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

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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 correlated with SLC7A1 expression. Tumour weight was positively correlated with SLC7A2 expression and negatively correlated 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 correlated 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 analyses in 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      |         |                   |

Table 2. 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.