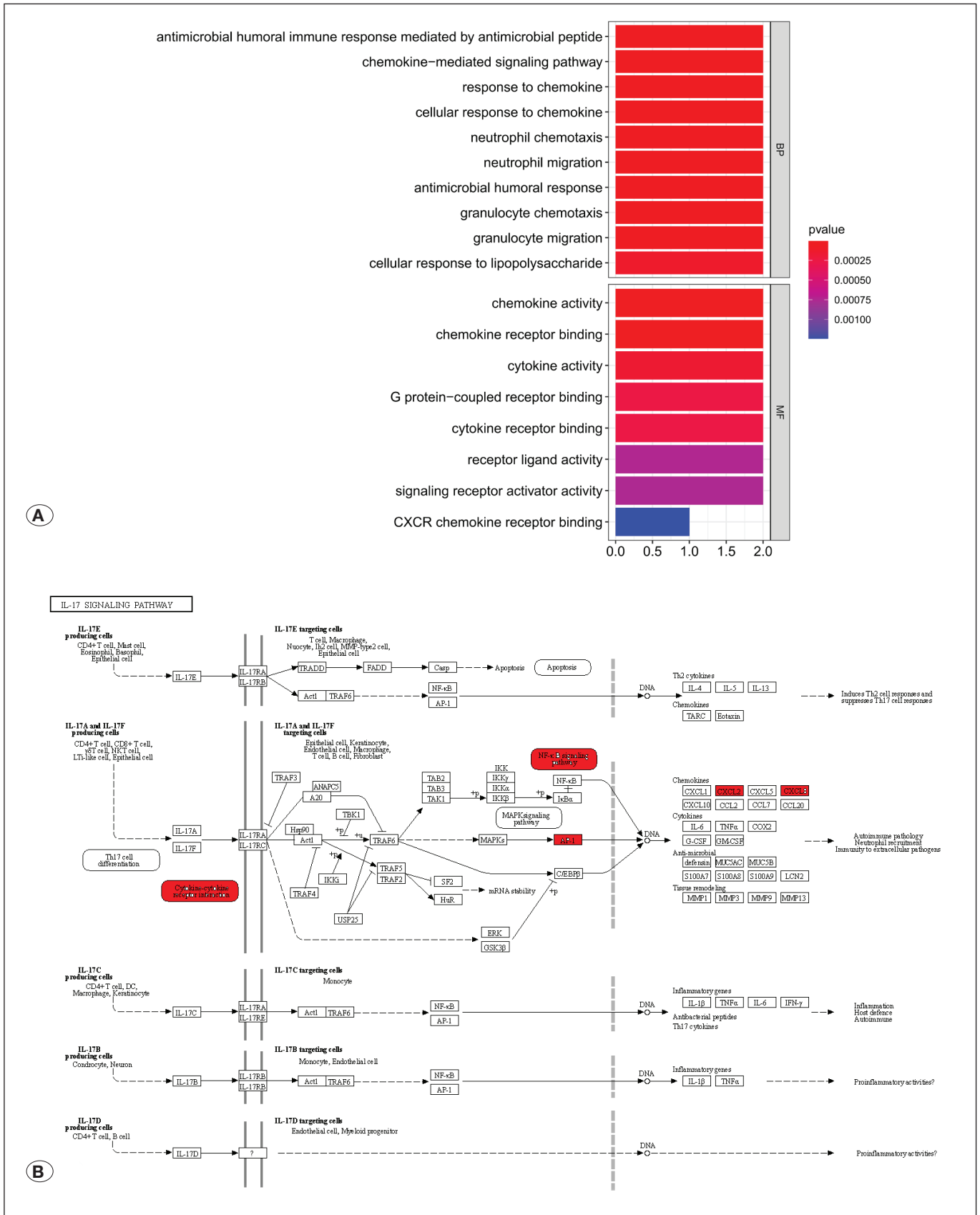


Figure 12: The GO and KEGG analysis of CXCL8, CXCL2.

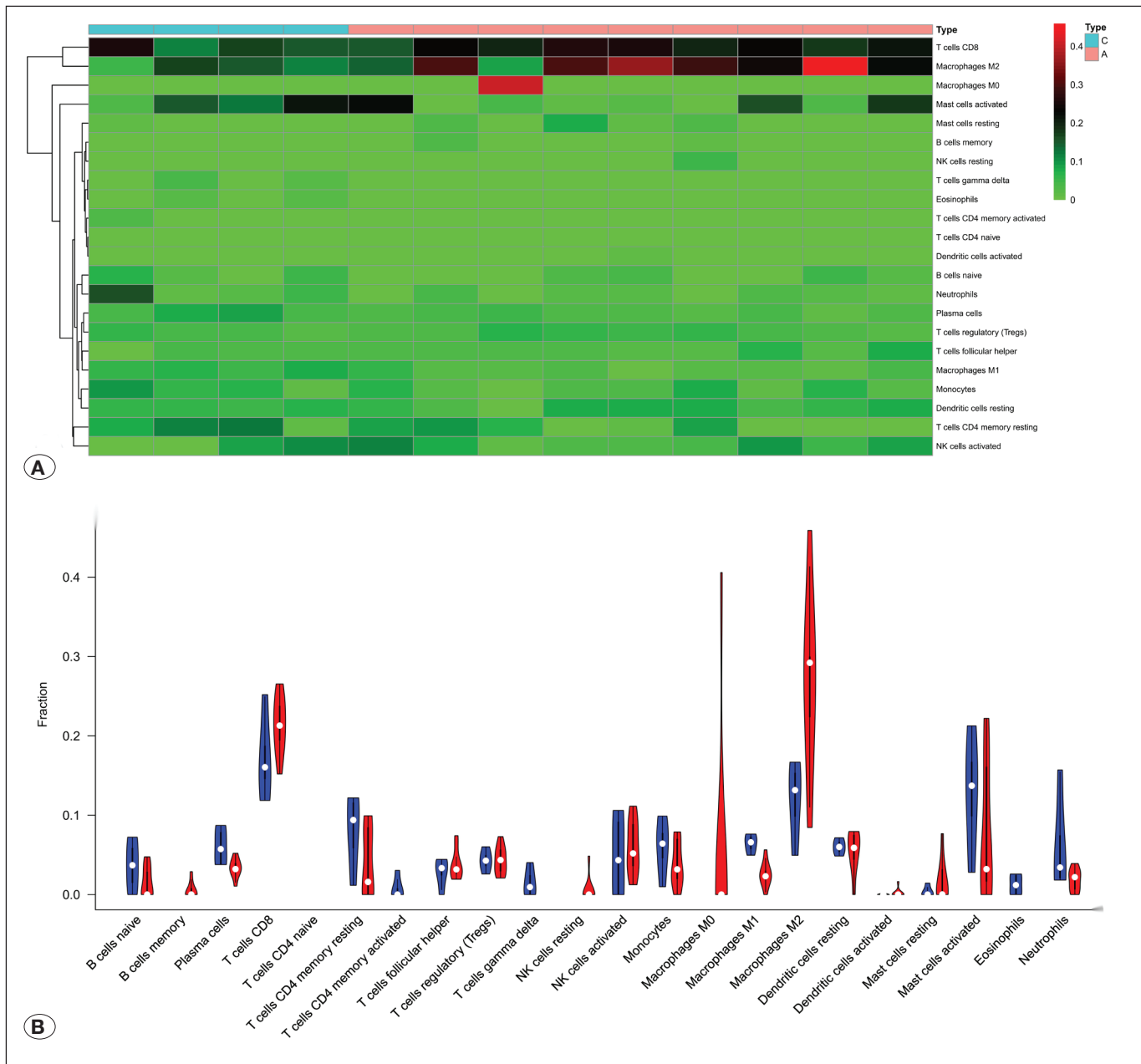


Figure 13: The immune cells between normal meninges and atypical meningiomas. C represents normal meninges. A represents atypical meningiomas.

In the last years, high-throughput sequencing and microarray data have played an important role in finding potential targets for cancer diagnosis and treatment. In the present study, microarray data from the datasets GSE43290 and GSE16581 downloaded from the GEO database were analyzed to identify the key genes that might contribute to the occurrence and recurrence of atypical meningioma. The selected hub genes were CXCL8 and CXCL2, which were related to tumor overall survival and recurrence. Then, we further explored the biological functions of these two genes and found that the key genes were enriched in mediating chemokine and cytokine responses, especially neutrophil and granulocyte responses.

Additionally, we evaluated the differences in the immune cells in the tumor microenvironment between atypical meningiomas and normal tissues.

CXCL8 encodes the chemokine C-X-C motif ligand 8, which plays a very important role in tumor growth, invasion, and metastases in an autocrine and paracrine manner (24). CXCL8 has been reported to be associated with numerous types of tumors, such as glioblastoma, lung adenocarcinoma, hepatocellular carcinoma, and colon cancer (17,25,27,35). Luo et al. demonstrated that increased expression levels of CXCL8 and VEGF were correlated with the recurrence of glioblastoma (27). Liu et al. showed that CXCL8 was an

independent unfavorable factor with recurrence-free survival and overall survival in patients suffering from adenocarcinoma, and that human Dachshund homologue 1 (DACH1) was able to antagonize CXCL8 through AP-1 and NF- κ B (25). Shen et al. reported that CXCL8 may initiate tumor proliferation and invasiveness inducing epithelial-mesenchymal transition through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B(AKT)/nuclear factor- κ B(NF- κ B) pathway (35). Daniel et al. reported that CXCL8 was emphatically associated with glioma formation and progression mediated by activator protein-1(AP-1) and NF- κ B (6). Finally, it has been demonstrated that human meningioma cells secrete CXCL8, which actively participates in the inflammatory response (4,12).

CXCL2 encoded chemokine C-X-C motif ligand 2, which is overexpressed in breast, hepatic, colon, and bladder cancer (21,42). Zhang et al. identified that the CXCL2/MIF-CXCR2 axis regulates the recruitment of myeloid-derived suppressor cells by NF- κ B, influencing their survival (42). Faget et al. illustrated that neutrophils are potential contributors to tumor progression, and that CXCL2 could enhance neutrophils infiltration (14).

The expression levels of CXCL2 and CXCL8 were correlated with age, as determined by correlation analysis when patients were divided in two groups, comprising younger and older than 60 years old, respectively. Further analyses are needed to elucidate why older people presented meningiomas with high CXCL2 and CXCL8 expression levels more frequently than young people. Additionally, these two key genes were also correlated with tumor survival and recurrence. GO and KEGG pathway enrichment analyses indicated that these two genes were implicated in chemokine signaling and cytokine production, specifically in the IL-17 signaling pathway, which may affect the neutrophil recruitment and immunity through AP-1 (20). Evaluations of the tumor immune infiltration indicated that macrophages M2 in atypical meningiomas were significantly different from normal meninges. Komohara et al. have previously reported that macrophages M2 cells were correlated with tumor angiogenesis and immune escape, processes that play an important role in tumor growth and invasion (22). Additionally, previous studies have illustrated that macrophages M2 were more abundant in meningiomas than other immune cells, and that they correlated with clinical prognosis in meningiomas (1,10). Although functional experiments are necessary to demonstrate the implication of CXCL8 and CXCL2 in meningiomas, the results of this study suggest they could be a suitable drug target for intractable tumors in the future.

■ CONCLUSION

The present study intended to investigate the key genes involved in oncogenesis, tumor proliferation and tumor invasion in atypical meningiomas. The two key genes identified, CXCL8 and CXCL2, were associated with tumor survival and recurrence, indicating that they might be suitable therapeutic targets in atypical meningiomas. However, additional functional studies are needed to validate the clinical significance of these genes in atypical meningiomas.

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■ AUTHORSHIP CONTRIBUTION

MC conceived the conception, searched the literature, and drafted the manuscript with help of YHW corrected the details and references. All authors read and approved the final manuscript.

■ AUTHORSHIP CONTRIBUTION

Study conception and design: MC

Data collection: MC

Analysis and interpretation of results: MC

Draft manuscript preparation: MC

Critical revision of the article: YHW

All authors (MC, YHW) reviewed the results and approved the final version of the manuscript.

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