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RESEARCH

# Revealing the Potential Pathogenesis of Glioma by Utilizing a Glioma Associated Protein-Protein Interaction Network

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**Abstract** This study aims to explore the potential mechanism of glioma through bioinformatic approaches. The gene expression profile (GSE4290) of glioma tumor and non-tumor samples was downloaded from Gene Expression Omnibus database. A total of 180 samples were available, including 23 non-tumor and 157 tumor samples. Then the raw data were preprocessed using robust multiarray analysis, and 8,890 differentially expressed genes (DEGs) were identified by using t-test (false discovery rate<0.0005). Furthermore, 16 known glioma related genes were abstracted from Genetic Association Database. After mapping 8,890 DEGs and 16 known glioma related genes to Human Protein Reference Database, a glioma associated protein-protein interaction network (GAPN) was constructed. In addition, 51 sub-networks in GAPN were screened out through Molecular Complex Detection (score≥1), and sub-network 1 was found to have the closest interaction (score=3). What' more, for the top 10 sub-networks, Gene Ontology (GO) enrichment analysis ($p$ value<0.05) was performed, and DEGs involved in sub-network 1 and 2, such as *BRMS1L* and *CCNA1*, were predicted to regulate cell growth, cell cycle, and DNA replication via interacting with known glioma related genes. Finally, the overlaps of DEGs and human essential, housekeeping, tissue-specific genes were calculated ($p$ value=1.0, 1.0, and 0.00014, respectively) and visualized by Venn Diagram package in R. About 61 % of human tissue-specific genes were DEGs as well. This research shed new light on the pathogenesis of glioma based on DEGs and GAPN, and our findings might provide potential targets for clinical glioma treatment.

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**Keywords** Glioma · Differentially expressed genes · Glioma associated protein-protein interaction network · Functional enrichment analysis

**Abbreviations**

| | |
|---|---|
| DEGs | Differentially expressed genes |
| GAPN | Glioma associated protein-protein interaction network |
| GO | Gene Ontology |
| NCBI | National Center for Biotechnology Information |
| GEO | Gene Expression Omnibus |
| RMA | Robust multiarray analysis |
| Gene ID | Gene identifier |
| FDR | False discovery rate |
| GAD | Genetic Association Database |
| HPRD | Human Protein Reference Database |
| PPIs | Protein-protein interactions |
| MCODE | Molecular Complex Detection |
| BINGO | Biological Networks Gene Ontology tool |
| BRMS1L | Breast cancer metastasis suppressor 1-like proteins |
| BRMS1 | Breast cancer metastasis suppressor 1 |
| CCNA1 | Cyclin A1 |
| MCM4 | Minichromosome maintenance complex component 4 |
| MCM6 | Minichromosome maintenance complex component 6 |

## Introduction

Also known as glioblastoma, glioma is the most common and malignant primary central nervous system tumor around the whole world [1]. Glioma includes astrocytomas, oligodendrogliomas, oligoastrocytomas, and ependymomas.

The main clinical manifestations of glioma are headache, vomiting, pain, weakness, seizures, visual loss, and the symptom of nerve circumscribed damages, because the intracranial pressure of glioma patients are at a significantly high level [2]. Despite aggressive treatment with surgery, irradiation, and chemotherapy have been developed, the average survival time of glioma patients remains within one and half years [3]. Thus, there is still an urgent need to explore the molecular mechanism of glioma.

During the past decades, many researchers have tried to explore the pathogenesis of glioma. Due to the advances in molecular methodologies and cytogenetic, certain molecular mechanism of glioma have been elucidated [4]. *INK4aARF* mutation, *EGFR* amplification or mutation, *CCND1/3* amplification or overexpression, *MDM2/4* amplification or overexpression, *PTEN* mutation, *BcI2L* overexpression, *P53* mutation, *PDGFR* overexpression, *CDK4/6* amplification or overexpression, *RB* mutation, 19q loss, 11p loss, and 10q loss, are involved in different glioma grades [5]. Moreover, pathways or bio-functions involved in glioma are: (1) cell cycle, including RB pathway, p53 pathway, MAPK pathway, and mitogenic signaling pathways [6, 7]; (2) apoptosis; (3) growth factor activation; (4) cell motility and invasion pathways [8]. Based on the illustrated mechanism of glioma, inhibitors like Erlotinib, Imatinib, Sorafenib, Bevacizumab, Perifosine, and Suberoylanilide hydroxamic acid have been applied to glioma treatment, targeting *EGFR*, *PDGFR*, *VEGFR* , *VEGF*, *Akt*, and *HDAC*, respectively [5]. However, the mortality rate of glioma is still at a high level, indicating that the mechanism of glioma needs more investigation.

In this study, bioinformatic methods were used to identify the differentially expressed genes (DEGs) between non-tumor and tumor samples. Then, a glioma associated protein-protein interaction network (GAPN) was constructed to reveal the potential mechanism of glioma. Meanwhile, the topological properties of nodes in GAPN were calculated, followed by sub-networks identification in GAPN. Furthermore, Gene Ontology (GO) enrichment analysis was performed to explore the bio-functions of genes in sub-networks. Finally, the overlaps between DEGs and human essential, housekeeping, tissue-specific genes were analyzed. Our findings in the present study might help researchers to understand the pathogenesis of glioma better, and provide new targets for glioma therapies.

## Materials and Methods

### Gene Expression Profile

The gene expression profile (GSE4290) [9] was downloaded from the NCBI (National Center for Biotechnology Information) GEO (Gene Expression Omnibus, http://www.ncbi.nlm.nih.gov/geo/) [10] database. A total of 180 chips were available, including 23 of epilepsy patients (non-tumor samples) and 157 of tumor samples. In addition, tumor samples consist of 26 samples from astrocytomas patients, 50 from oligodendrogliomas patients, and 81 from glioblastomas patients. The corresponding platform was Affymetrix GPL570 platform data (Affymetrix Human Genome U133 Plus 2.0 Array) [11].

### Data Preprocessing

The downloaded raw data were preprocessed using robust multiarray analysis (RMA) [12] in Affy package [13]. The Affy package provides an extensible and interactive environment for the analysis of Affymetrix oligonucleotide array data, and contains flexible functions which permit the conversion from probe level data to expression values [13]. For Affymetrix gene expression microarrays, RMA is the most widely used preprocessing algorithm, which has the advantage of analyzing multiple arrays simultaneously [12]. In preprocessing, convolution background was corrected, missing values were estimated, expression values were log2 transformed and then normalized. Furthermore, the probe sets that had no Gene identifier (Gene ID) were removed, and the expression values of probes mapped to same Gene ID were averaged.

### DEGs Screening

The classical t-test [14], which has been widely used to determine whether two datasets are significantly different from each other, was applied to screening genes that were differentially expressed between the 23 non-tumor and 157 tumor samples. Then the raw p values of t-test were adjusted by Benjamini-Hochberg algorithm [15]. Only the genes with adjusted p value, namely, false discovery rate (FDR)$<0.0005$ were screened out, and defined as DEGs. FDR$<0.0005$ implies that only less than 0.05 % of significant DEGs are false positive [15], indicating that the results of our DEGs screening are reliable.

### GAPN Construction and Topological Analysis

The known glioma related genes were extracted from the GAD (Genetic Association Database, http://geneticassociationdb.nih.gov/) [16]. The Human Protein Reference Database (HPRD) [17] is an online protein database, including 95,148 genes and 37,041 protein-protein interactions (PPIs). In this study, the known glioma related genes abstracted from GAD and the screened DEGs were mapped to HPRD simultaneously. Then, GAPN was constructed and visualized by Cytoscape [18], which is one of the most widely used software for analysis and visualization

of biological networks. Furthermore, the topological properties of GAPN were investigated, including degree, betweenness centrality, closeness centrality, and clustering coefficient [19]. The degree represents the number of nodes related to a certain node, the betweenness centrality stands for the control capacity of a certain node on other nodes, the closeness centrality is the sum-distance between a certain node with all the other nodes, and the clustering coefficient represents the interconnectivity among the neighbors of a certain node [19, 20].

### Sub-Network Exploring and Enrichment Analysis

To explore the densely connected genes in GAPN, namely sub-networks, Molecular Complex Detection (MCODE) was used, which is a graph theoretic clustering algorithm [21]. The MCODE score which reflects the density of genes in a potential sub-network was calculated, and the sub-networks with MCODE score≥1 were screened out. Additionally, the top 2 sub-networks were visualized by Cytoscape. Furthermore, for the genes in top 10 sub-networks, GO enrichment analysis [22] was performed through BINGO (Biological Networks Gene Ontology tool) [23], a Cytoscape plugin used to assess the ontology categories of genes in biological networks. Then, the bio-functional regions with $p$ value<0.05 were identified.

### The Overlaps Between DEGs and Human Essential, Housekeeping, and Tissue-Specific Genes

Human genes were abstracted from Li's report [24], including 2,486 essential genes, 1,467 housekeeping genes and 907 tissue-specific genes. The overlaps between the DEGs in GAPN and human essential, housekeeping, tissue-specific genes were calculated ($p$ value=1.0, 1.0, and 0.00014, respectively) and visualized by Venn Diagram package in R [25]. Venn Diagram package has been widely used to visualize orthogonal or overlapping datasets, and generate Venn and Euler diagrams with high graphical accuracy and visual appeal [25].

## Results

### Data Preprocessing and DEGs Screening

To identify DEGs between non-tumor and tumor samples, we downloaded publicly available gene expression dataset (GSE4290) from GEO database. After data preprocess through RMA in the Affy package, a gene expression profile matrix (21,186×180) was obtained, in which rows represented genes, and columns stood for samples. Then, through classical t-test, a total of 8,890 genes were identified as DEGs (FDR<0.0005), including 4,150 up-regulated and 4,740 down-regulated genes.

### GAPN Construction and Topological Analysis

Totally, 16 known glioma related genes, among which 13 genes were DEGs as well, were extracted from GAD database. By mapping the 16 known genes and the 8,890 DEGs to HPRD simultaneously, GAPN was constructed, and then visualized by Cytoscape software (Fig. 1).

To investigate the differences between DEGs and the other genes in GAPN, we calculated the topological properties of all genes in GAPN. As shown in Fig. 2, the degree, betweenness centrality, and closeness centrality of DEGs - were significantly higher than the other genes in GAPN. Furthermore, the relationship between degrees and clustering coefficients is shown in Fig. 3. The results revealed that the GAPN is a scale—free network with the classical power-law distribution of node degrees, indicating that there exist sub-networks in GAPN.

### Sub-Networks Exploring and Visualization

Through MCODE, a total of 51 sub-networks (score≥1) were screened out from GAPN, and the top 10 sub-networks are listed in Table 1. It's demonstrated that the genes in sub-network 1 (score=3), including 1 DEG (*BRMS1L*) and 6 known glioma genes (*HDAC1*, *ING1*, *RBBP7*, *RBBP4*, *BRMS1*, and *SAP30*), had the closest relationship with each

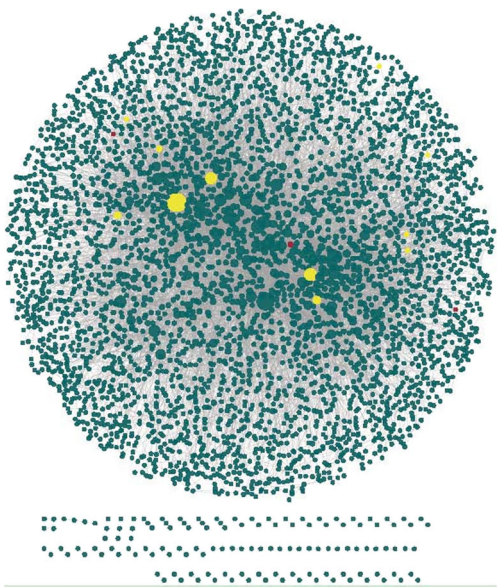

**Fig. 1** Glioma associated protein-protein interaction network (GAPN). The *blue-green nodes* represent differentially expressed genes (DEGs), *red nodes* are the known glioma related genes, and *yellow nodes* are the genes which belong to both known glioma related genes and the DEGs. The size of the nodes stands for degree

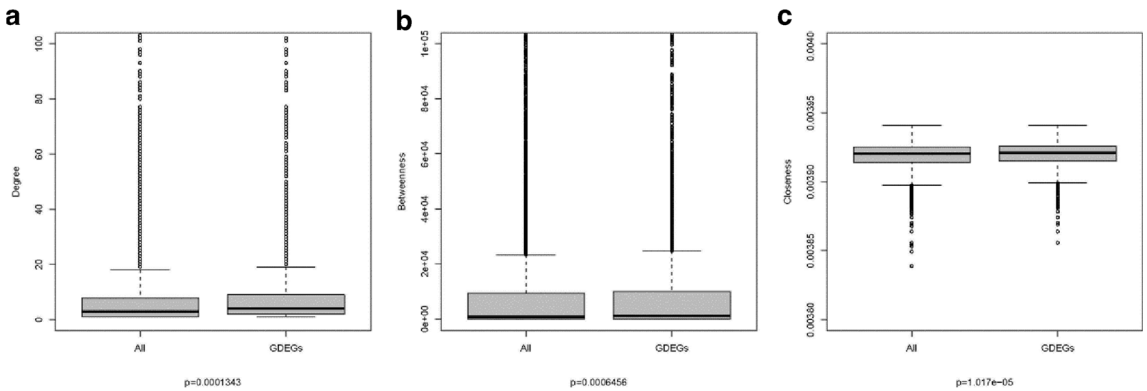


**Fig. 2** Comparison of connectivity, betweenness centrality, and closeness centrality between DEGs and the other genes in GAPN. DEGs: differentially expressed genes; GAPN: Glioma associated protein-protein interaction network

other. Another gene cluster with high density was sub-network 2 (score=2.222) with 9 genes, including 1 DEG (*CCNA1*), 1 special gene (*RB1*), and 7 known genes (*CDK6*, *MCM2*, *MCM3*, *MCM6*, *ORC61*, *MCM7*, and *MCM4*). Then the top 2 sub-networks were visualized by Cytoscape software (Fig. 4).

## GO Enrichment Analysis of the top 10 sub-Networks

For the top 10 sub-networks, GO enrichment analysis was conducted, and the top 3 GO terms ($p$ value<0.05) for each sub-network are listed in Table 2. It's indicated that most genes in sub-network 1, like *BRMS1L* and *RBBP4*, were significantly enriched in negative regulation of cell cycle ($p$ value=2.12E-03), regulation of cell growth ($p$ value=2.38E-03), and DNA replication ($p$ value=3.71E-03). Additionally, in sub-network 2, *RB1* participated in myeloid cell differentiation ($p$ value=2.37E-04), and *CCNA1* might play a role in macromolecule metabolic process ($p$ value=1.85E-03).

## The Overlaps Between DEGs and Human Essential, Housekeeping and Tissue-Specific Genes

The overlaps between 4,665 DEGs in GAPN and 2,486 essential genes ($p$ value=1.0), 1,467 housekeeping genes ($p$ value=1.0), 233 tissue-specific genes ($p$ value=0.00014) were calculated. As shown in Fig. 5, approximately 61 % tissue-specific genes, 38 % housekeeping genes, and 43 % essential genes were DEGs.

# Discussion

Given the clinical heterogeneity and high prevalence of glioma, there is an urgent need to study the pathogenesis of glioma. In the present research, 8,890 DEGs between non-tumor and tumor samples were screened out, and 16 known glioma related genes were extracted from GAD. Then, through mapping the 8,890 DEGs and 16 known genes to

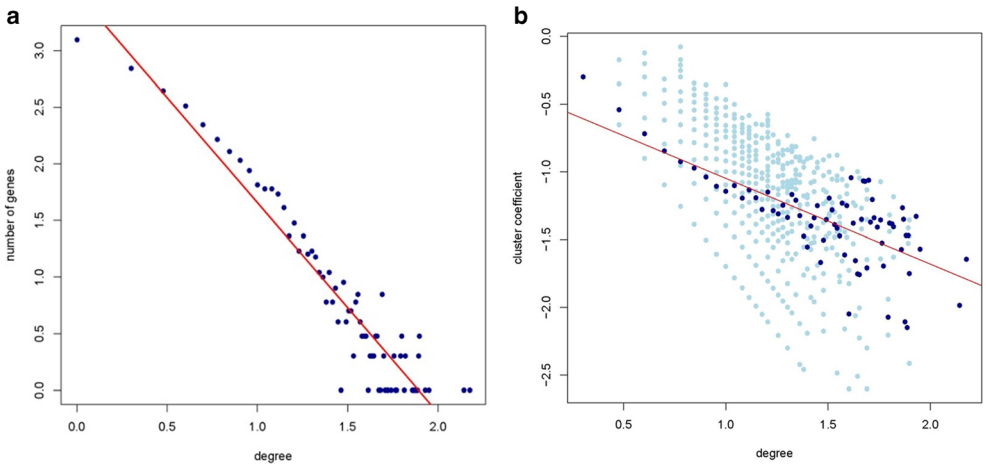


**Fig. 3** The topological properties of DEGs in GAPN. **a** The power law distribution of nodes degree in GAPN. **b** The relationship between node degree and clustering coefficient in GAPN. DEGs: differentially expressed genes; GAPN: Glioma associated protein-protein interaction network

**Table 1** The top 10 sub-networks in GAPN

| Sub-network | Score | Nodes | Edges | Genes |
|---|---|---|---|---|
| 1 | 3 | 7 | 21 | *BRMS1L*, *HDAC1*, *ING1*, *RBBP7*, *RBBP4*, *BRMS1*, *SAP30* |
| 2 | 2.222 | 9 | 20 | *MCM7*, *CCNA1*, *RB1*, *CDK6*, *MCM2*, *MCM3*, *MCM6*, *ORC6L*, *MCM4* |
| 3 | 2 | 5 | 10 | *COPS7A*, *COPS8*, *COPS3*, *COPS2*, *COPS4* |
| 4 | 2 | 5 | 10 | *CRY1*, *PER3*, *PER1*, *CSNKLE*, *PER2* |
| 5 | 1.93 | 43 | 83 | *PDGFRA*, *STAT5B*, *KIT*, *DOK1*, *LYN*, *MUC1*, *ERBB3*, *ERBB2*, *ERBB4*, *PTPRC*, *PPFIA1*, *PPFIA3*, *PPFIA2*, *PTPRD*, *PTPRF*, *LSM1*, *LSM6*, *LSM8*, *LSM7*, *LSM5*, *LSM2*, *CD22*, *PDGFRB*, *POU2F1*, *RELA*, *TAF1*, *TBN*, *TAF12*, *TAF7*, *TAF4*, *HDAC3*, *EED*, *EZH2*, *DNMT3A*, *DNMT1*, *DAXX*, *TGFB1*, *TGFB2*, *ENG*, *TGFBR2*, *MET*, *INPPL1*, *CBL* |
| 6 | 1.8 | 5 | 9 | *SYK*, *SHC1*, *PLCG1*, *PTK2*, *PTK2B* |
| 7 | 1.625 | 72 | 117 | *CBLB*, *RNF11*, *RPS27A*, *TRIP6*, *VCL*, *EPS8*, *HOOK2*, *HOOK1*, *HOOK3*, *VPS41*, *AKTIP*, *MCM10*, *CCND3*, *CASP2*, *CASP10*, *CFLAR*, *IKBKB*, *PEBP1*, *PRKCD*, *MBP*, *PRMT5*, *WDR77*, *YWHAQ*, *KLC2*, *KIF2A*, *CLSTN1*, *SH3BP2*, *SH3KBP1*, *SOS1*, *FGFR1*, *NRP1*, *NRP2*, *PGF*, *VEGFA*, *FYN*, *FAS*, *APAF1*, *HIP1*, *TFAP2A*, *SYT1*, *RIMS1*, *YWHAH*, *TNFAIP3*, *CDC25B*, *SUMO4*, *HNRPF*, *NCBP2*, *NCBP1*, *HNRPH1*, *NFKBIA*, *STAT1*, *RPS6KA5*, *NMI*, *STAT6*, *JAK1*, *HLA-DRA*, *HLA-DMB*, *HLA-DMA*, *CD74*, *PLSCR1*, *FANCA*, *FANCF*, *HES1*, *FANCE*, *CASP7*, *DLG1*, *ADRB1*, *DLGAP2*, *NOS1*, *EGFR* |
| 8 | 1.533 | 15 | 23 | *DSN1*, *POLD2*, *POLD3*, *POLD1*, *KIAA1377*, *SAT1*, *CHD3*, *TAF1A*, *TAF1B*, *TAF1C*, *TRIM24*, *CBX5*, *TRIM28*, *CBX3*, *MIS12* |
| 9 | 1.5 | 4 | 6 | *BLOC1S2*, *SNAPAP*, *MUTED*, *CNO* |
| 10 | 1.5 | 4 | 6 | *EXOSC8*, *EXOSC6*, *UPF2*, *EXOSC4* |

*GAPN* glioma associated protein-protein interaction network

HPRD, GAPN was constructed, including 4,665 DEGs, and its 51 sub-networks were identified. Furthermore, roles of the genes in top 10 sub-networks were analyzed by GO enrichment analysis.

In sub-network 1, *BRMS1L* was the only glioma DEG without known specific relation to glioma. *BRMS1L* was enriched in regulation of cell growth, and interacted with 6 known glioma related genes: *BRMS1*, *ING1*, *HDAC1*, *SAP30*, *RBBP7*, and *RBBP4*. There are few reports about the roles of *BRMS1L* in gliom progression. However, *BRMS1L* codes a family of breast cancer metastasis suppressor 1-like (BRMS1L) proteins. Breast cancer metastasis suppressor 1 (BRMS1) is a member of the mSin3-HDAC transcription co-repressor complex [26], and is significantly down-regulated in glioma compared with adjacent non-tumor tissue [27]. The overexpression of *BRMS1* inhibits glioma cell invasion, migration, and adhesion capacity by suppressing *NF-κB*, *uPA*, *MMP-2*, and Src-FAK pathway [27, 28]. Furthermore, among the BRMS1L proteins, p40 is also a component of the mSin3A/p33(ING1b)/HDAC1 deacetylase complex, which binds to the promoters of target genes, and represses gene transcription [29]. In addition, the overexpression of p40 significantly inhibits human cell growth [29]. In this study, the expression value of *BRMS1L* was down-regulated, which is consistent with the previous studies about *BRMS1* and p40 [27, 29]. These findings indicated that *BRMS1L* might play a

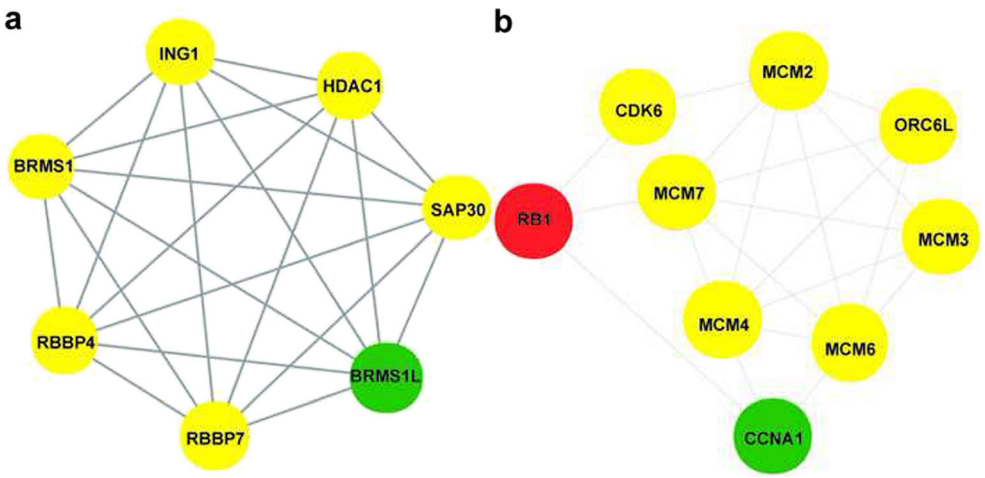


**Fig. 4** The visualization results of sub-network 1 and 2. **a** sub-network 1; **b** sub-network 2. The *blue-green nodes* represent differentially expressed genes (DEGs), *red nodes* are the known glioma related genes, and *yellow nodes* are the genes which belong to both known glioma related genes and the DEGs

**Table 2** The top 3 GO terms in each sub-network

| Sub-network | GO ID | Description | P value | Genes |
|---|---|---|---|---|
| 1 | 45786 | Negative regulation of cell cycle | 2.12E-03 | *BRMS1*, *ING1*, et al. |
| | 1558 | Regulation of cell growth | 2.38E-03 | *BRMS1*, *ING1*, et.al |
| | 6260 | DNA replication | 3.71E-03 | *RBBP7*, *RBBP4*, et al. |
| 2 | 45637 | Regulation of myeloid cell differentiation | 2.37E-04 | *RB1*, *CDK6*, et al. |
| | 43170 | Macromolecule metabolic process | 1.85E-03 | *CCNA1*, *MCM7*, et al. |
| | 44238 | Primary metabolic process | 7.30E-03 | *ORC6L*, *MCM4*, et al. |
| 3 | | | | |
| 4 | 48511 | Rhythmic process | 2.06E-09 | *CRY1*, *PER3*, et al. |
| | 6355 | Regulation of transcription, DNA-dependent | 3.01E-03 | *CSNKLE*, et al. |
| | 51252 | Regulation of RNA metabolic process | 3.09E-03 | *PER2*, et al. |
| 5 | 44237 | Cellular metabolic process | 9.85E-07 | *PDGFRA*, *STAT5B*, et al. |
| | 8152 | Metabolic process | 1.20E-05 | *ERBB2*, *ERBB4* , et al. |
| | 8151 | Cellular process | 4.77E-04 | *PTPRC*, *PPFIA1*, et al. |
| 6 | 7165 | Signal transduction | 6.00E-04 | *SYK*, *SHC1*, et al. |
| | 7154 | Cell communication | 9.73E-04 | *PLCG1*, *PTK2*, et al. |
| | 44238 | Primary metabolic process | 1.59E-02 | *PTK2B*, et al. |
| 7 | 2504 | Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II | 1.34E-04 | *HLA-DRA*, *HLA-DMB*, *HLA-DMA*, et al. |
| | 7173 | Epidermal growth factor receptor signaling pathway | 1.54E-04 | *EGFR*, *EPS8*, *RPS6KA5*, et al. |
| | 30335 | Positive regulation of cell migration | 2.02E-04 | *VEGFA*, *EGFR*, et al. |
| 8 | 6297 | Nucleotide-excision repair, DNA gap filling | 4.81E-07 | *POLD2*, *POLD3*, *POLD1*, et al. |
| | 6360 | Transcription from RNA polymerase I promoter | 1.29E-05 | *TAF1C*, *TAF1A*, et al. |
| | 6289 | Nucleotide-excision repair | 1.62E-05 | *POLD2*, *POLD3*, et al. |
| 9 | 48753 | Pigment granule organization and biogenesis | 4.13E-04 | *CNO*, et al. |
| | 32438 | Melanosome organization and biogenesis | 4.13E-04 | *CNO*, et al. |
| | 7269 | Neurotransmitter secretion | 3.44E-03 | *SNAPAP*, et al. |
| 10 | 6365 | rRNA processing | 4.85E-07 | *EXOSC8*, *EXOSC6*, et al. |
| | 16070 | RNA metabolic process | 1.09E-05 | *UPF2*, *EXOSC4*, et al. |
| | 184 | Nuclear-transcribed mRNA catabolic process, nonsense-mediated decay | 5.77E-03 | *UPF2*, et al. |

*GO* gene ontology; *ID* identifier

role in the development of glioma via a mechanism similar to *BRMS1* or p40.

In sub-network 2, *CCNA1* was a newly screened up-regulated DEG between glioma tumor and non-tumor tissues, interacted with known glioma related genes (*MCM4*, *MCM6*, and *RB1*), and enriched in macromolecule metabolic process. There are few reports about the roles of *CCNA1* in gliom progression. CCNA1 (cyclin A1) is a cell cycle factor in Cdc2/ Cyclin A/B complex, regulating the transition from G2 to M stage in cell cycle [30]. Additionally, *CCNA1* is the target of tumor suppressor gene *LATS1* in glioma progression [31]. The genes interacting with *CCNA1* are strongly associated with glioma. It's reported that hypermethylation and mutation/homozygous deletion of *RB1* occurred in the development of anaplastic oligodendrogliomas and primary astrocytic gliomas, respectively, resulting in the alteration of RB1/CDK4/$p16^{INK4a}$/$p15^{INK4b}$ signaling pathway [32]. Because RB1/CDK4/$p16^{INK4a}$/$p15^{INK4b}$ signaling pathway regulates the transition from G1 to 3 S stage in cell cycle, the alteration of *RB1* promotes the formation of glioma through enhancing cell cycle and proliferation [32]. MCM4 (Minichromosome maintenance complex component 4) and MCM6 (Minichromosome maintenance complex component 6) are components of the DNA replication fork helicase in eukaryotes, hydrolyzing ATP and providing energy for the unwinding function [33]. Further, *MCM4* and *MCM6* were significantly up-regulated in glioma progression, promoting DNA replication and cell proliferation [34]. In the present study, *CCNA1* was a DEG interacting with *RB1*, *MCM4*, and *MCM6* closely in sub-network 2, indicating that *CCNA1*

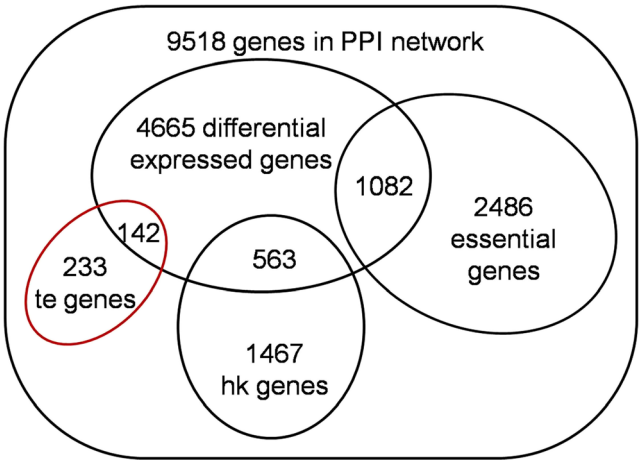


**Fig. 5** The overlaps between DEGs and human essential, house-keeping, tissue-specific genes. DEGs: differentially expressed genes. About 61 % human tissue-specific genes, 38 % housekeeping genes, and 43 % essential genes are DEGs, respectively. The hypergeometric distribution p values are 1.0, 1.0, and 0.00014, respectively

might play a role in glioma progression by interacting with *RB1*, *MCM4*, and *MCM6*, and regulating cell cycle and DNA replication. These identified genes, including *BRMS1L* and *CCNA1*, might be new targets for the glioma therapies.

In addition, our research demonstrated that only about 38 % housekeeping genes and 43 % essential genes were DEGs in the GAPN. This finding indicated that the expression changes of DEGs don't damage the necessary or basic functions of human [35, 36]. Nevertheless, about 61 % human tissue-specific genes were DEGs in GAPN. Tissue-specific genes are a class of genes whose functions and expressions are preferred in one or several tissues or cell types [37]. Tissue-specific genes tend to represent significant physiological processes, and are prevalent candidates for drug target [38]. That is to say, tissue-specific genes have more potential to be DEGs in GAPN than human housekeeping and essential genes, and these genes may play roles in the pathogenesis of glioma.

In conclusion, by establishing a GAPN using bioinformatic approaches, we focused on exploring the underlying molecular mechanism of glioma. Topological properties of DEGs in GAPN, such as degree, betweenness centrality, and closeness centrality, indicated that there exist sub-networks in GAPN. Then sub-networks were screened out, and their bio-functions were investigated thoroughly through functional enrichment analysis. Consequently, several screened DEGs in GAPN, such as *BRMS1L*, and *CCNA1* might play important roles in the development of glioma by regulating some biological processes, including cell cycle, cell growth, DNA replication and metabolism processes. Therefore, these genes might serve as targets for glioma therapies. However, due to the possible inherent errors of bioinformatics approaches, these predictions need *in vivo* validation.

**Conflict of interest** The authors have declared that no competing interests exist.

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