

Identification of Key Genes with Clinical Outcome in Benign Meningioma Using Bioinformatic Analysis

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Identification of key genes with clinical outcome in benign meningioma using bioinformatic analysis

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ABSTRACT

Background: Meningioma is the second most common type of brain neoplasms. However, the underlying molecular mechanisms are still not clear, and the main treatment is mainly surgery plus radiotherapy.

Material and method: To explore the key genes in benign meningioma, we downloaded microarray dataset GSE43290 from Gene Expression Omnibus (GEO) database. The differential genes (DEGs) between benign meningioma and normal meninges were identified by GEO2R. The gene ontology (GO) and Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway were performed by the Database for Annotation, Visualization and Integrated Discovery (DAVID). The protein-protein interaction (PPI) network and module analysis were performed and visualized by the Search Tool for the Retrieval of Interacting Gene database (STRING) and Cytoscape. The hub genes were evaluated by the Cytohubba and further explored by MCODE plugin of Cytoscape and Enrichr. The relationship between hub genes and clinical factors were further explored by GSE16581 through R software.

Result: A total of 358 DEGs were identified, including 15 upregulated genes and 343 downregulated genes. The main enriched functions were extracellular matrix organization, inflammatory response, cell adhesion, extracellular space and integrin binding. The main KEGG pathways were Malaria and focal adhesion. Among these DEGs, 5 overlapping genes (CXCL8, AGT, CXCL2, CXCL12, CXCR4) were selected as hub genes. CXCL2 and CXCL8 were correlated with age and tumor recurrence, which could be clinical therapeutic targets.

Conclusion: This study indicates the key genes in benign meningioma which may help us understand the molecular mechanisms and provide the candidate therapeutic targets.

Keywords: meningioma; GEO data; hub gene; bioinformatic analysis.

1. Background

Meningioma, originating from arachnoid meningotheial cells, is the second most common neoplasm in central nervous system, accounting for approximately 30% of newly diagnosed CNS tumors. In 2016 WHO classification of CNS tumors, meningiomas were classified into three types: I, II, III, and the grade I meningiomas belong to typical/benign meningiomas, approximately equaling to

88-94% of all meningiomas^[1-3]. The median diagnosed age is 65 years, the atypical or anaplastic meningiomas often occurring in elderly people than younger group, and the ratio of female to male is 2.2:1^[4]. The primary diagnosis of suspected meningioma is mostly based on magnetic resonance imaging (MRI), which could probably distinguish benign from atypical meningioma^[5]. The pathological diagnosis is the golden standard, but histological diagnosis wouldn't explain the reason that benign meningioma shows signs of malignant proliferation or long-distance metastasis^[6]. With advanced molecular profiling technology, we could define the most significant two types of meningioma: a group of tumors with neurofibromatosis 2 mutations which tend to be atypical or anaplastic pathologies, and meningiomas with non-NF2 mutations which tend to be benign pathology, including TRAF7、KLF4、SMO、AKT1、POLR2A^[7, 8]. But those mutational analysis alone couldn't help clinical conditions which patients need follow-up or alternative therapies.

The most important therapy for meningioma is surgical resection. Some researches reported that patients undergoing Simpson Grade I resection showed lower risk of recurrence than those with Simpson Grade II-IV resection, and besides high-grade WHO lesions, advanced sinus invasion、high Ki-67 expression and MIB index >3% were significantly associated with a higher risk of recurrence^{[9][10][11]}. Patients who only underwent subtotal resection had a higher risk of recurrence than those undergoing surgical resection and post-operative radiotherapy^[12-14]. But as we all know, radiation was strongly associated with higher risk of meningioma, radiotherapy could induce treatment-related side effects and long-term toxicity, including inducing malignant transformation^[15-17]. So many physicians turned to chemotherapy in order to control the recurrence or those tumors which couldn't be totally resected. Otsuka et al^[18] reported that the expressions of VEGF and VEGFR were related to each other and played an important role in the formation of peritumoral brain edema. Nakada et al^[11] also reported that patients with VEGFR-2-positive meningiomas showed shorter progression-free survival, and sunitinib, as a tyrosine kinase inhibitor, showed positive effects in prolonging the progression-free survival in VEGFR positive patients, aiming to become a new type of chemotherapy^[19]. Due to limited number of patients who accepted chemotherapy, including Hydroxyurea、Temozolomide、Tamoxifen、Erlotinib, there were many researches which lacked medical evidence-based support^[20].

Hence, it is important to investigate the molecular mechanisms of malignant behaviour and identify the potential therapeutic markers. In recent years, microarray technology at the genetic level has developed fast and widely used to identify the differentially expressed genes (DEGs) and functional pathways which could help to illustrate the underlying mechanisms. Therefore, we compared gene expression profiles between benign meningioma and normal meninges from the National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database (<http://www.ncbi.nlm.nih.gov/geo>) to identify DEGs and pathways, aiming to understand the molecular mechanisms underlying carcinogenesis and find potential therapeutic targets.

2. Materials and methods

Microarray data

The GEO database (<http://www.ncbi.nlm.nih.gov/geo>) was a public functional genomics of high throughput gene expression data. The gene expression dataset (GSE43290) was downloaded from GEO database (Affymatrix GPL96 platform, Affymatrix Human Genome U133A Array). The GSE43290 contained 33 benign meningioma tissue samples and 4 normal meninges tissue samples.

Identification of DEGs

The DEGs between benign meningioma and normal meninges samples were detected by GEO2R (<http://www.ncbi.nlm.nih.gov/geo/geo2r>), and the adjusted P-value and $|\text{LogFC}|$ were calculated. Probe sets without meaningful gene symbol and genes with more than one probes were eliminated. The $|\text{LogFC}| \geq 2$ and adjusted P-value < 0.01 were considered statistically significant.

GO and KEGG pathway enrichment analysis of DEGs

The Database for Annotation, Visualization and Integrated Discovery (DAVID) was an online gene analysis database which integrated bioinformatic data, biological pathways and provides functional annotations genes^[21, 22]. The GO and KEGG pathway enrichment were performed by DAVID. The GO analyses which was a tool to annotate and analyze genes were classified into biological process (BP), cellular component (CC) and molecular function (MF)^[23]. The KEGG pathway contained pathway maps for the molecular systems in both normal and perturbed states^[24]. The gene counts ≥ 10 and FDR (adjusted P-value) < 0.05 were considered statistically significant.

PPI network construction and module analysis

The Search Tool for the Retrieval of Interacting Gene database (STRING; <http://string-db.org>) was an online database to analyze interactions between proteins^[25]. In this study, previous DEGs were mapped by STRING to evaluate the potential interactions of proteins with combined score > 0.9 . After that, PPI network was constructed and visualized by Cytoscape software (version 3.7.2) which was an open source bioinformatic software platform^[26]. The plugin Molecular Complex Detection (MCODE, version 1.6) was used to find the intensively densely connected region based on topology^[27]. The most significant network was detected by MCODE with following criteria: degree cutoff = 2, node score cutoff = 0.2, k-core = 2, max depth = 100.

Identification and analysis of hub genes

The plugin CytoHubba which provided 11 topological analysis methods of Cytoscape was being used to rank node in previous PPI network^[28]. In this study, the top 10 genes were ranked by Cytohubba with Degree, the maximal clique centrality (MCC), maximum neighborhood component (MNC) and edge percolated component (EPC). The overlapping genes were considered as hub genes and further explored the

GO and KEGG pathways using Enrichr^[29]. The adjusted P-value < 0.01 was considered statistically significant. We further downloaded and analyzed GEO dataset (GSE16581) by R software (version 4.0.1), illuminating the relationship between the expression of hub genes and clinical factors, including age and recurrence.

3. Results

Identification of DEGs

With the criteria $|\text{LogFC}| \geq 2$ and adjusted P-value < 0.01, a total of 358 DEGs were identified respectively, consisting of 15 upregulated genes and 343 downregulated genes between normal meninges and benign meningiomas, as showing in figure 1.

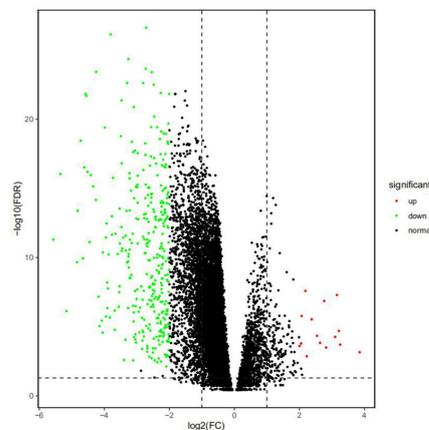


Figure 1. Differential expression of data among two datasets.

Note: The red points represent upregulated genes with $|\text{LogFC}| \geq 2$ and adjusted P-value < 0.01. The green points represent downregulated genes with $|\text{LogFC}| \geq 2$ and adjusted P-value < 0.01. The black points represent genes with no statistical significance.

GO and KEGG pathway enrichment of DEGs

The GO function and KEGG pathway analysis of DEGs were performed by DAVID. GO function analysis showed that changes in biological process (BP) were mainly enriched in extracellular matrix organization, inflammatory response, cell adhesion, regulation of blood pressure. Changes in cellular components (CC) were mainly enriched in extracellular space, extracellular region, axon-extracellular matrix. Changes in molecular function (MF) were mainly enriched in integrin binding. The KEGG pathways showed that DEGs were mainly enriched in Malaria, Focal adhesion (Table 1, Figure 2).

Table 1. Significantly enriched GO terms and KEGG pathways of DEGs

Category	Term	Description	Count	FDR
BP	GO:0030198	extracellular matrix organization	22	5.28E-07
BP	GO:0006954	inflammatory response	30	7.68E-07

BP	GO:0007155	cell adhesion	32	4.01E-06
BP	GO:0008217	regulation of blood pressure	11	8.98E-04
BP	GO:0001666	response to hypoxia	16	0.002754706
BP	GO:0001525	angiogenesis	18	0.003633709
BP	GO:0016337	single organismal cell-cell adhesion	12	0.008203143
BP	GO:0070374	positive regulation of ERK1 and ERK2 cascade	15	0.016753029
BP	GO:0071347	cellular response to interleukin-1	10	0.0174516
BP	GO:0032496	response to lipopolysaccharide	14	0.038385128
CC	GO:0005615	extracellular space	64	4.63E-09
CC	GO:0005576	extracellular region	61	1.02E-04
CC	GO:0030424	axon	18	1.00E-03
CC	GO:0031012	extracellular matrix	20	0.003230368
CC	GO:0048471	perinuclear region of cytoplasm	29	0.01529324
CC	GO:0009986	cell surface	26	0.031262473
CC	GO:0043209	myelin sheath	13	0.031929
CC	GO:0070062	extracellular exosome	81	0.032123168
MF	GO:0005178	integrin binding	11	0.037757175
KEGG_PATHWAY	hsa05144	Malaria	10	0.002806854
KEGG_PATHWAY	hsa04510	Focal adhesion	18	0.012479012

Note:BP,biological process;CC,cellular component;MF,molecular function;GO,gene ontology.

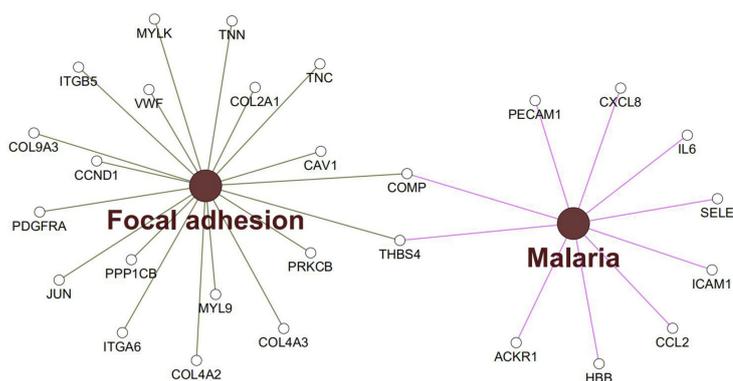


Figure 2. Significant pathways and enriched differential expressed genes.

PPI network construction and module analysis

The PPI network of EDGs were constructed by STRING and visualized by Cytoscape. A total of 341 nodes and 324 edges were involved in PPI network (Figure

3).The most significant module was constructed by MCODE plugin(Figure 4),including 14 nodes and 91 edges.

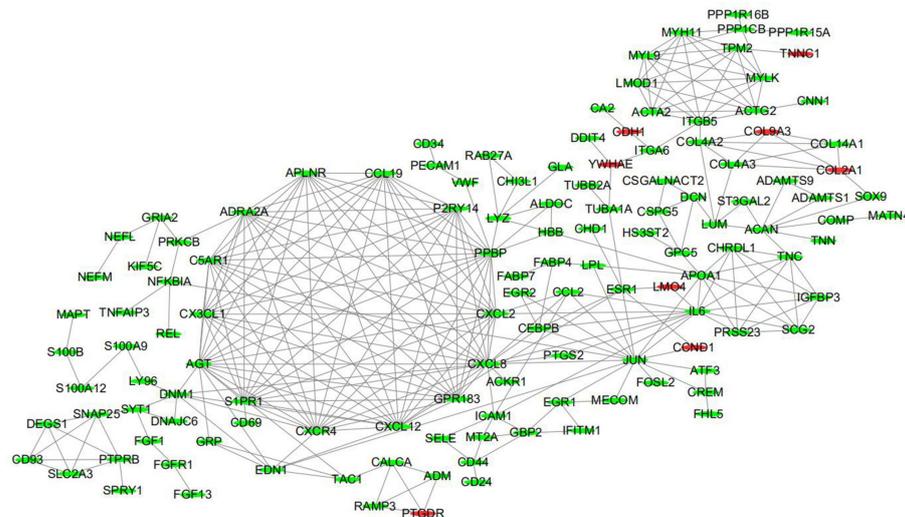


Figure 3. Protein-protein network interaction constructed with differential expressed genes. Note: Red terms represent upregulated genes. Green terms represent downregulated genes.

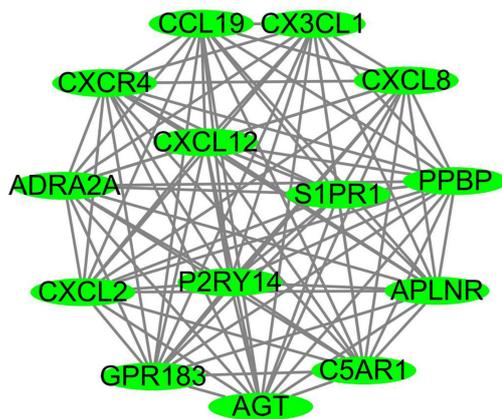


Figure 4. Module analysis using MCODE: Node Score Cutoff: 0.2, Haircut: true, Fluff: false, K-Core: 2, Max. Depth from Seed: 100.

Hub genes selection and analysis

To further explore hub genes, the Cytohubba plugin were being used to rank the top 10 nodes in the above PPI network with four topological methods, including Degree, MCC, MNC and EPC (Table 2). A total of 5 overlapping genes were selected as hub genes and further explored the GO and KEGG pathways by Enrichr (Table 3). The clinical outcomes of hub genes were showed in figure 5 and 6.

Table 2. Hub genes of DEGs ranked in the Cytohubba

Category	Rank methods in Cytohubba			
	MNC	MCC	EPC	Degree
gene symbol	CXCL8	AGT	GPR183	CXCL8

AGT CXCL8 APLNR AGT
CXCR4 CXCL12 CXCR4 PPBP
CXCL12 CXCR4 CXCL12JUN
CXCL2 PPBP CXCL8 CXCL12
GPR183 CXCL2 CXCL2 CXCR4
APLNR ADRA2AP2RY14 CXCL2
ADRA2AS1PR1 AGT ADRA2A
IL6 GPR183 CCL19 IL6
P2RY14 APLNR PPBP S1PR1

Note:Bold genes were the overlapping hub genes in the top 10 ranked genes with four methods in the Cytohubba.MNC,maximum neighbourhood component. MCC,maximal clique centrality.EPC,edge percolated component.Degree,node connect degree.

Table 3.Hub genes further analysis by Enrichr

Category	Description	Adjusted P-value	Genes
BP	chemokine-mediated signaling pathway(GO:0070098)	8.43E-04	CXCL8;CXCL12;CXCL2
BP	positive regulation of leukocyte chemotaxis(GO:0002690)	6.86E-04	CXCL8;CXCL12;CXCL2
BP	second-messenger-mediated signaling (GO:0019932)	4.80E-04	CXCL8;CXCR4;AGT
BP	induction of positive chemotaxis(GO:0050930)	0.002868053	CXCL8;CXCL12
BP	positive regulation of positive chemotaxis(GO:0050927)	0.006114914	CXCL8;CXCL12
MF	CXCR chemokine receptor binding (GO:0045236)	5.86E-06	CXCL8;CXCL12;CXCL2
MF	chemokine activity (GO:0008009)	6.53E-05	CXCL8;CXCL12;CXCL2
MF	chemokine receptor binding (GO:0042379)	5.28E-05	CXCL8;CXCL12;CXCL2
MF	cytokine activity (GO:0005125)	0.001298787	CXCL8;CXCL12;CXCL2
KEGG_PATHWAY	Chemokine signaling pathway	1.21E-05	CXCL8;CXCL12;CXCR4;CXCL2
KEGG_PATHWAY	Cytokine-cytokine receptor interaction	3.48E-05	CXCL8;CXCL12;CXCR4;CXCL2
KEGG_PATHWAY	NF-kappa B signaling pathway	1.06E-04	CXCL8;CXCL12;CXCL2
KEGG_PATHWAY	Pathways in cancer	1.84E-04	CXCL8;CXCL12;CXCR4;AGT
KEGG_PATHWAY	Human cytomegalovirus infection	8.51E-04	CXCL8;CXCL12;CXCR4
KEGG_PATHWAY	Intestinal immune network for IgA production	0.002881915	CXCL12;CXCR4
KEGG_PATHWAY	Legionellosis	0.003249738	CXCL8;CXCL2
KEGG_PATHWAY	Salmonella infection	0.006977051	CXCL8;CXCL2
KEGG_PATHWAY	Rheumatoid arthritis	0.006944943	CXCL8;CXCL12
KEGG_PATHWAY	IL-17 signaling pathway	0.006528466	CXCL8;CXCL2
KEGG_PATHWAY	AGE-RAGE signaling pathway in diabetic complications	0.006862441	CXCL8;AGT
KEGG_PATHWAY	Leukocyte transendothelial migration	0.007889946	CXCL12;CXCR4

Note:BP,biological process;MF,molecular function;GO,gene ontology.

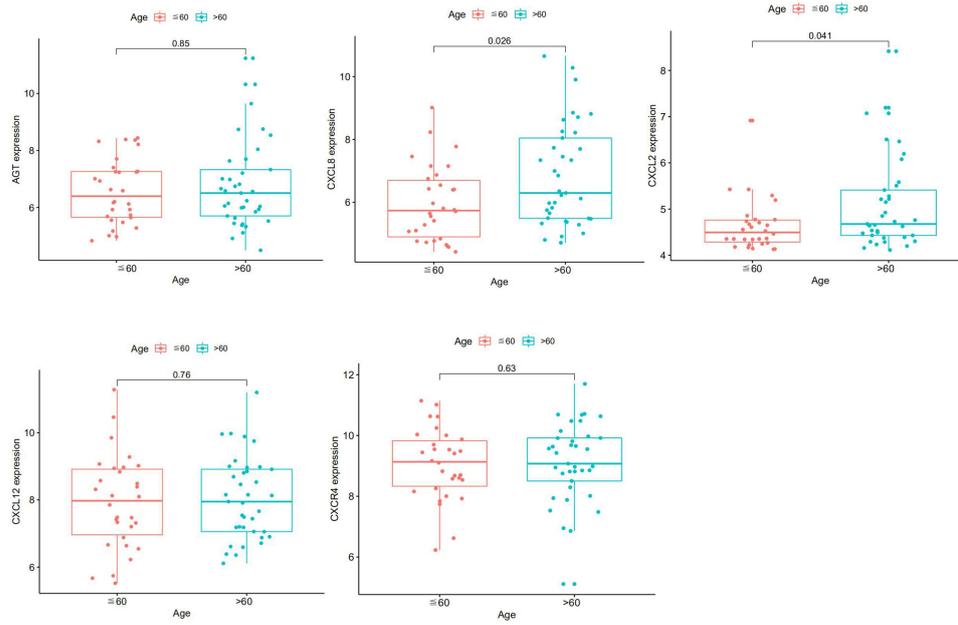


Figure 5. The clinical relationship between expression of hub genes and age

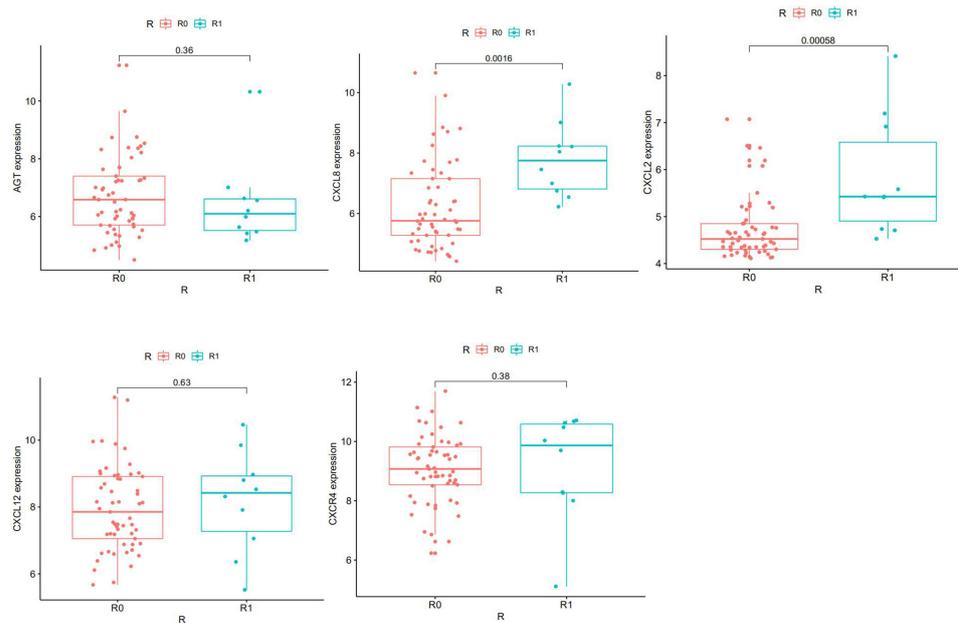


Figure 6. The clinical relationship between expression of hub genes and age. Note: R0 represents no recurrence. R1 represents recurrence.

4. Discussion

The growth pattern of meningioma can't be predicted precisely and need long-term follow-up^[30]. Complete resection may not be applied to every single type of meningiomas, but tumor location is strongly associated with different Simpson grade removal and there could be many serious functional impairment, such as vascular insults or the 9th through 12th nerve deficit in ventral foramen magnum meningiomas^[31-33]. Radiotherapy is regarded as supplementary post-operative

treatment but should be applied discreetly, because of radiation resistance or the potential malignant transformation^[17, 34]. Because of lacking potential therapeutic targets, we can use few ways to control meningioma. Thus, it's important to explore the molecular mechanisms of benign meningioma and find the potential chemotherapeutic targets.

Nowadays, microarray data and high-throughput sequence which detect millions of genes play an important role in finding potential targets for cancer diagnosis and treatment. In present study, microarray data GSE43290 downloaded from GEO database was further analyzed to identify the key genes which might contribute to the occurrence and development of benign meningioma. A total of 358 DEGs were identified respectively, consisting of 15 upregulated genes and 343 downregulated genes. GO enrichment analysis showed that DEGs were mainly enriched in extracellular matrix organization, inflammatory response, cell adhesion, extracellular space and integrin binding. The significant KEGG pathway of DEGs were malaria and cell adhesion. At last, the selected hub genes were AGT, CXCL8, CXCL2, CXCL12 and CXCR4.

AGT, also called angiotensinogen, was known as precursor of the renin-angiotensin system. The human AGT gene, which coded for a 485-amino acid protein, consisted of five exons and four introns. Mature AGT protein contained 452 amino acid residues, which consisted of des(Ang I) AGT and angiotensin I(Ang I), an inactive decapeptide which is converted into Ang II^[35]. Local Ang II in tumor environment(TME) produced by hypoxia-lactate-chymase-dependent mechanism was involved in immune escape and mediating radioresistance in tumor cells^[36-38]. And augmented AGT and angiotensin-converting enzyme(ACE) released from apoptotic endothelial cells played a vital role in turning to Ang II to accelerate the progress of vascular remodeling^[39]. It was demonstrated that human AGT inhibits endothelial cell proliferation and angiogenesis in vivo, and prevents tumor sinusoids from remodeling and arterIALIZATION, thus inhibits tumor progression^[40, 41]. Sun et al^[42] also reported that high glucose promoted tumor proliferation by suppressing AGT expression. In this study, the downregulation of AGT represented that AGT expression decreased and the role of delaying tumor angiogenesis was weakened.

CXCL8, also known as chemokine (C-X-C motif) ligand 8, plays a very important role in tumor growth, invasion and metastases in an autocrine and paracrine manner^[43]. Some researches demonstrated that CXCL8 was associated with many types of tumors, such as glioblastoma, lung adenocarcinoma, hepatocellular carcinoma and colon cancer^[44-46]. Luo et al^[44] demonstrated that high gene expression levels of CXCL8 and VEGF was correlating with recurrent glioblastoma. Daniel et al^[47] showed that IL-8 was strongly associated with glioma formation and progression mediated by activator protein-1(AP-1) and nuclear transcription factor-kappa(NF- κ B) site. Liu et al^[45] showed that CXCL8 was an independent unfavorable factor with recurrence free survival and overall survival in patients suffering from adenocarcinoma, and the human Dachshund homologue 1(DACH1) was able to antagonize CXCL8 through AP-1 and NF- κ B. Shen et al^[46] reported that CXCL8 may induce tumor proliferation, invasiveness through induction of epithelial-mesenchymal

transition via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B(AKT)/nuclear factor- κ B(NF- κ B) pathway. Researches demonstrated that human meningioma cells secreted specifically the CXC chemokine-8^[48, 49]. In our study, the differential expression of CXCL8 between two datasets suggested it as an important target.

CXCL2, also known as chemokine (C-X-C motif) ligand 2, was a member of chemokine subfamily. Some researches demonstrated that CXCL2 was overexpressed in breast, hepatic, colon and bladder cancer^[50-53]. Typically, Ding et al^[51] reported that CXCL2 was downregulated in hepatocellular carcinoma. Overexpression of CXCL2 significantly emasculated HCC cell proliferation, and the overall survival rates of high CXCL2 expression group were significantly higher than group with low CXCL2 expression. In this study, we manifested that CXCL2 was downregulated in benign meningiomas other than normal meninges, which may not inhibit meningioma proliferation.

CXCL12, also known as chemokine (C-X-C motif) ligand 12 or stromal cell-derived factor-1(SDF-1), also was a member of chemokine subfamily, widely expressed in many tissues^[54, 55]. CXCL12 was secreted by meningeal cells as a chemotactic factor attracting external granulocytes and played an important role in embryogenesis, including vasculature, neurodevelopment, and maintained hemostasis in the mature brain system^[56, 57]. CXCL12 regulated tumor cell adhesion with laminin, fibrinogen and endothelial cells, and removal of CXCL12 abolished the chemotactic effect entirely^[58, 59]. Du R et al^[58] and Santiago B et al^[59] reported that under hypoxic conditions, tumor cells or fibroblasts upregulated SDF-1 mRNA to facilitate angiogenesis. Some researches^[60, 61] demonstrated that hypoxia could also significantly stimulate CXCR4 expression. CXCR4, also known as chemokine (C-X-C motif) ligand receptor 4, was a G protein-coupled receptor activated by CXCL12^[62]. Zhang et al^[63] reported that the expression of CXCR4 was positively correlated with CXCL12 expression, and the chemotactic effect of CXCL12 was modulated by controlling CXCR4 expression. Moreover, Hartmann et al^[64] reported that CXCL12-induced integrin activation and CXCR4 co-operated in mediating adhesion and survival signals from the TME. CXCL12/CXCR4 axis was also involved in blood vessel growth and remodeling^[65], and Hiratsuka et al^[66] demonstrated that inhibition of both VEGF1 and CXCR4 signaling showed greater effects on tumor vascular density, growth and metastasis than inhibition of VEGF1 alone. So we could know that CXCL12/CXCR4 axis plays a crucial role in tumor formation, proliferation and metastasis, thus causing tumor formation and invasion^[49, 64, 67, 68]. Mo et al^[69] demonstrated that CXCL12/CXCR4 promoted neurofibromatosis 1-associated malignant peripheral nerve sheath tumor (MPNST) proliferation, which illustrated that high CXCR4 expression was correlated with poor survival. Zeng et al^[70] reported that blockage of CXCL12/CXCR4 axis by plerixafor prolonged survival of tumor-bearing mice by immunosuppression in the TME. Cai et al^[60] reported that plasminogen kringle 5 reduced nuclear HIF-1 α accumulation and impaired HIF-1 α DNA-binding and transactivation function, thus suppressing the expression of CXCL12/CXCR4 to inhibit the neovascularization and tumor growth.

In those hub genes, the expressions of CXCL2 and CXCL8 were correlated with age, which was divided into two groups with the limits of 60 years old. With more genes and more pathways involving in tumorigenesis, it could be explained why elder people were frequently found with meningioma. Meanwhile these two hub genes were correlated with tumor recurrence. But we need further evidence to prove the effects in cell and tissue level.

5. Conclusion

The present study intended to investigate the DEGs which involved in the mechanism of tumor generation, proliferation and invasion. A total of 358 DEGs and 5 hub genes were identified and two hub genes, CXCL8 and CXCL2, were found to be correlated with tumor recurrence. Thus we have more methods to handle those meningiomas which can't be resected completely in the long run. But more studies are needed to illustrate the clinical significance of these genes in meningioma.

Abbreviations:

GEO : Gene Expression Omnibus
DEG : differential expressed genes
GO : gene ontology
KEGG : Kyoto Encyclopedia of Gene and Genomes
DAVID : Database for Annotation, Visualization and Integrated Discovery
PPI : protein-protein interaction
STRING : Search Tool for the Retrieval of Interacting Gene database
CNS : central nervous system
MRI : magnetic resonance imaging
TME : tumor microenvironment
AGT : angiotensinogen
CXCL8 : chemokine (C-X-C motif) ligand 8
CXCL2 : chemokine (C-X-C motif) ligand 2
CXCL12 : chemokine (C-X-C motif) ligand 12
SDF-1 : stromal cell-derived factor-1
CXCR4 : chemokine (C-X-C motif) ligand receptor 4
MPNST : malignant peripheral nerve sheath tumor

Declarations:

Ethics approval and consent to participate: Not applicable.

Consent for publication: All the authors have read and approved the final version of manuscript and give consent.

Availability of data and materials: Not applicable.

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Authors' contributions: MC conceived the conception, MC and CS searched the literature, MC drafted the manuscript with help of JZ. YHW corrected the details and references. All authors read and approved the final manuscript.

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Figures

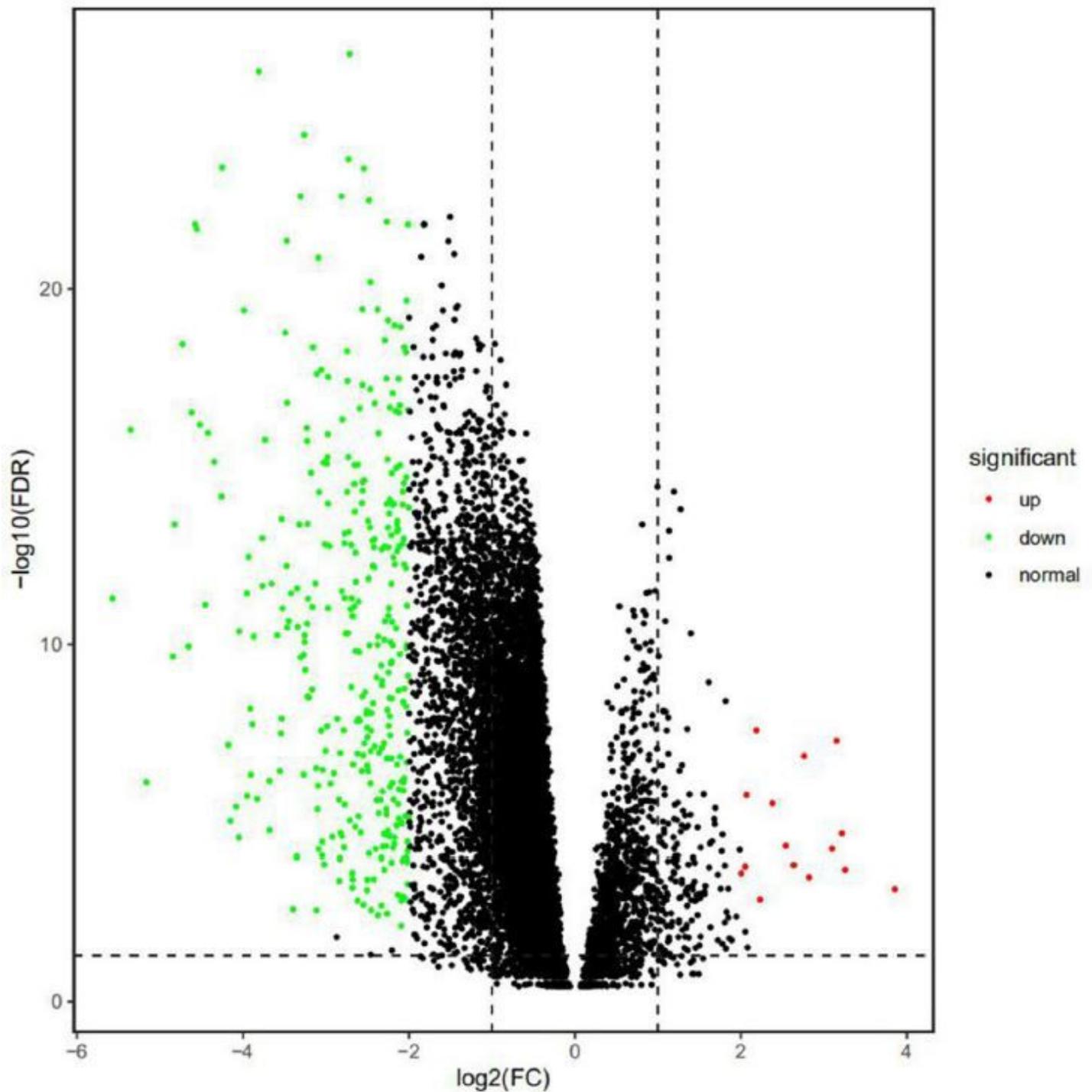


Figure 1

Differential expression of data among two datasets. Note: The red points represent upregulated genes with $|\text{LogFC}| \geq 2$ and $\text{adjust P-value} < 0.01$. The green points represent downregulated genes with $|\text{LogFC}| \geq 2$ and $\text{adjust P-value} < 0.01$. The black points represent genes with no statistical significance.

Protein-protein network interaction constructed with differential expressed genes. Note: Red terms represent upregulated genes. Green terms represent downregulated genes.

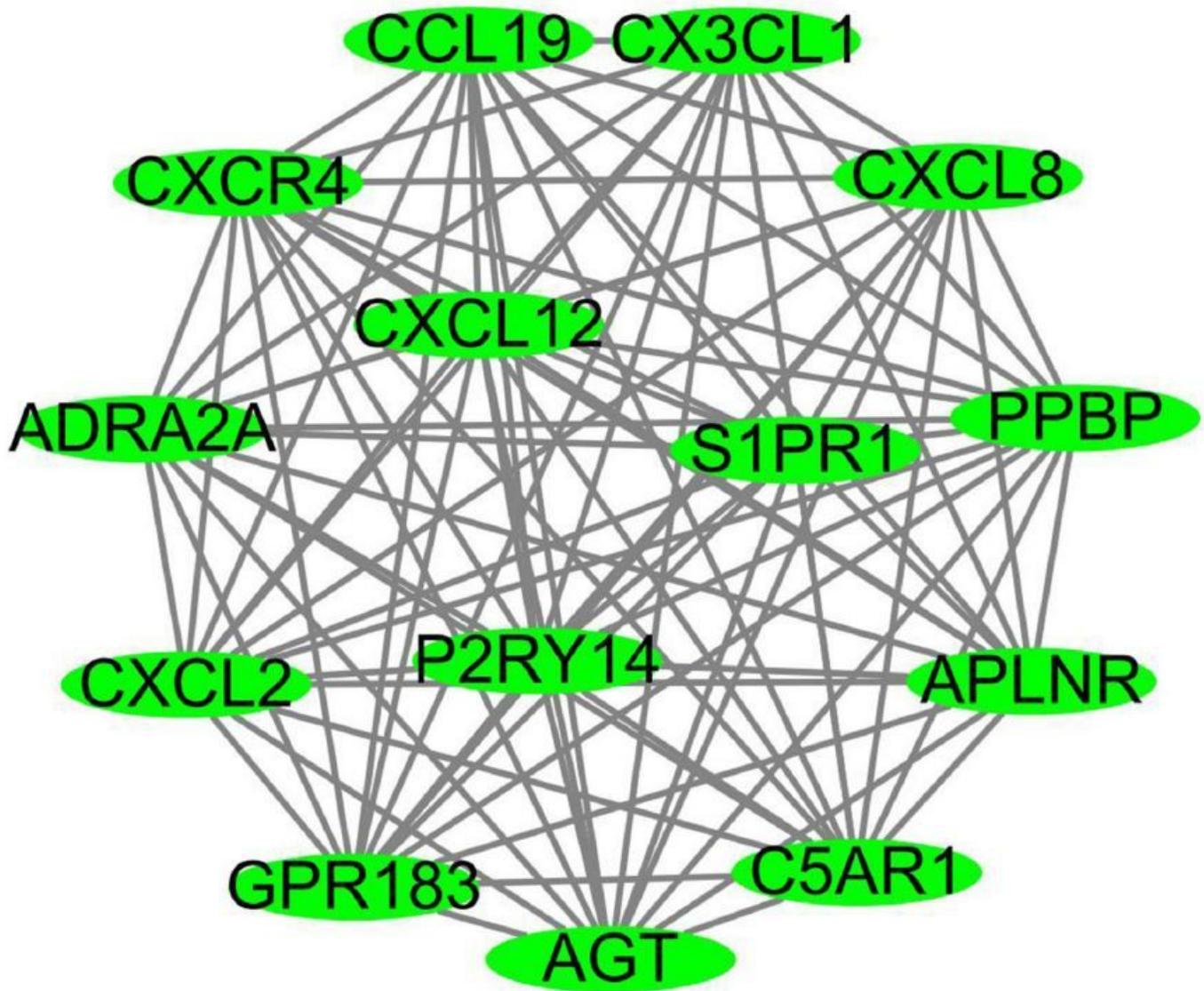


Figure 4

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

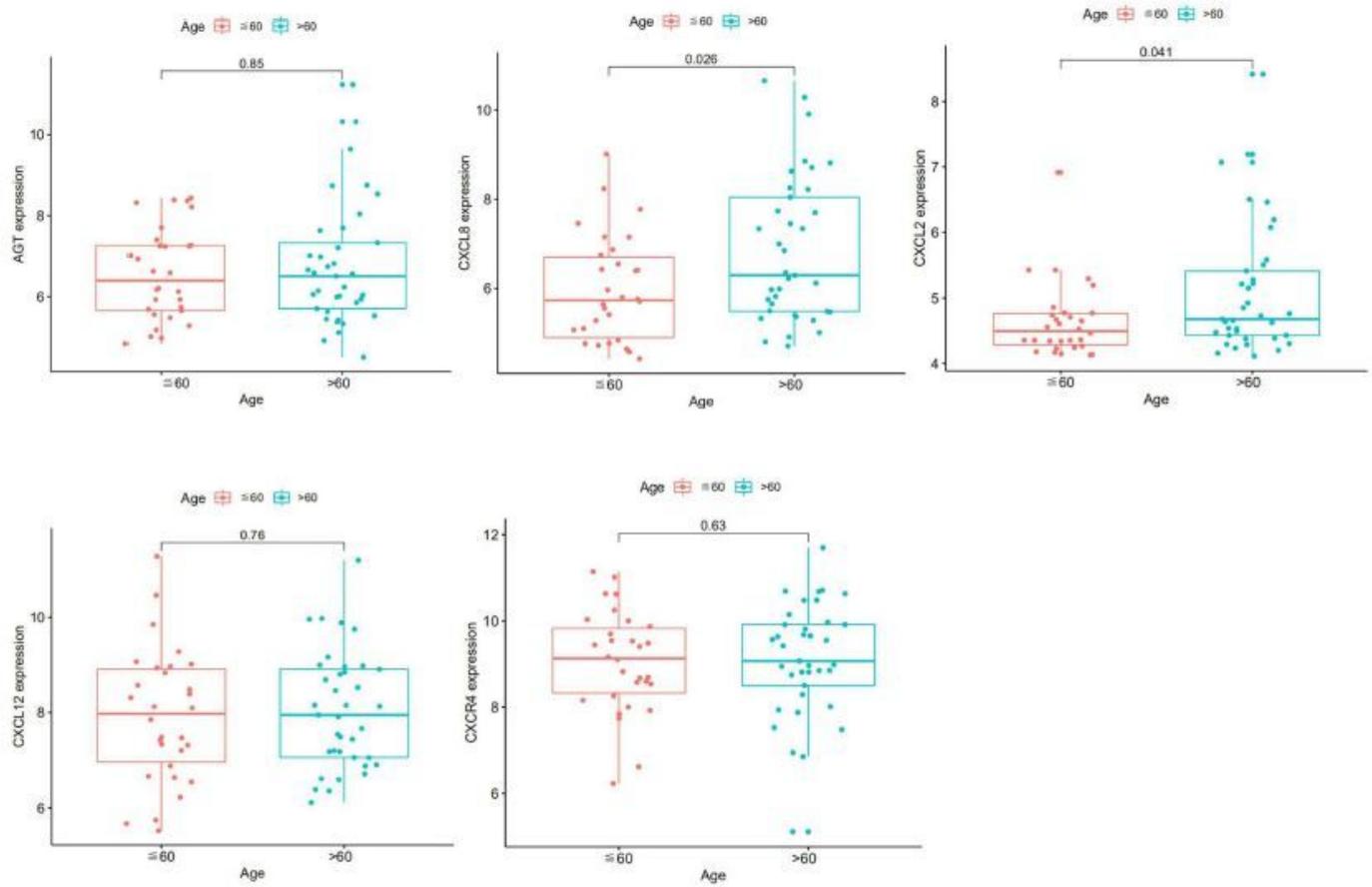


Figure 5

The clinical relationship between expression of hub genes and age

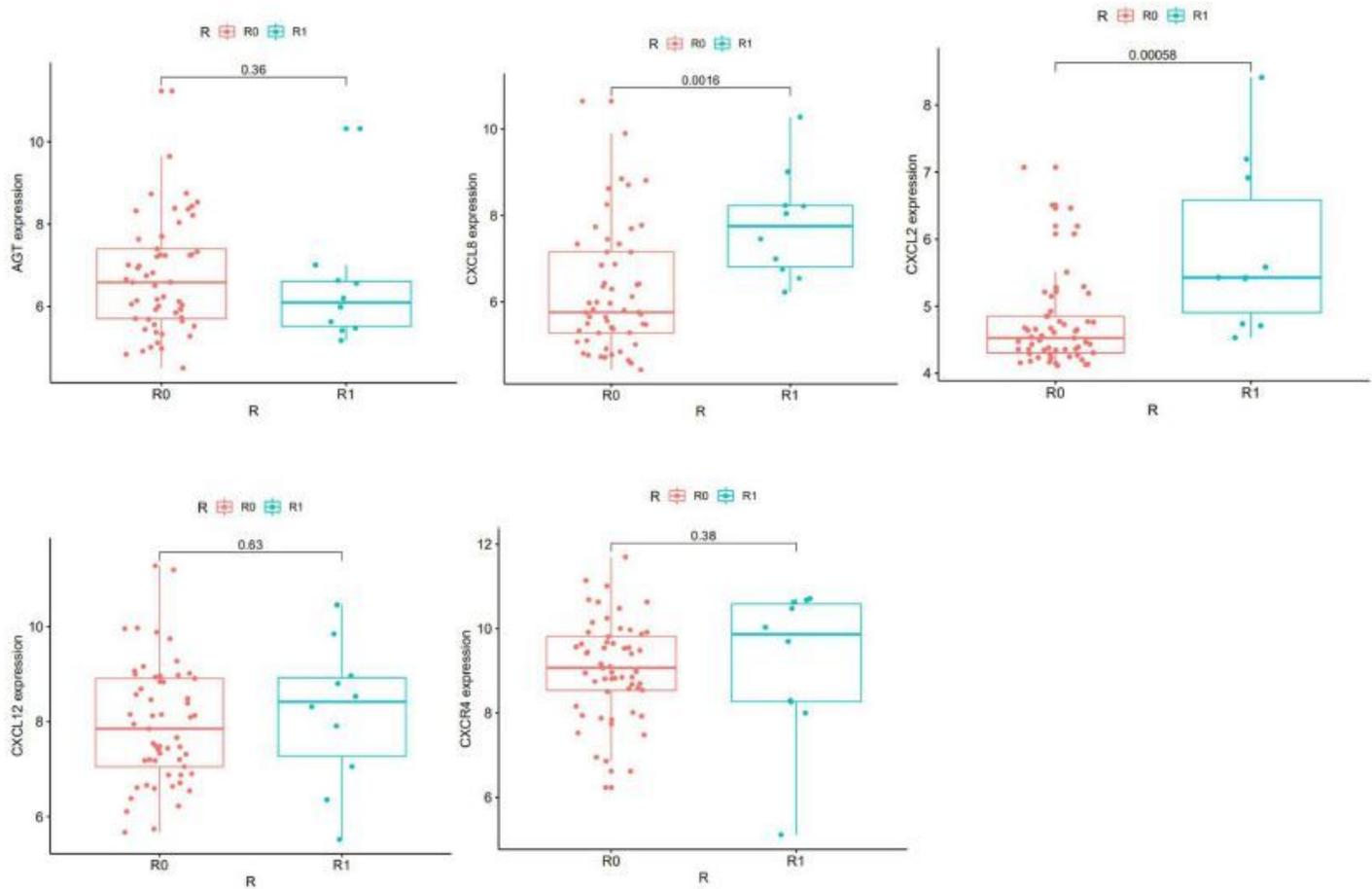


Figure 6

The clinical relationship between expression of hub genes and age. Note:R0 represents no recurrence.R1 represents recurrence.