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Identification of key genes and pathways in meningioma by bioinformatics analysis

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Abstract. Meningioma is the most frequently occurring type of brain tumor. The present study aimed to conduct a comprehensive bioinformatics analysis of key genes and relevant pathways involved in meningioma, and acquire further insight into the underlying molecular mechanisms. Initially, differentially expressed genes (DEGs) in 47 meningioma samples as compared with 4 normal meninges were identified. Subsequently, these DEGs were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. In addition, a protein-protein interaction (PPI) network of the identified DEGs was constructed using the Search Tool for the Retrieval of Interacting Genes and visualized using Cytoscape. In total, 1,683 DEGs were identified, including 66 upregulated and 1,617 downregulated genes. The GO analysis results revealed that the DEGs were significantly associated with the 'protein binding', 'cytoplasm', 'extracellular matrix (ECM) organization' and 'cell adhesion' terms. The KEGG analysis results demonstrated the significant pathways included 'AGE-RAGE signaling pathway in diabetic complications', 'PI3K-Akt signaling pathway', 'ECM-receptor interaction' and 'cell adhesion molecules'. The top five hub genes obtained from the PPI network were JUN, PIK3R1, FOS, AGT and MYC, and the most enriched KEGG pathways associated with the four obtained modules were 'chemokine signaling pathway', 'cytokine-cytokine receptor interaction', 'allograft rejection', and 'complement and coagulation cascades'. In conclusion, bioinformatics analysis identified a number of potential biomarkers and relevant pathways that may represent key mechanisms involved in the development and progression of meningioma. However, these findings require verification in future experimental studies.

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Introduction

Meningiomas are common intracranial tumors that account for ~36% of all primary central nervous system tumors (1). According to the World Health Organization classification (2), meningiomas may be divided into three grades, including benign (Grade I), atypical (Grade II) and anaplastic (Grade III) meningiomas. Although the majority of meningiomas are benign tumors that are curable by surgery, atypical and anaplastic tumors remain therapeutically challenging due to the high risk of tumor relapse (3,4). Furthermore, even after complete resection, relapse occurs in >5% of benign meningiomas (5,6).

The pathogenesis of meningioma is a complex process associated with an accumulation of various genetic and epigenetic alterations that occur during the initiation and progression of the tumor (7). Monosomy 22, 22q deletion and/or mutation of the neurofibromatosis type 2 gene have been identified as important initiating events and represent the most common genetic alterations in meningiomas (8-10). Other common chromosomal alterations include deletions of 1p, 6q, 10q and 14q, and insertions of 1q, 9q, 12q, 15q, 17q and 20q (7,11,12). However, there is insufficient evidence to verify the capability of these chromosomal alterations to predict tumor recurrence and progression.

Several gene expression profiling studies have been conducted on meningiomas, and several candidate genes have been proposed as recurrence-associated predictors or progression-associated biomarkers of meningiomas among the differentially expressed genes (DEGs), including KLF4, GAB2, TRAF7, LMO3, SMO and TSLC1 (13-16). Additionally, the prognostic capabilities of CKS2, PTTG1 and the leptin receptor have also been indicated by mixed transcriptome analyses (17,18). However, research has mainly focused on identifying candidate genes that may be potential novel biomarkers for meningioma, while the possible intrinsic links among DEGs have not been extensively investigated. Studies aimed at identifying the key pathways and characteristics of the biology involved in this tumor remain limited (11,14,17,18).

Traditional biology research can reveal molecular mechanisms based on the variation and function of an individual

gene, mRNA or protein; however, it only describes the biological phenomenon of a disease from a partial viewpoint, rather than describing it in the context of the entire system. Bioinformatics analysis is a powerful tool that provides a novel platform to study the characteristics of biology at a more holistic perspective and elaborate the association of different functional elements (7,15,18).

In the present study, bioinformatics analysis was conducted to determine several potential biomarkers of meningioma (namely JUN, PIK3R1, FOS, AGT and MYC), as well as to identify relevant pathways (including the AGE-RAGE signaling pathway in diabetic complications, PI3K-Akt signaling pathway, ECM-receptor interaction and cell adhesion among others), which are potentially involved in the onset and progression of meningioma. Furthermore, clinical evidence exists to verify the capability of these aforementioned biomarkers and pathways in the prediction of meningioma recurrence and progression. In conclusion, the findings of the present study provide further insight into the pathogenesis of meningiomas and provide potential therapeutic targets for further studies.

Materials and methods

Source of data. Initially, the microarray expression profile of the GSE43290 data set was downloaded from the Gene Expression Omnibus (GEO) database (19). The GSE43290 data set, which includes 47 meningioma samples and 4 normal meningeal samples, was submitted by Tabernero *et al* (20). The platform of these microarray data, GPL96 [HG-U133A] Affymetrix Human Genome U133A Array, was also downloaded from the GEO database. Using the affy package in R software (version 3.25; www.r-project.org) (21), the obtained raw data were preprocessed, which involved background correction, quartile normalization and probe summarization.

Extraction of differentially expressed genes (DEGs). A Student's t-test in the Limma package in R software (22) was performed to identify the DEGs between the meningioma and normal meningeal (control) samples. All genes that met the following criteria were selected as DEGs: P-value of <0.05 and $|\log_2(\text{fold change})|$ of >1. A heat map of the extracted DEGs was then created through the gplots package in R, in order to visualize the expression values of genes in the different samples.

Functional enrichment analysis of DEGs. Following extraction of the DEGs, Gene Ontology (GO) and Kyoto Encyclopedia Genes and Genomes (KEGG) pathway enrichment analyses were conducted. GO analysis is a common bioinformatics method for identifying characteristic biological attributes in large-scale genomic and transcriptomic data (23). KEGG is a database for the systematic analysis of genetic functions that links genomic information with higher order functional information (24). In the present study, the GO analysis was conducted via the Database for Annotation, Visualization and Integrated Discovery (DAVID; https://david.ncifcrf.gov), a web-based tool for systematic functional analysis (25). The GO categories selected included 'biological process', 'molecular function' and 'cellular component'. The KEGG pathway analysis of the DEGs was conducted through the ClusterProfiler package in R software. A P-value of <0.05 was selected as the cut-off criterion.

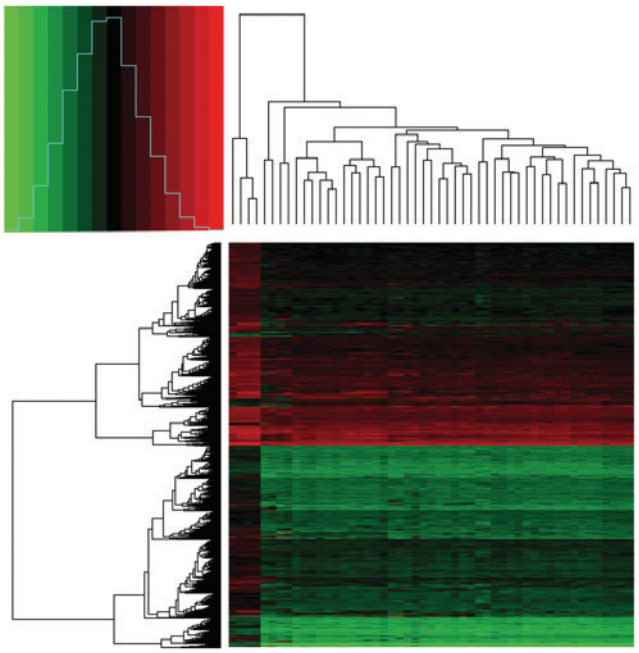

Figure 1. Heat map of differentially expressed genes associated with meningioma. The data are presented in a matrix format, in which rows represent individual genes and columns represent each sample. The red and green colors indicate upregulated and downregulated genes, respectively.

Integration of protein-protein interaction (PPI) network and module analysis. PPI network analysis is a method for identifying the associations among various proteins. To acquire further insights into the molecular mechanisms of meningioma, the list of DEGs was entered into the Search Tool for the Retrieval of Interacting Genes (STRING) database, which is an online database designed to evaluate PPI information (26). Using this tool, gene-gene interactions with a combined score of >0.9 were selected to construct the PPI network. Cytoscape software (version 3.4.0) was then used to visualize the obtained PPI network (27).

All genes with a connectivity degree (defined as the number of other genes that directly interact with that particular gene) of >20 were selected as hub genes in the network. The core genes were the most likely to be involved in meningioma and to be potential biomarkers of tumor development and progression. In addition, significant modules of the PPI network were identified using the Molecular Complex Detection (MCODE) Cytoscape plug-in. An MCODE score (indicating the density of nodes) of >10 and node number of >10 were selected as the significance threshold criteria. Next, KEGG pathway enrichment analysis of the DEGs in these modules was performed using DAVID aiming to evaluate the genetic functions at the molecular level. A P-value of P<0.05 was selected as the cut-off criterion for identifying the significant pathways associated with these modules.

Results

DEGs in meningioma vs. normal meningeal tissues. According to the t-test analysis of the DEGs in the 47 tumor samples

Table I. GO analysis of differentially expressed genes associated with meningioma.

Category	Term	Count	P-value
GOTERM_MF_DIRECT	Protein binding	931	$5.26x10^{-15}$
GOTERM_CC_DIRECT	Cytoplasm	587	$1.36x10^{-13}$
GOTERM_BP_DIRECT	Extracellular matrix organization	53	$1.22x10^{-12}$
GOTERM_CC_DIRECT	Cytosol	397	$2.33x10^{-12}$
GOTERM_BP_DIRECT	Cell adhesion	91	$2.85x10^{-12}$
GOTERM_CC_DIRECT	Extracellular exosome	344	$8.41x10^{-12}$
GOTERM_CC_DIRECT	Extracellular matrix	61	$5.24x10^{-10}$
GOTERM_CC_DIRECT	Focal adhesion	73	$9.24x10^{-10}$
GOTERM_CC_DIRECT	Z disc	34	$1.06x10^{-9}$
GOTERM_BP_DIRECT	Angiogenesis	51	$2.10x10^{-9}$
GOTERM_CC_DIRECT	Extracellular space	181	$2.87x10^{-9}$
GOTERM_BP_DIRECT	Signal transduction	166	$5.42x10^{-9}$
GOTERM_BP_DIRECT	Positive regulation of transcription from RNA polymerase II promoter	140	$1.15x10^{-7}$
GOTERM_CC_DIRECT	Extracellular region	201	$1.16x10^{-7}$
GOTERM_MF_DIRECT	Transcription factor binding	54	$2.02x10^{-7}$
GOTERM_CC_DIRECT	Stress fiber	19	$3.71x10^{-7}$
GOTERM_BP_DIRECT	Positive regulation of angiogenesis	30	$3.72x10^{-7}$
GOTERM_MF_DIRECT	Identical protein binding	109	$3.97x10^{-7}$
GOTERM_CC_DIRECT	Integral component of plasma membrane	178	$4.34x10^{-7}$
GOTERM_CC_DIRECT	Cell surface	83	$6.11x10^{-7}$
GOTERM_BP_DIRECT	Type I interferon signaling pathway	21	$6.20x10^{-7}$
GOTERM_BP_DIRECT	Negative regulation of cell proliferation	68	$6.72x10^{-7}$
GOTERM_BP_DIRECT	Immune response	71	$7.37x10^{-7}$
GOTERM_BP_DIRECT	Response to hypoxia	38	$7.54x10^{-7}$
GOTERM_CC_DIRECT	Myelin sheath	34	$7.94x10^{-7}$
GOTERM_CC_DIRECT	Membrane raft	41	$1.24x10^{-6}$
GOTERM_CC_DIRECT	Neuron projection	45	$1.34x10^{-6}$
GOTERM_CC_DIRECT	Actin filament	20	$1.73x10^{-6}$
GOTERM_BP_DIRECT	Positive regulation of apoptotic process	54	$2.63x10^{-6}$
GOTERM_CC_DIRECT	Proteinaceous extracellular matrix	48	$3.10x10^{-6}$

GO, Gene ontology; MF, molecular function; CC, cellular component; BP, biological process.

compared with the 4 normal meningeal samples, a total of 1,683 DEGs were identified, including 66 upregulated and 1,617 downregulated genes. The heat map of DEG expression is shown in Fig. 1.

Enriched GO terms and KEGG pathways of the identified DEGs. In the present study, a total of 649 enriched GO terms and 34 KEGG pathways were identified. The top 30 enriched GO terms of the DEGs according to the P-value threshold ($P<0.05$) are shown in Table I. The downregulated genes were significantly associated with 'protein binding', 'cytoplasm', 'extracellular matrix (ECM) organization' and 'cell adhesion', whereas there were no GO terms that were significantly enriched among the upregulated DEGs. The enriched KEGG pathways of the DEGs are shown in Table II. A number of the enriched KEGG pathways were directly associated with cancer, including the 'pathways in cancer' and 'small cell lung cancer' pathways. Furthermore, there was enrichment of certain other pathways that are potentially involved in the development and progression of meningiomas via various biological processes, including the 'AGE-RAGE signaling pathway in diabetic complications', 'PI3K-Akt signaling pathway', 'ECM-receptor interaction' and 'cell adhesion molecules'.

Module screening from the PPI network. Based on the STRING data, a PPI network of 807 nodes and 2,598 edges was obtained. Nodes with a connectivity degree of >20 were determined as hub genes (Table III). Among them, the top five genes according to their connectivity degree were JUN, PIKR1, FOS, AGT and MYC. In addition, according to the connectivity degree of nodes in modules. The top 4 modules with MCODE score of >10 and node number of >10 were obtained (Fig. 2). Functional annotation results revealed that the genes in modules 1, 2 and 4 were mainly associated with the 'chemokine signaling pathway', 'cytokine-cytokine receptor interaction', 'allograft rejection', and 'complement and coagulation cascades', while there were no enriched pathways associated with the DEGs in module 3 (Table IV).

Table II. Enriched Kyoto Encyclopedia of Genes and Genomes pathways of differentially expressed genes associated with meningioma.

Pathway ID	Description	Gene count	P-value
hsa04933	AGE-RAGE signaling pathway in diabetic complications	32	7.86×10^{-9}
hsa04151	PI3K-Akt signaling pathway	70	3.98×10^{-8}
hsa04668	TNF signaling pathway	32	7.73×10^{-8}
hsa04512	ECM-receptor interaction	26	1.98×10^{-7}
hsa04510	Focal adhesion	46	3.84×10^{-7}
hsa05410	Hypertrophic cardiomyopathy	23	1.28×10^{-5}
hsa04066	HIF-1 signaling pathway	26	2.21×10^{-5}
hsa04210	Apoptosis	32	2.36×10^{-5}
hsa05146	Amoebiasis	25	2.62×10^{-5}
hsa05414	Dilated cardiomyopathy	23	5.30×10^{-5}
hsa05200	Pathways in cancer	67	9.01×10^{-5}
hsa05144	Malaria	15	1.21×10^{-4}
hsa05222	Small cell lung cancer	21	2.22×10^{-4}
hsa05134	Legionellosis	15	4.93×10^{-4}
hsa05031	Amphetamine addiction	17	6.46×10^{-4}
hsa04657	IL-17 signaling pathway	21	6.90×10^{-4}
hsa05161	Hepatitis B	29	7.24×10^{-4}
hsa04978	Mineral absorption	14	8.68×10^{-4}
hsa04068	FoxO signaling pathway	27	8.68×10^{-4}
hsa04010	MAPK signaling pathway	44	9.13×10^{-4}
hsa04064	NF-κB signaling pathway	21	9.27×10^{-4}
hsa04060	Cytokine-cytokine receptor interaction	46	9.30×10^{-4}
hsa05416	Viral myocarditis	15	1.10×10^{-3}
hsa05412	Arrhythmogenic right ventricular cardiomyopathy	17	1.29×10^{-3}
hsa05202	Transcriptional misregulation in cancer	33	1.39×10^{-3}
hsa04514	Cell adhesion molecules	28	1.40×10^{-3}
hsa05166	HTLV-I infection	43	2.10×10^{-3}
hsa04261	Adrenergic signaling in cardiomyocytes	28	2.14×10^{-3}
hsa04022	cGMP-PKG signaling pathway	30	3.39×10^{-3}
hsa04145	Phagosome	28	3.51×10^{-3}
hsa04610	Complement and coagulation cascades	17	3.71×10^{-3}
hsa04621	NOD-like receptor signaling pathway	30	4.06×10^{-3}
hsa05162	Measles	25	4.86×10^{-3}
hsa04921	Oxytocin signaling pathway	28	5.09×10^{-3}

Discussion

Although previous studies have proposed numerous potential biomarkers associated with the progression and recurrence of meningiomas, the knowledge regarding the molecular mechanisms of meningioma remains relatively limited (13,16-18). In the present study, a comprehensive analysis of the gene expression profiles of meningiomas and normal meninges was conducted using a combined bioinformatics approach. A total of 1,683 DEGs (66 upregulated and 1,617 downregulated) were identified. Functional enrichment analysis revealed that these DEGs were mainly involved in ECM organization, cell adhesion, angiogenesis and signal transduction. By constructing a PPI network, a number of hub genes were identified as potential prognostic biomarkers for meningioma.

The gene expression data of 47 meningioma samples and 4 normal controls included in the present study were downloaded from the GEO database with the accession number GSE43290. The 47 tumor samples were composed of 18 diploid tumors, 12 tumors with monosomy 22/del (22q) alone, 4 tumors with del (1p36) alone, and 13 with complex karyotypes associated with del (1p36) and/or del (14q), which are the most frequently altered cytogenetic subgroups of meningiomas in clinical practice (5,12).

The approach used in the current study identified 1,683 DEGs, including 1,617 downregulated and 66 upregulated genes, in meningioma samples as compared with those in normal meninges. These results indicated that gene expression in meningiomas was generally downregulated, which may be attributed to the loss of chromosomal material in meningioma.

Table III. Hub genes and their corresponding degree.

Gene symbol	Degree
JUN	79
PIK3R1	56
FOS	53
AGT	53
MYC	50
STAT3	47
LPAR1	47
IL8	44
HSP90AA1	41
CXCL12	41
NFKB1	41
RPS27A	40
GNAI1	39
PPBP	37
CXCR4	35
HIF1A	33
NPY	32
S1PR1	32
CCL5	31
SST	30
IL6	30
EDN1	30
EGR1	28
STAT1	28
IRF1	28
CCR7	28
CXCL2	28
SSTR2	27
CCL19	27
RGS1	27
RGS4	27
CXCL9	27
CXCL1	27
ADRA2A	27
HTR1B	27
HTR1D	27
CXCL3	27
C5AR1	27
MTNR1B	27
APLNR	27
P2RY14	27
HCAR3	27
ICAM1	25
CDKN1A	24
CCND1	23
PTEN	23
NOS3	23
ACTN1	23
IRF7	23
KALRN	23
IRF9	22
HLA-A	22
YWHAE	22
SIRT1	21
CDH1	21
GNAQ	21
ISG15	20

In addition, GO analysis revealed that the enriched ontological categories among the DEGs mainly included ECM organization, cell adhesion, angiogenesis, signal transduction and negative regulation of cell proliferation. Previous studies have revealed that matrix metalloproteinases (MMPs), which are mediators of invasion and angiogenesis, may serve important roles in the invasion and recurrence of meningioma (28,29). Indeed, cumulative evidence has demonstrated that the contribution of MMPs to tumor progression may be associated with the regulation of cell adhesion, the control of apoptosis via the release of factors associated with cell death or survival, and the proteolysis of the ECM (28,30,31). Previous studies have demonstrated that the aforementioned GO terms are potentially important events in meningioma development and tumor progression. Furthermore, the KEGG pathway analysis results in the present study revealed that 'ECM-receptor interaction', 'apoptosis' and 'cell adhesion molecules' were among the significantly enriched pathways associated with the DEGs. These findings were consistent with those of a study by Keller *et al* (32), which also suggested that 'ECM-receptor interaction' and 'cell adhesion molecules' were significantly dysregulated pathways in meningioma. Therefore, monitoring these biological processes and pathways may aid in the prediction of meningioma development and progression. Furthermore, 31 other enriched pathways were identified in the current study, including 'AGE-RAGE signaling pathway in diabetic complications', 'PI3K-Akt signaling pathway', 'TNF signaling pathway' and 'focal adhesion'. The PI3K-Akt signaling pathway is an intracellular signaling pathway that is important in regulating the cell cycle progression, cell death and cell growth (33). Alterations in this pathway are frequently identified as being involved in the development of various types of cancer (34,35).

The top five hub genes identified from a PPI network constructed from the DEGs in the present study were JUN, PIK3R1, FOS, AGT and MYC. Among these hub genes, JUN, a protein-coding gene, exhibited the highest degree of connectivity. JUN is an important component of activator protein 1 (AP-1), a transcription factor that recognizes the specific DNA sequence TGAC/GTCA. This gene modulates numerous biological functions involved in the regulation of cell proliferation, apoptosis and transformation (36). The aberrant expression of JUN has been reported in various types of cancer, including glioblastoma and hepatocellular carcinoma (37,38). Furthermore, FOS is a member of the Fos family that encodes leucine zipper proteins that form heterodimers with the JUN family, resulting in the formation of AP-1 (39). Thus, this gene also serves important roles in cell proliferation, differentiation and transformation (40). Significant associations between

Table IV. Enriched Kyoto Encyclopedia of Genes and Genomes pathways of four modules.

Pathway term	P-value	Nodes
Module 1		
Chemokine signaling pathway	$1.14x10^{-10}$	CXCL1, CCR7, PPBP, IL8, GNAI1, CXCR4, CXCL3, CXCL2, CXCL9, CCL19, CCL5, CXCL12
Cytokine-cytokine receptor interaction	$7.02x10^{-8}$	CXCL1, CCR7, PPBP, IL8, CXCR4, CXCL3, CXCL2, CXCL9, CCL19, CCL5, CXCL12
Neuroactive ligand-receptor interaction	$7.93x10^{-7}$	APLNR, HTR1B, SSTR2, C5AR1, S1PR1, P2RY14, ADRA2A, MTNR1B, LPAR1, HTR1D
Module 2		
Allograft rejection	0.0418	HLA-A, HLA-C
Graft-versus-host disease	0.0452	HLA-A, HLA-C
Type I diabetes mellitus	0.0486	HLA-A, HLA-C
Module 3		
No record	-	-
Module 4		
Complement and coagulation cascades	0.0012	VWF, A2M, F13A1, SERPINE1
Calcium signaling pathway	0.0018	AGTR1, EDNRB, GNAQ, PTGFR, HTR2A
Renal cell carcinoma	0.0198	VEGFC, TGFB3, PIK3R1

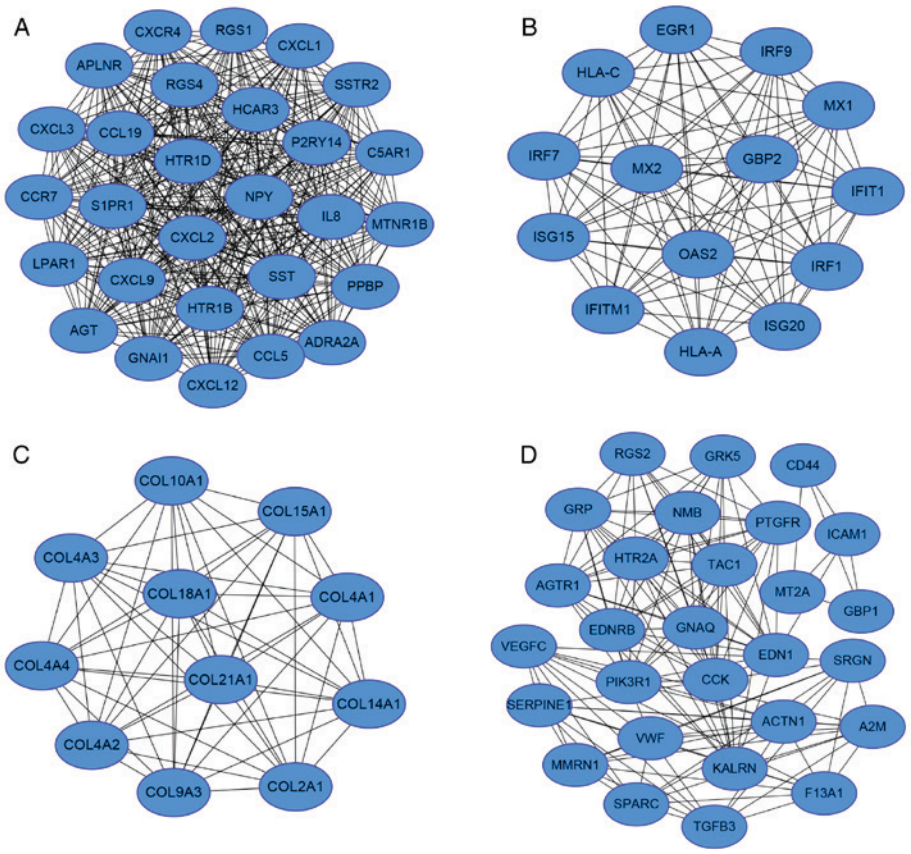

Figure 2. Top 4 modules with the higher connectivity degrees identified in the protein-protein interaction network analysis. (A) Module 1, (B) module 2, (C) module 3 and (D) module 4 are shown.

FOS and various tumors have also been identified in previous studies (41,42).

PIK3R1, another hub gene identified in the present study, is a critical mediator of insulin sensitivity, and mutation of this gene is associated with insulin resistance, which is an important mechanism involved in human obesity (43,44). McCurdy *et al* (45) reported that, in diet-induced obese mice, attenuated PIK3R1 expression was able to prevent insulin resistance. Recently,

a large case-control study further suggested that obesity was positively associated with a risk of meningioma (46).

The AGT gene, also identified in the current study, is a member of the renin-angiotensin system-associated gene family, which is physiologically important for blood pressure regulation and may be involved in the pathogenesis of hypertension (47). Accumulating evidence has demonstrated that increased blood pressure is an independent and additive risk factor for the development of brain tumors, particularly meningiomas (46).

Another hub gene, MYC, is located on chromosome 8 and has been closely correlated with cell growth, apoptosis and cellular transformation (48). Mutation, overexpression, rearrangement and translocation of this gene have been detected in a variety of tumors, including Burkitt's lymphoma, medulloblastoma and hepatocellular carcinoma among others (49-51).

In the present study, module analysis of the PPI network revealed that the development of meningioma was possibly associated with the chemokine signaling pathway, cytokine-cytokine receptor interaction, allograft rejection, and complement and coagulation cascades. This is consistent with the observations of the study by Keller *et al* (32), which analyzed the expression profiles of 24 meningiomas and identified 'cytokine-cytokine receptor interaction' and 'complement pathway and coagulation cascades' as two of the main pathways enriched among the downregulated genes.

In conclusion, by applying a comprehensive bioinformatics analysis of DEGs, the present study identified several hub genes, including JUN, PIK3R1, FOS, AGT and MYC, that may be functionally relevant to the pathogenesis of meningioma. The functional analysis results also revealed a number of potentially significant pathways that may participate in meningioma development and progression, including 'AGE-RAGE signaling pathway in diabetic complications', 'PI3K-Akt signaling pathway', 'ECM-receptor interaction' and 'cell adhesion molecules'. These results provided further insight into the underlying molecular mechanisms of meningioma. Further experimental studies are required to confirm these observations and to determine their potential as molecular targets in the development of novel therapeutic approaches for meningioma.

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Availability of data and materials

The datasets analyzed during the current study (GSE43290) were downloaded from a public dataset webset from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE43290).

Authors' contributions

JD analyzed and interpreted the microarray data regarding meningomas. YM and SC renalyzed the data and confirmed the results' authenticity. NL and JC designed this bioinformatic study and wrote the manuscript. YW was responsible for making tables, drawing the fgures, and helped JD to interprete the findings from the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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