The Solute Carrier Family 7 Genes Are Potential Diagnostic and Prognostic Biomarkers in Lower Grade Glioma

Wentao Liu
Qingdao Jiaozhou Central Hospital
Yu Ji
Qingdao Jiaozhou Central Hospital
Rijun Ren
Qingdao Jiaozhou Central Hospital
Gentang Zhang (1298863412@qq.com)
Qingdao Jiaozhou Central Hospital

Research Article

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Abstract

Background: The solute carrier (SLC) 7 family genes are a group of cationic amino acid/glycoprotein transporters and of importance to the maintenance of amino acid nutrition and survival of tumour cells. This study was to investigate the diagnostic values of SLC7 family genes and their associations with overall survival (OS) and relapse-free survival (RFS) in Lower grade glioma (LGG).

Methods: SLC7 family gene expression and clinical data were retrieved from The Cancer Genome Atlas and the Chinese Glioma Genome Atlas database. The expression difference of SLC7 family genes was compared between 523 LGG and 1141 normal brain tissues. The associations between gene expression, clinicopathologic factors, patients' OS and RFS were analysed by various statistical methods in the two datasets.

Results: As compared to normal brain tissues, *SLC7A10* expression was significantly down-regulated, while *SLC7A5, SLC7A7* expression was significantly up-regulated in LGG tissues. Multivariate analysis and validation analysis confirmed that increased *SLC7A7* expression was associated with increased mortality (P≤0.001, Odd ratio [OR]:2.66, 95% Confidence interval [CI]: 1.56–4.6). While, increased *SLC7A4* and *SLC7A14* expression was associated with reduced mortality (P=0.02, OR:0.38, 95% CI: 0.16–0.81; P≤0.001, OR:0.38, 95% CI: 0.21–0.67; respectively). Increased *SLC7A11* expression was associated with decreased RFS (P=0.01, OR:0.61, 95% CI: 0.43–0.88).

Conclusion: *SLC7A5*, *SLC7A7*, *SLC7A10* might serve as diagnostic biomarkers in LGG. High *SLC7A4*, *SLC7A7* and *SLC7A14* expression is significantly associated with OS. SLC7 family gene expression represents a potentially diagnostic and prognostic biomarker to predict survival in LGG.

Background

Gliomas are malignant tumours that originate from glial cells and the most prevalent type of adult brain tumours. The incidence rate of the disease is 6.03 per 100,000 in USA [1]. Gliomas show high histological diversity, with astrocytoma the most common histological subtype [1]. Gliomas are classified as Grades I to IV based on histology and clinical criteria [2]. Diffuse low-grade and intermediate-grade gliomas refer to World Health Organization grades II and III gliomas (hereafter referred to as lower-grade gliomas [LGG]) and include astrocytomas, oligodendrogliomas, and oligoastrocytomas[1,2].The mean survival time is approximately seven years, the percentage of LGG patients who can survive for more than two decades is as low as 20% [3]. Recent study has demonstrated the 1p-19q deletion is a powerful predictor of chemotherapy response and survival for oligodendrogliomas which account for less than 5% of gliomas [4]. Thus, identifying key prognostic biomarkers is critical to the improvement of prognosis prediction of LGG patients.

The solute carrier (SLC) 7 family genes consist of two classes of family genes, namely the cationic amino acid transporters (*SLC7A1-4*) and glycoprotein-associated transporters (*SLC7A5-14*) [5]. Amino acid transporters are critical to the supply of amino acid nutrition and survival of tumour cells [6]. The *SLC7A1* plays a role in arginine uptake and, together with PRL/E2-induced NOS, contributes to NO production for the survival of MCF-7 and T47D cells. Knockdown of *SLC7A1* significantly inhibited L-[2,3,4,5-H(3)]-arginine uptake, decreased viability and induced apoptosis of MCF-7 and T47D cells [7]. The *SLC7A1* gene was up-regulated in colorectal cancer samples at the mRNA and protein levels. Silencing *SLC7A1* expression significantly induced apoptosis of HCT-116 cells and subsequently inhibited cell growth [8]. *SLC7A5* expression is up-regulated and plays a significant role in tumor progression in several cancer types [9–14]. *SLC7A5* expression is a negative prognostic factor in pancreas cancer [14, 15], melanoma [16], bile duct adenocarcinomas [17] and clear cell renal cell carcinoma [18].

Though the functional involvements of *SLC7A1* and *SLC7A5* in cancers have been characterized, it remains largely unknown regarding the diagnostic values of SLC7 family genes and their associations with survival in LGG. Therefore, this study was conducted to investigate the diagnostic values of SLC7 family genes and their prognostic values by analysing a large set of LGG patient data from The Cancer Genome Atlas (TCGA) [19] and the Chinese Glioma Genome Atlas (CGGA) database[20].

Methods And Materials

Data acquisition

SLC7 family gene expression, *IDH1, TP53* mutation and clinical information data of 506 adult LGG patients were obtained from the TCGA database [19]. The *SLC7A12 and SLC7A13* genes were eliminated from the study, due to lack of expression values in 90% of LGG samples. 444 adult LGG patients from the CGGA database was utilized to validate the associations between SLC7 family gene expression, clinical characteristics and mortality. Detailed information regarding the two LGG cohorts are presented in supplementary Table1 and 2. All patients provided written informed consent prior to enrollment in the study. As all the data used in the study were collected from public databases, the study didn't need to be approved by the ethical board of Qingdao Jiaozhou Central Hospital.

Differential gene expression analysis of the SLC7 family genes

Expression data (Transcripts Per Million [TPM]) of SLC7 family genes of 523 LGG patients were downloaded from the TCGA database. Expression data of 1141 normal brain tissues were obtained from The Genotype-Tissue Expression (GTEx) project [21]. Gene expression differences of SLC7 family genes between LGG patients and normal brain tissues were compared by the student t test. ROC curve analysis was conducted by the R package of pROC to determine the diagnostic values of the SLC7 family genes[22]. AUC values were computed accordingly by the R package pROC for the SLC7 family genes.

Statistical analyses and Protein-protein interaction network analysis

Student's t test was utilized to examine the associations between OS, RFS and quantitative variables of glioma patients. Fisher exact test was used to investigate the associations between OS, RFS and count variables. The linear regression model was applied to study the associations between clinical features and SLC7 family gene expression. Pearson correlation was used to characterize the co-expression pattern between different SLC7 family genes. All statistical analyses were conducted in the R platform (version 3.2.2), and $P < 0.05$ was predefined as statistically significant. Protein-protein interaction (PPI) network was established by Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) [23].

Gene ontology term and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis

In order to characterize the functions of the SLC7 family genes, we performed gene ontology (GO) term and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis for 12 SLC7 family genes on the home page of g:profiler [24].Adjusted P value < 0.05 was predefined as statistically significant.

Survival analyses

The R package pROC was used to build the receiver operating characteristic (ROC) curves and determine the optimal cut-off values for SLC7 family members[22]. LGG patients were split into the high and low expression groups according to the cut-off values. Kaplan-Meier survival analysis was performed, and the log-rank test was utilized to compare the difference in OS and RFS between the two groups using the survival package [25]. Then, univariate and multivariate survival analyses were performed using cox proportional hazards model. $P < 0.05$ indicates statistical significance.

Results

The associations between OS, RFS and clinicopathologic factors in LGG

Patients' age, tumor weight, histological type, histologic grade, *IDH1* mutation and targeted therapy were significantly associated with OS in the TCGA cohort ($P<0.05$ for all cases, student's t test or Fisher exact test, Table1). Moreover, *IDH1* mutation was significantly associated with favourable RFS in the TCGA cohort ($P<0.05$, Fisher exact test, Table1). The remaining factors did not show significant association with OS in the TCGA cohort ($P > 0.05$ for all cases, student's t test or Fisher exact test, Table1). The CGGA cohort was utilized to validate the associations of clinicopathologic factors with survival in LGG patients. Histologic grade, *IDH1* mutation and 1p19q codeletion were significantly correlated with patients' OS in the CGGA cohort ($P < 0.05$, Fisher exact test, supplementary Table3). While, histologic grade and chemotherapy were significantly associated with RFS in the LGG dataset ($P < 0.05$ for all cases, Fisher exact test, student's t test, supplementary Table3).

The associations between clinicopathologic factors and SLC7 family gene expression in LGG

A linear regression model was utilized to investigate the associations between clinicopathologic factors and mRNA expression values of SLC7 family genes. Patients' age was positively correlated with *SLC7A2, SLC7A3*, *SLC7A11* and *SLC7A14* expression and negatively corelated with *SLC7A1* expression. Tumour weight was positively correlated with *SLC7A2* expression and negatively corelated with *SLC7A5, SLC7A6* and *SLC7A9* expression. Histological type showed negative correlation with *SLC7A3*, *SLC7A7*, *SLC7A9* and positive correlation with *SLC7A1, SLC7A4, SLC7A5* and *SLC7A14* expression. Histologic grade was negatively associated with *SLC7A2, SLC7A4, SLC7A11,SLC7A14* and positively associated with *SLC7A3, SLC7A5, SLC7A6* and *SLC7A7* expression. *IDH1* mutation was positively associated with *SLC7A1, SLC7A14* and negatively associated with *SLC7A2, SLC7A3, SLC7A4, SLC7A7, SLC7A8, SLC7A9, SLC7A10* and *SLC7A11* expression. *TP53* mutation was positively associated with *SLC7A7, SLC7A9* and negatively associated with *SLC7A1, SLC7A4, SLC7A5, SLC7A8, SLC7A10, SLC7A11* and *SLC7A14* expression. Radiation therapy exhibited negative correlation with *SLC7A1, SLC7A14* and positive correlation with *SLC7A7, SLC7A9* expression. Targeted molecular therapy was negatively corelated with *SLC7A11* expression (P values< 0.05 for all cases, Table2). In line with the results above, many SLC7 genes were significantly correlated with clinical factors in the CGGA dataset, with detailed results presented in the supplementary table4.

Diagnostic values of SLC7 family genes

Of the 12 SLC7 family genes, *SLC7A4*, *SLC7A9*, *SLC7A10* expression was significantly down-regulated, while *SLC7A1*, *SLC7A2*, *SLC7A3*, *SLC7A5*, *SLC7A6*, *SLC7A7*, *SLC7A11* expression was significantly up-regulated in LGG tissues in comparison with normal brain tissues (P values< 0.05 for all cases, student t test, Figure1A). ROC curves were constructed to further explore the diagnostic values of the ten genes. *SLC7A5*, *SLC7A7*, *SLC7A10* particularly exhibited good performance in differentiating glioma tissues from normal brain tissues, with AUC values > 0.80 for all cases (Figure1B). All the results suggest these three genes might serve as diagnostic biomarkers in LGG.

The co-expression patterns and protein-protein interactions of SLC7 family genes

The expression of SLC7 family genes was highly correlated, of the 11 SLC7 family members, *SLC7A1* expression was significantly correlated with all SLC7 family genes.*SLC7A4, SLC7A6 SLC7A7, SLC7A9* expression showed significant correlation with the expression of other eight family members (P <0.05 for all cases, pearson correlation, Figure2A). The PPI network of SLC7 family genes consisted of 12 nodes and 12 edges, with a median node degree of 2. The PPI network exhibited more interactions than expected (PPI enrichment p-value<0.0001, Figure2B). The co-expression patterns and PPI networks suggested that the SLC7 family genes were co-expressed at the mRNA level and exhibited extensive homology at the protein level.

The GO term and KEGG pathway enrichment analysis

We performed GO term and KEGG pathway enrichment analysis for 12 SLC7 family genes and found the 12 genes were significantly enriched in 50 GO terms and 1 KEGG pathway (protein digestion and absorption). The top five GO terms showing the highest enrichment for SLC7 family genes were amino acid transmembrane transport, carboxylic acid transmembrane transport, organic acid transmembrane transport, amino acid transport and L-alpha-amino acid transmembrane transport (adjusted P value < 0.05 for all cases, supplementary Table5).

Overall survival analysesin LGG

Kaplan-Meier survival analysis showed significant differences in patients' OS between the high and low expression groups for *SLC7A3, SLC7A6, SLC7A7*, *SLC7A10, SLC7A1, SLC7A4, SLC7A8, SLC7A11* and *SLC7A14* in the TCGA cohort (P <0.05 for all cases, log rank test, Figure3 and supplementary table6). Univariate analysis showed that elevated *SLC7A7* and *SLC7A10* expression levels were significantly associated with increased mortality, while increased *SLC7A1, SLC7A4, SLC7A8, SLC7A11* and *SLC7A14* expression levels were significantly associated with reduced mortality (P<0.05 for all cases, supplementary table6). Then multivariate analysis was performed between patients' OS and *SLC7* family gene expression levels, the mortality-associated factors, including patients' age, tumour weight, histological type, histologic grade and *IDH1* mutation. Multivariate analysis confirmed that increased *SLC7A7* expression was associated with increased mortality (P≤0.001, Odd ratio [OR]:2.66, 95% Confidence interval [CI]: 1.56–4.6, supplementary table6). While, increased *SLC7A4, SLC7A8, SLC7A11* and *SLC7A14* expression was significantly associated with

reduced mortality (P=0.02, OR:0.38, 95% CI: 0.16–0.81; P≤0.001, OR:0.44, 95% CI: 0.26–0.77; P=0.03, OR:0.54, 95% CI: 0.31–0.95; P≤0.001, OR:0.38, 95% CI: 0.21–0.67, respectively, supplementary table6).

Validation of overall survival analyses in LGG

Kaplan-Meier survival analysis confirmed that high *SLC7A7* expression was associated with inferior prognosis, while high expression levels of *SLC7A4* and *SLC7A14* were associated with favourable prognosis in the CGGA cohort (P <0.05 for all cases, log rank test, supplementary table7). Univariate analysis showed that increased *SLC7A7* expression, decreased *SLC7A4* and *SLC7A14* expression were significantly associated with increased mortality (P<0.05 for all cases, supplementary Table7). Then multivariate analysis was applied between patients' OS and the mortality-associated features as well as *SLC7A4, SLC7A7*and *SLC7A14* expression levels. Multivariate analysis confirmed that increased *SLC7A7* expression was associated with increased mortality following the adjustment of survival-related clinical features (P=0.02, OR:1.45, 95% CI: 1.05–2.01, supplementary Table7).

Relapse-free survival analyses

Kaplan-Meier RFS analysis showed that high *SLC7A1, SLC7A8*, *SLC7A11* and *SLC7A14* expression levels were associated with favourable RFS, whereas, high *SLC7A3* and *SLC7A7* expression levels were indicative of poor RFS in the TCGA cohort (P <0.05 for all cases, log rank test, Figure4 and supplementary table8). Univariate and multivariate analysis exhibited that increased *SLC7A1, SLC7A8*, *SLC7A11,* and *SLC7A14* expression levels were associated with favourable RFS, while, increased *SLC7A7* expression levels were associated with poor RFS (P <0.05 for all cases, supplementary table6). In order to validate the findings above, we analysed the associations of RFS and SLC7 family member expression in the CGGA cohort. The Kaplan-Meier analysis together with univariate and multivariate analysis confirmed that increased *SLC7A11* expression was associated with decreased RFS (P <0.05 for all cases, supplementary Table9).

Discussion

In the present study, we have investigated the diagnostic values of SLC7 family genes and their associations with clinicopathologic characteristics and patient mortality in LGG. As expected, we demonstrated patients' age and histological grade were significantly positively associated with mortality in LGG patients. Recent study has revealed *IDH1* mutation is a positive prognostic indicator for LGG survival [26]. *IDH1* plays an important role in cellular protection from oxidative stress and the production of nicotinamide adenine dinucleotide phosphate. *IDH* mutations are associated with CpG island DNA hypermethylator phenotype by remodelling the methylome and transcriptome [27] and with longer overall survival in LGG [26] as well as LGG response to temozolomide treatment [28, 29]. The findings in our study are in consistent with previously published results.

Of the 12 SLC7 family genes, *SLC7A4*, *SLC7A9*, *SLC7A10* expression was significantly down-regulated, while *SLC7A1*, *SLC7A2*, *SLC7A3*, *SLC7A5*, *SLC7A6*, *SLC7A7*, *SLC7A11* expression was significantly up-regulated in LGG tissues in comparison with normal brain tissues. *SLC7A5*, *SLC7A7*, *SLC7A10* in particular exhibited high accuracy in differentiating LGG tissues from normal brain tissues and might serve as diagnostic biomarkers in LGG. *SLC7A5* functions as a L-type amino-acid transporter [9]. *SLC7A5* expression is up-regulated and involved in the growth and survival in several cancer types [9–14]. *SLC7A5* expression is a negative prognostic factor in pancreas cancer [14, 15], melanoma [16], bile duct adenocarcinomas [17] and clear cell renal cell carcinoma [18]. Up to date, there is no report regarding the involvement of *SLC7A5* and *SLC7A10* in the gliomagenesis. Our study revealed that *SLC7A5*, *SLC7A10* are potentially diagnostic factors for LGG patients.

We found three genes, *SLC7A4*, *SLC7A7* and *SLC7A14*, showed significant associations with mortality in glioma, which might be clinically valuable. Y+LAT1 protein, encoded by the *SLC7A7* gene, forms the cationic amino acid transport system y+L, which transports cationic and large neutral amino acids from the cell to the extracellular space. Knockdown of *SLC7A7* increased the cell apoptosis but decreased the G1 phase and cellular invasion in T-cell acute lymphoblastic leukemia [30].The common single nucleotide polymorphism (rs12436190) in *SLC7A7* increases the risk of glioma in Chinese population [31]. Our study demonstrated that high *SLC7A7* expression was associated with decreased OS and RFS in glioma patients. In line with the results in our study, glioblastoma specimens exhibit significantly higher expression of *SLC7A7* than normal tissues at mRNA and protein levels. Moreover, increased *SLC7A7* expression is a significant and independent indicator for predicting poor prognosis of glioblastoma patients[32].

SLC7A14 is primarily expressed in neural tissue, skin fibroblasts and primary endothelial cells. The SLC7A14 protein mediates lysosomal uptake of cationic amino acids. *SLC7A14* is linked to autosomal recessive retinitis pigmentosa, mutations within the gene account for 2% of autosomal recessive retinitis pigmentosa cases [33]. Up to date, there is no report regarding the involvement of *SLC7A14* in the gliomagenesis. Our study revealed that *SLC7A14* expression is a positive prognostic factor for LGG patients.

SLC7A11 is a component of the cysteine/glutamate transporter. Enhanced expression of *SLC7A11* down-regulates endogenous ROS levels and inhibits cellular invasion in glioblastoma [34]. Increased *SLC7A11* expression is associated with accelerated growth and tumour-associated seizures [35] and inferior survival in glioma patients [35, 36]. The findings are not in line with our study, in which *SLC7A11* may serve as a positive prognostic factor for RFS in LGG. The difference may be attributable to the different cohorts of LGG patients and the relatively short follow-up of the LGG patients from the TCGA database.

SLC7A4, *SLC7A7* and *SLC7A14* expression profiling may outperform the known genetic biomarkers, such as 1p-19q deletion and *IDH1* mutation which are confined to a fraction of glioma patients. Glioma patients with high expression of *SLC7A7* and low expression of *SLC7A4* and *SLC7A14* are associated to inferior OS, which is informative for guiding the treatment and follow-up for the LGG patients. *SLC7A7* may also become promising druggable targets for LGG patients. Take *SLC7A7* for example, inhibition of *SLC7A7* expression increased the cell apoptosis, decreased the G1 phase and inhibited cell invasion in T-cell acute lymphoblastic leukemia [30].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary files.

Competing interests

The authors declare there is no competing interests.

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None

Authors' contributions

GT Z designed the study, RJ R, YJ obtained expression and clinical data from the TCGA database. WT L and GT Z were responsible for the statistical analysis and survival analysis. WT L and YJ drafted the manuscript and all authors were involved in the writing and revision of the final manuscript.

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Tables

Table1. Association between the clinicopathologic characteristics and patients' OS as well as RFS in the LGG dataset

Variables	Group	Alive	Dead	P value	Non-relapse	Relapse	P value	Statistical method
Age		41.68	49.06	<=0.001	42.09	43.62	0.29	Student t test
Tumour weight		338.38	285.01	0.02	331.86	328.05	0.89	Student t test
Gender	Female	179	45	0.24	123	60	0.83	Fisher's exact test
	Male	237	45		150	69		
History of cancer	No	183	27	0.34	122	49	0.3	Fisher's exact test
	Yes	107	22		76	40		
Histological type	Astrocytoma	151	41	0.17	94	54	0.26	Fisher's exact test
	Oligoastrocytoma	112	17		77	28		
	Oligodendroglioma	153	32		102	47		
2007 WHO grade	Grade2	217	26	<=0.001	140	57	0.20	Fisher's exact test
	Grade3	198	64		132	72		
IDH1 mutation	Wild-type	79	34	<=0.001	44	41	<=0.001	Fisher's exact test
	Mutant	337	56		229	88		
TP53 mutation	Wild-type	211	47	0.82	139	57	0.24	Fisher's exact test
	Mutant	205	43		134	72		
Radiation therapy	No	104	14	0.29	65	28	0.88	Fisher's exact test
	Yes	116	24		81	33		
Targeted therapy	No	167	22	0.03	124	46	0.08	Fisher's exact test
	Yes	199	48		145	80		

Table2. Linear regression analysis between clinicopathologic characteristics and SLC7 family gene expression in LGG dataset

Training	Age	Tumour weight	Gender	History of cancer	Histological type	Histologic grade	*TP53* mutation	*IDH1* mutation	Radiation therapy	Targeted therapy
SLC7A1	--				+++		-	+++	—	
SLC7A2	++	++				-		—		
SLC7A3	++				-	++		—		
SLC7A4					++	--	—	-		
SLC7A5		--			+++	+	—			
SLC7A6		-				+				
SLC7A7					—	+++	+++	—	++	
SLC7A8							--	—		
SLC7A9		-			—		+++	—	+++	
SLC7A10							—	—		
SLC7A11	++					--	—	—		—
SLC7A14	++				+++	-	—	+++	--	

+, ++, +++ represent positive correlation with P value < .05, P value < .01 and P value < .001 respectively.

-, --, — represent negative correlation with P value < .05; P value < .01 and P value < .001 respectively.

Figures

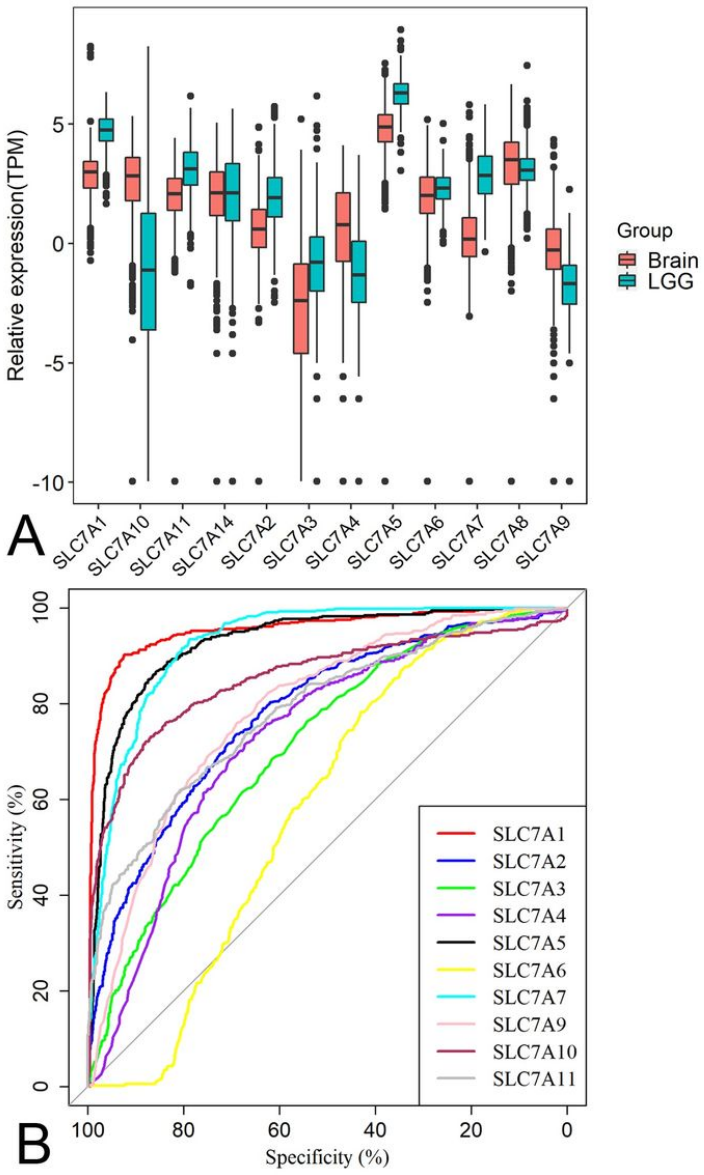

Figure 1

Differential gene expression analysis for SLC7 family genes. (A) The expression differences of SLC7 family genes between LGG and normal brain tissues; (B) The ROC curves for the SLC7 family genes.

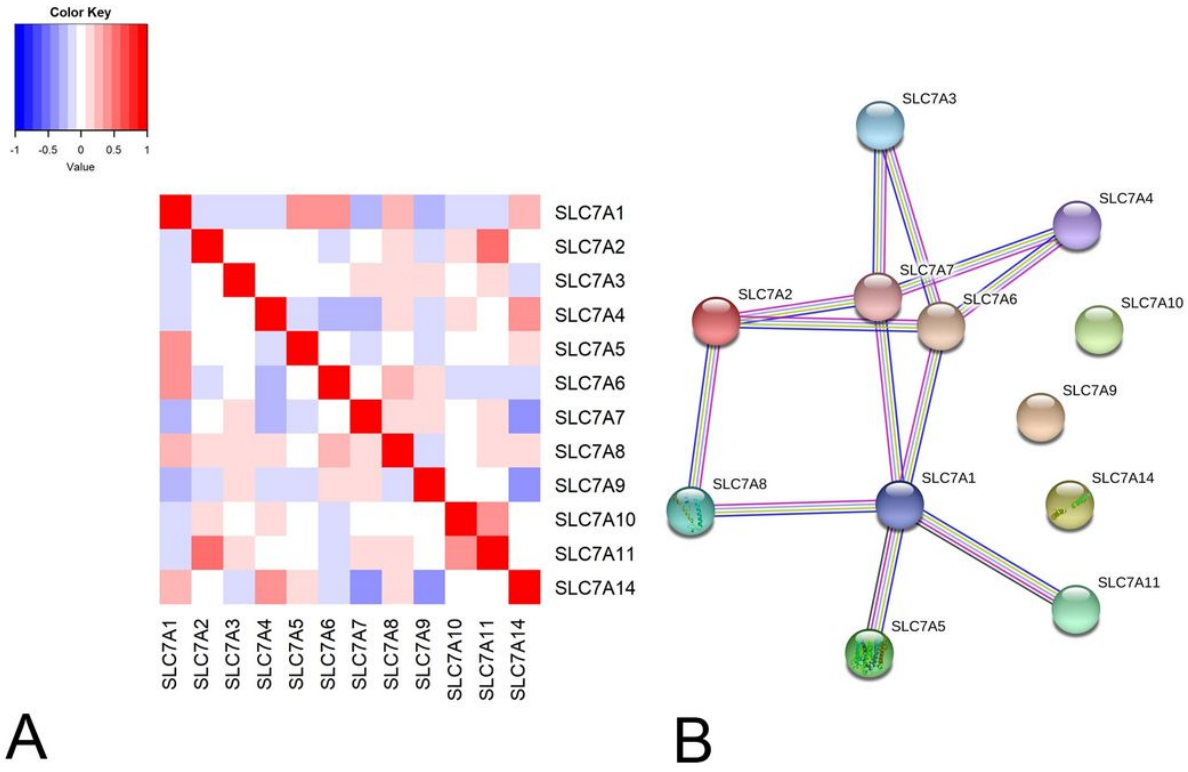

Figure 2

Co-expression pattern and PPI networks of SLC7 family genes. (A) co-expression patterns of SLC7 family genes. (B) PPI of SLC7 family genes. Network nodes and edges denote proteins and PPIs respectively. Light blue lines denote annotated interactions from the Kyoto Encyclopedia of Genes and Genomes database, green lines denote genes that are frequently observed in each other's genomic neighborhood, purple lines denote experimentally validated PPIs, dark blue lines indicate gene families with similar occurrence patterns across genomes, black lines refer to genes where expression are correlated across numerous experiments and light grey lines denote proteins which exhibit similar amino acid sequences.

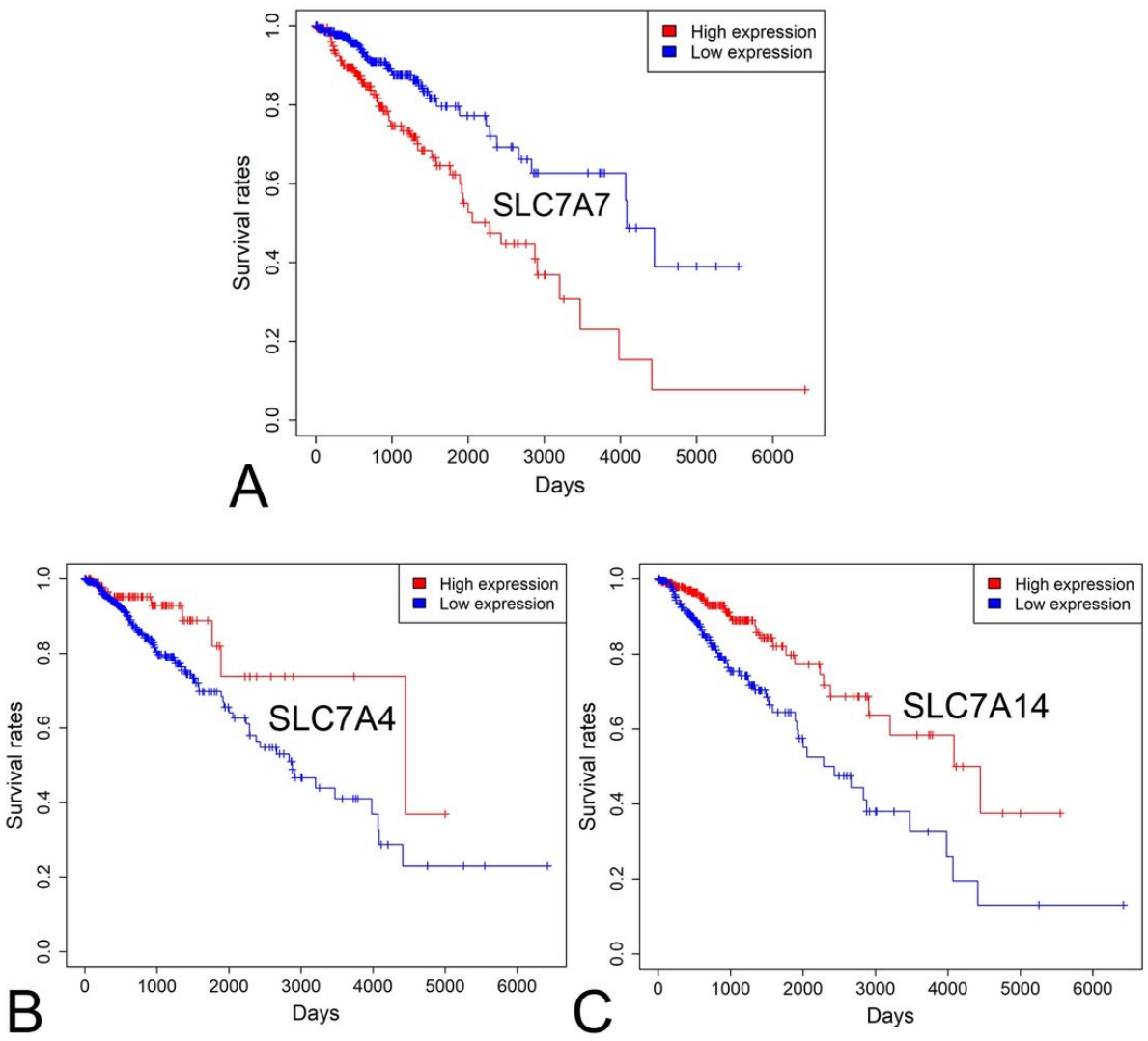

Figure 3

Kaplan-Meier survival analysis exhibited SLC7A7 (A), SLC7A4 (B) and SLC7A14 (C) expression levels were significantly associated with OS of LGG patients in the TCGA cohort.

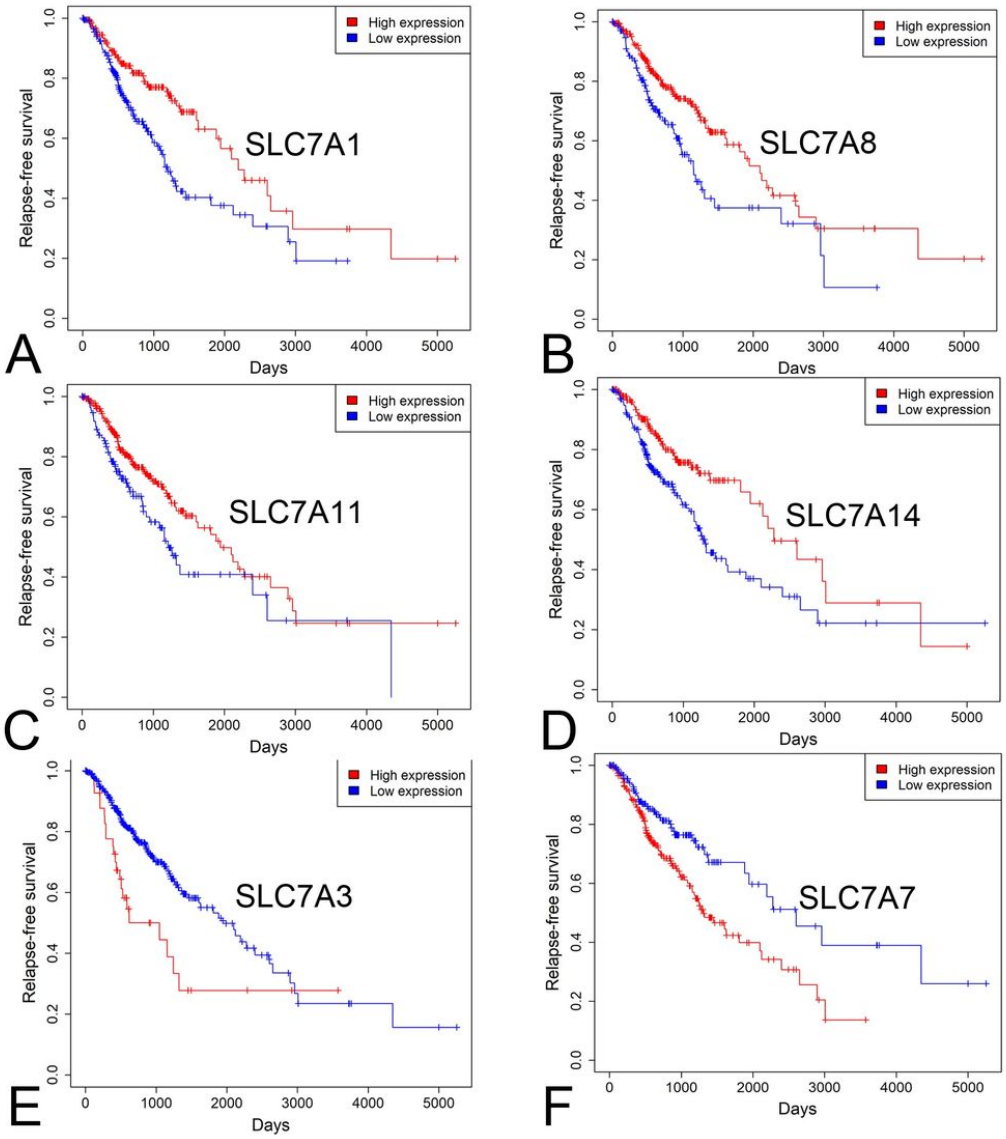

Figure 4

Kaplan-Meier survival analysis exhibited SLC7A1(A), SLC7A8(B), SLC7A11(C), SLC7A14 (D) SLC7A3 (E) and SLC7A7(F), expression levels were significantly associated with RFS in the TCGA cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STables.docx