Original Research

Genetic variants in SLC7A7 are associated with risk of glioma in a Chinese population

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Abstract

Dysregulation of the amino acid transporter SLC7A7 is involved in multiple types of cancer including gliobastoma (GBM), the most malignant form of glioma. We hypothesized that SLC7A7 genetic variants may influence glioma risk. To test this hypothesis, we conducted a case–control study in 736 incident glioma cases and 793 cancer-free controls in a Chinese population by genotyping 22 common single nucleotide polymorphisms in SLC7A7. In single-locus analysis, we found an increased risk was associated with the variant genotypes of rs12888930 (adjusted odds ratio [OR] = 1.25, 95% confidence interval [CI] 1.02–1.54, $P = 0.034$), rs12433985 (adjusted OR = 1.38, 95%CI = 1.13–1.70), rs2065134 (adjusted OR = 1.43, 95% CI 1.05–1.95) in a dominant genetic model and rs12436190 (adjusted OR = 1.37, 95%CI 1.06–1.77) in a recessive model. Multivariate analysis confirmed that rs12433985 and rs2065134 were significant and independent risk factor for glioma as well as GBM subtype (for rs12433985, OR = 1.21, 95%CI 1.04–1.42, $P = 0.016$ for all types of gliomas and $P = 0.013$, OR = 1.30, 95%CI 1.06–1.60 for GBM. For rs2065134, OR = 1.39, 95%CI 1.02–1.89, $P = 0.039$ for all types of gliomas and OR = 1.66, 95%CI 1.12–2.24, $P = 0.011$). These results, for the first time, provide suggestive evidence of polymorphisms in SLC7A7 is involved in the aetiology of glioma.

Keywords: SLC7A7, polymorphism, glioma, susceptibility

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Introduction

Brain tumour accounts for approximately 9% of human cancers, of which almost 80% are gliomas.[1] In China, the incidence rate is 3–6/100,000, with an increase of 1.2% annually, leading to 100,000 deaths in 2009.[2] Although tumourectomy as well as radiotherapy and chemotherapy have been employed to combat this malignancy, prognosis remains dismal with a median survival of only 15 months.[3] Familial clustering suggests genetic factors play a crucial aetiological role in this disease. Mounting evidences suggest that abnormal metabolic states are at the origin of many diseases including cancer. In other words, cancer can be considered in many aspects as a metabolic disease.[4,5] Amino acids are important regulators of cell function and energy metabolism.[6] Together with other nutrients, they serve as the buildings blocks for synthesis of macromolecules (DNA, RNA, proteins and lipids).[7] Tumour cells have an increased metabolic demand for amino acids to support their rapid growth and accelerated mitosis. This demand is met in part by enhanced cellular entry of nutrients through the upregulation of specific transporters. Solute carriers (SLCs), the second largest super-family of membrane proteins in the human genome,[8] are in charge of the uptake and exchange of amino acids. As an important member of SLCs, SLC7A7 (SLC family 7, amino acid transporter light chain, y + L system, member 7) is responsible for the influx/efflux of cationic and large neutral amino acids across membrane in a sodium-independent manner.[9] Dysregulation of SLC7A7 has been observed in various types of cancers including ovarian cancer, non-small cell lung cancer and multiple myeloma.[10–12] Gene deletion of SLC7A7 was first identified in gliobastoma (GBM) by The Cancer Genome Atlas (TCGA) and expression data derived from this project demonstrated that SLC7A7 protein was upregulated. Moreover, data from our group confirmed that SLC7A7 was upregulated at both mRNA and protein level and overexpression of SLC7A7 was associated with

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poor prognosis of GBM patients.[13] Protein encoded by this gene is the light subunit of a cationic amino acid transporter. This sodium-independent transporter is formed when the light subunit encoded by this gene dimerizes with the heavy subunit transporter protein SLC3A2 and is involved in the influx/efflux of cationic and large neutral amino acids from the cell to the extracellular space. Especially in the central nervous system, transporters of this kind regulate the transport of amino acids across the blood–brain barrier and are important for the metabolic coupling of gliacytes and neurons.[14]

In light of these findings, we investigated tag single nucleotide polymorphisms (SNPs) spanning the *SLC7A7* gene and their impacts on glioma risk in the present study.

Materials and methods

Study population

The study design and subjects recruitment have been described previously.[15–17] Briefly, patients with histologically confirmed glioma were consecutively recruited between August 2005 and August 2010 from Department of Neurosurgery at Huashan Hospital, Fudan University (Shanghai, China). The exclusion criteria included previous cancer history, spinal gliomas, metastasized cancer from other organs and previous radiotherapy or chemotherapy for unknown disease conditions. In total, 736 eligible patients were recruited with a response rate of 91.5%. The cancer-free controls were randomly selected from visitors to the health examination clinic for a general check-up at the same hospital during the same study period. Those who had a central nervous system-related disease, self-reported history of any cancer and previous radiotherapy and chemotherapy were excluded and 793 controls were recruited with a response rate of 85.8%. Control subjects were frequency matched to the cases by age (±5 years), gender and residential area (urban or rural). All subjects were genetically unrelated ethic Han Chinese. Each participant was scheduled for an interview after a written informed consent was obtained and a structured questionnaire we described previously was administered by trained personnel to collected information on demographic data. After the interview, each subject provided 3–5 mL venous blood. This study was approved by the institutional review board of Fudan University, Shanghai, China.

Selection of tag SNPs and genotyping

SLC7A7 harbours ~46 kb of genomic DNA at chromosome 14q11.2 in the anti-sense strand. Genotype data on the SLC7A7 from Han Chinese in Beijing (CHB) population were downloaded from the phase 2 HapMap SNP database (available at http://www.hapmap.org/ [access August, 2011]). Then, tag SNPs were selected based on a pairwise Tagger method with a criteria of linkage disequilibrium (LD) $r^2 > 0.8$ and minor-allele frequency (MAF) > 0.05 using HaploView program 4.2 (http://www.broad.mit.edu/mpg). A total of 22 SNPs which met the above criteria were chosen for this study (Table 1).

Genomic DNA was prepared from peripheral leukocytes using the Qiagen Blood Kit (Qiagen, Chatsworth, CA). SNP spanning fragments were amplified by polymerase chain reaction, and genotyping was performed with the MassARRAY iPLEX platform (Sequenom, San Diego, CA) through the use of an allele-specific matrix-assisted laser desorption/ionization time-of-flight mass spectrometry assay.[18] Primers for amplification and extension reactions were designed using MassARRAY Assay Design software, version 3.1 (Sequenom), and SNP genotypes were obtained according to the iPLEX protocol provided by the manufacturer. Laboratory staff was blinded to the case–control status of the samples. All assays were carried out in 384-well arrays and eight blank controls as well as eight random duplicates were used for quality control. Results were more than 99% concordant between the duplicated ones. On average, 99% of genotypes were successfully determined for all SNPs.

Statistical analysis

Departure from the Hardy–Weinberg equilibrium (HWE) expectation in control was assessed by Pearson χ^2 test (degree of freedom = 1) for each SNP. Differences in selected demographic variables between cases and controls were evaluated by the Student's *t*-test for continuous variables and χ^2 test for categorical variables. All tests are two-tailed with a significant level of *P* value less than 0.05. The associations between SLC7A7 variants and glioma risk were estimated by computing the odds ratio (OR) and 95% confidence interval (CI) from both univariate and multivariate logistic regression analyses. For multivariate logistic regression analysis, SNPs that stand for independent signal in univariant analysis were included. rs12888930 and rs12433985 were relatively strong LD with each other (Figure 1, $r^2 = 0.72$). Therefore, for these two signals, SNP with a relatively weak significance was excluded in the multivariate model for high potential of surrogate of the other one. The remaining pairs were in weak LD ($r^2 \leq 0.05$), indicating they are independent with each other.

The Akaike's information criterion was employed to determine the best fitting model for each SNP.[19] False discovery rate (FDR) was applied to address the multiple comparisons problem. All the statistical analyses were performed with SPSS statistical software package (version 17.0; SPSS Inc., Chicago).

Results

Characteristics of the study population

In order to carry out this study, we recruited 736 cases and 793 controls from East China. The median age at enrolment was 47 years (range, 18–81) in cases and 48 years (range, 20–79) in controls. Males comprised 71.3% of cases and 79.9% of controls. There were no significant differences in the distributions of age and gender between the cases and the controls ($P = 0.26$ and 0.16, respectively). The case group was comprised of 285 (38.7%) GBM; 451 (63.1%) lower grade gliomas including 156 (21.2%) grade III anaplastic astrocytoma, 285 grade II astrocytomas and 10 (1.4%)

Table 1 Information of 22 genotyped SNPs of *SLC7A7* gene

SNP ID	Chromosome	Chromosome position	Location in gene region[a]	Base change	Genotyping rate (%)	*P*-value for HWE[b]	Minor-allele frequency			*P*[d] value	Adjusted *P*[e] value
							Database[c]	Control	Case		
rs1061040	14	23242828	Exon11	C:T	100	1.000	0.122	0.081	0.084	0.771	0.808
rs11568422	14	23242980	Intron10	A:G	100	0.112	0.122	0.105	0.120	0.222	0.407
rs12436256	14	23244138	Intron8	T:C	100	0.852	0.330	0.388	0.382	0.764	0.808
rs12891079	14	23244542	Intron8	T:C	100	0.868	0.060	0.053	0.065	0.150	0.330
rs3850290	14	23245301	Intron6	C:T	100	0.321	0.298	0.208	0.230	0.150	0.330
rs4981439	14	23247323	Intron5	A:C	99.9	0.511	0.182	0.180	0.168	0.377	0.533
rs8013531	14	23247687	Intron5	T:C	100	0.466	0.489	0.439	0.460	0.256	0.433
rs1805061	14	23248112	Exon5	A:G	99.9	0.147	0.293	0.349	0.322	0.116	0.319
rs12888930	14	23248583	Intron4	T:C	100	0.934	0.432	0.359	0.401	**0.017**	0.154
rs11568429	14	23249292	Intron3	A:G	99.9	0.093	0.344	0.332	0.318	0.412	0.533
rs12433985	14	23249539	Intron3	G:A	99.9	0.732	0.422	0.325	0.378	**0.003**	0.066
rs7151065	14	23250157	Intron3	G:A	99.9	0.191	0.333	0.293	0.326	0.047	0.172
rs12436190	14	23257316	Intron3	G:A	99.7	0.309	0.452	0.407	0.448	**0.021**	0.154
rs2065134	14	23258189	Intron3	T:G	99.7	0.104	0.056	0.056	0.075	**0.028**	0.154
rs8006372	14	23259699	Intron3	T:C	99.9	0.139	0.489	0.466	0.478	0.497	0.607
rs17211943	14	23263665	Intron3	G:A	100	0.512	0.300	0.299	0.307	0.622	0.720
rs10134338	14	23269234	Intron3	C:T	100	0.208	0.178	0.231	0.205	0.087	0.273
rs12879369	14	23273057	Intron3	C:A	99.9	0.188	0.278	0.261	0.275	0.369	0.533
rs12884337	14	23273114	Intron3	T:C	99.9	0.489	0.330	0.307	0.341	0.046	0.172
rs1805059	14	23282449	Exon3	T:C	100	0.703	0.170	0.224	0.221	0.842	0.842
rs2281678	14	23284168	Intron2	G:A	99.9	0.806	0.367	0.363	0.386	0.186	0.372
rs2281677	14	23284572	Exon2	G:A	100	0.067	0.278	0.365	0.351	0.403	0.533

A: adenine; C: cytosine; CHB: Chinese Han in Beijing, China; G: guanine; HWE: Hardy–Weinberg equilibrium; SNP: single nucleotide polymorphism; T: thymidine.
Significant differences ($P < 0.05$) are indicated in bold. All *P* values for χ^2 test were two-sided.
[a]SNP position in NCBI build 36, dbSNP (http://www.ncbi.nlm.nih.gov/snp/).
[b]Hardy-Weinberg equilibrium, *P* values were calculated from the control group.
[c]Minor-allele frequencies from dbSNP databases in CHB population.
[d]*P* values for differences in allele distributions between cases and controls were calculated by χ^2 test.
[e]*P* values were controlled by FDR for multiple comparisons.

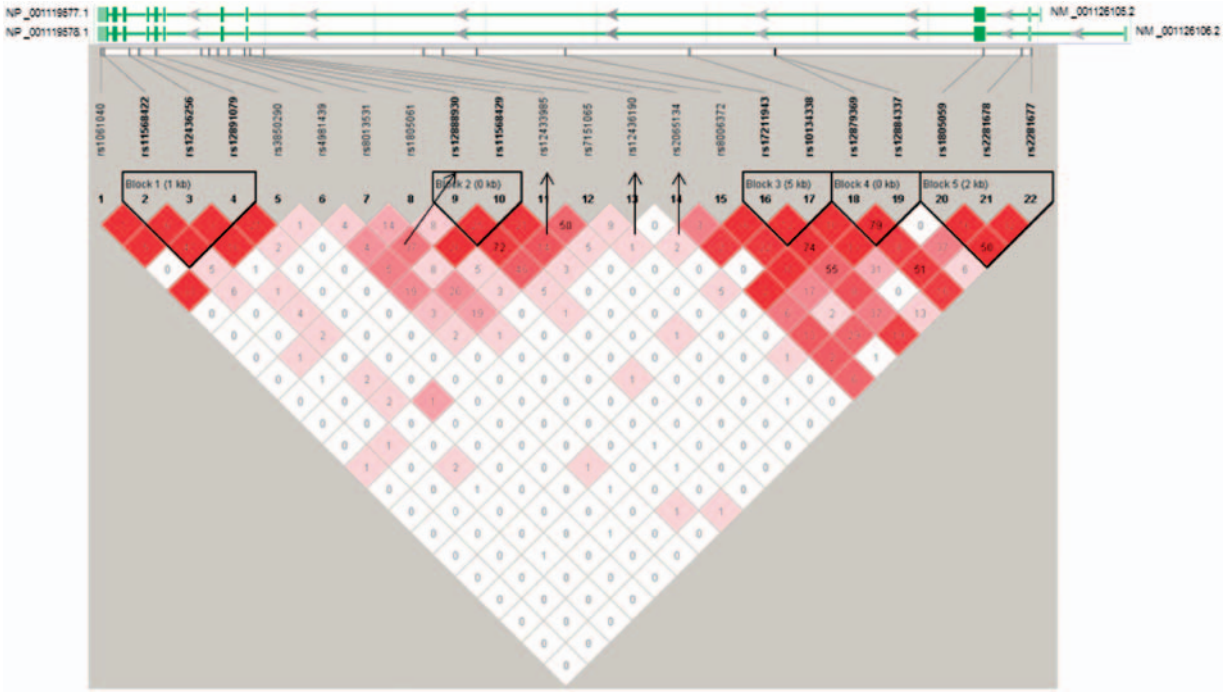

Figure 1 The pattern of linkage disequilibrium (LD) in the study population with the alignment of gene location (Chr 14: 23284572–23242828, SLC7A7). Arrows denote the significant SNPs associated with glioma risk in χ^2 test. Red scale stands for the coefficient of pairwise r^2. (A color version of this article is available in the online journal)

grade I astrocytic tumours. Besides, mixed oligodendroglial or pure oligodendrogliomas were also included in grade II and III gliomas.

A total of 22 SNPs were chosen for this study. Table 1 shows detailed information about the selected tag SNPs and their associations with glioma risk. Figure 1 shows the patterns of LD of the 22 SNPs in the control population. All the polymorphisms were in HWE among the controls. MAF of some of the genotyped SNPs is divergent from those reported in the Hapmap SNP database, which may reflect either population differences or small sample sizes from which the databases derived.

Association between SLC7A7 polymorphisms and glioma risk

Allele frequencies of four SNPs were significantly different between cases and controls (Table 1, $P=0.018$ for rs12888930, $P=0.003$ for rs12433985, $P=0.021$ for rs12436190 and $P=0.028$ for rs2065134, P value was controlled by FDR). The pattern of LD within SLC7A7 was presented in Figure 1.

Multivariate logistic regression analyses revealed that rs12433985 A allele was an independent risk compared with wild-type G allele in a log model (OR = 1.21, 95%CI 1.04–1.41, $P=0.018$). In addition, independent risk of glioma risk was also observed for variant homozygotes GG of rs2065134 in a dominant model (OR = 1.39, 95%CI 1.02–1.89, $P=0.039$). For GBM, the most malignant form of glioma, similar results were observed in multivariate logistic regression model (OR = 1.31, 95%CI 1.07–1.60, $P=0.009$ for rs12433985 in log-additive model and OR = 1.66, 95%CI 1.12–2.24, $P=0.011$ for rs2065134 in a dominant model, Table 2).

Table 2 Multivariate analysis of the risk SNPs

Covariates in the model	OR (95%CI)[a]	*P* value[a]
All types of gliomas		
rs12433985 G:A		**0.018**
Log-additive	**1.21 (1.04–1.41)**	
rs12436190 G:A		0.747
Dominant	1.04(0.83–1.29)	
rs2065134 T:G		**0.039**
Dominant	**1.39 (1.02–1.89)**	
GBM		
rs12433985 G:A		**0.009**
Log-additive	**1.31 (1.07–1.60)**	
rs12436190 G:A		0.774
Dominant	1.04 (0.78–1.41)	
rs2065134 T:G		**0.011**
Dominant	**1.66 (1.12–2.24)**	

Significant differences ($P<0.05$) are indicated in bold.
[a]OR 95%CI and *P* value were calculated from multivariate unconditional logistic regression analyses.

Furthermore, we performed stratified analysis by histological types, age and gender on these two SNPs (rs12433985 and rs2065134, respectively, Tables 3 and 4). Increased risk was observed for rs12433985 in GBM group (OR = 1.34, 95%CI 1.10–1.64, $P=0.004$); the association for lower grade gliomas was borderline significant ($P=0.055$), while the direction was the same (OR = 1.19, 95%CI

Table 3 Association between the genotypes of selected SNPs and risk of GBM as well as lower grade gliomas

SNP ID	Genotype	Lower grade gliomas				Logistic regression[b]		GBM				Logistic regression	
		No. of cases	%	No. of controls	%	OR (95%CI)	*P*	No. of cases	%	No. of controls	%	OR (95%CI)	*P*
rs12433985	GG	172	38.1	364	45.9	1.00 (reference)		107	37.5	364	45.9	1.00 (reference)	
	AG	232	51.4	342	43.1	**1.39 (1.08–1.79)**	**0.011**	128	44.9	342	43.1	1.33 (0.98–1.80)	0.068
	AA	47	10.4	87	11.0	1.22 (0.81–1.84)	0.335	49	17.2	87	11.0	**1.82 (1.19–2.77)**	**0.005**
Log-additive						1.19 (1.00–1.43)	0.055					**1.34 (1.10–1.64)**	**0.004**
rs2065134	TT	394	87.4	707	89.2	1.00 (reference)		237	83.2	707	89.2	1.00 (reference)	
	GT	53	11.8	76	9.6	1.22 (0.83–1.79)	0.309	47	16.5	76	9.6	**1.87 (1.25–2.81)**	**0.002**
	GG	4	0.9	6	0.8	1.16 (0.31–4.28)	0.830	1	0.4	6	0.8	0.55 (0.07–4.67)	0.587
Dominant	TT/GT + GG	57	12.6	82	10.4	1.21 (0.84–1.76)	0.303	48	16.8	82	10.4	**1.78 (1.20–2.64)**	**0.004**

GBM: glioblastoma.
Significant differences ($P < 0.05$) are indicated in bold.
[a]OR 95%CI and *P* value were calculated from unconditional logistic regression analyses.

1.00–1.43) in a log additive model. For rs2065134, similar results were obtained (OR = 1.78, 95%CI 1.20–2.64, $P = 0.004$ for GBM and OR = 1.21, 95%CI 0.84–1.76, $P = 0.303$ for lower grade gliomas in dominant model).

For stratified analysis by gender and age, we derived more pronounced association and elevated ORs for rs12433985 among male cases compared with female cases and those who were younger than 47 years compared with cases older than 47 years (OR = 1.30, 95%CI 1.09–1.55, $P = 0.004$ for male cases and OR = 1.27, 95%CI 1.03–1.56, $P = 0.013$ for younger cases in a log additive model). Borderline association with rs2065134 was observed among males (OR = 1.45, 95%CI 1.00–2.08, $P = 0.049$ in a dominant model; Table 4).

Discussion

To investigate the role of multiple common variants of SLC7A7 on the susceptibility of glioma, we carried out this case–control study in a Chinese Han population. We found, for the first time, that 2 (rs12433985 and rs2065134) of the 22 tag SNPs showed significant associations with glioma risk. Although after controlled for multiple comparisons by FDR, the adjusted *P* values exceeded 0.05 threshold, the consistent association signals in the stratified analysis among histological types, gender and age suggested these two SNPs are promising susceptible loci for glioma risk.

Functional annotation indicates risk allele A of rs12433985 creates a Gfi-1 binding site compared with the major G allele according to TFSEARCH (http://www.cbrc.jp/research/db/TFSEARCH.html), which is consistent with the evidences that important cis-elements exist in the first several introns and exons.[20] Therefore, rs12433985 may possibly exert an impact on the level of gene expression through regulation of transcription.

Gene deletion of SLC7A7 was first identified in GBM tissues by TCGA (http://cancergenome.nih.gov/). Moreover, dysregulation of SLC7A7 also occurred in GBMs. Our previous study confirmed these findings and suggested that stepwise upregulation (mRNA and protein level) of human SLC7A7 might participate in the carcinogenesis of GBM.[13]

Taken together, these evidences suggested that genetic variants of SLC7A7 may influence the susceptibility of glioma and motivated us to conduct this case–control study in a Chinese Han population. Our study provided evidences that genetic variants contribute to the occurrence of glioma.

There are mounting evidences that tumours have their root in altered metabolism. In this study, we provide such an effort. It is a first attempt to investigate the role a transporter of amino acids with the occurrence of glioma and notably, rs12433985 which lies in a potentially regulation region of SLC7A7 may modulate risk of glioma.

It is of importance to note that rs12433985 is the peak signal with a relatively large effect size and this association is significant among all histological types of gliomas. Further multivariant analysis confirmed that rs12433985 was an independent risk SNP for glioma risk in a log-additive model. Altogether, these robust observations

Table 4 Stratified analysis between the genotypes of selected SNPs and glioma risk

SNP	No./Logistic regression	No./Genetic Model	Gender		Age (year)	
			Male	Female	≤47	>47
rs12433985	Cases/controls (736/793)	GG	194/267	85/97	164/226	115/138
		AG	259/256	101/86	221/223	139/119
		AA	71/63	25/24	50/45	46/42
	OR (95%CI)	GG	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
		AG	**1.38 (1.07–1.78)[a]**	1.37 (0.89–2.01)	**1.37 (1.04–1.80)[b]**	**1.57 (1.15–2.14)[c]**
		AA	**1.58 (1.07–2.33)[d]**	1.19 (0.63–2.23)	1.54 (0.98–2.41)	1.32 (0.81–2.14)
		Log-additive	**1.30 (1.09–1.55)[e]**	1.16 (0.87–1.55)	1.23 (0.99–1.54)	**1.27 (1.03–1.56)[f]**
rs2065134	Cases/Controls (736/793)	TT	452/525	179/182	374/440	257/267
		GT	69/53	31/23	58/47	42/29
		GG	4/6	1/0	3/4	2/2
		Dominant	73/59	32/23	61/51	44/31
	OR (95%CI)	TT	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
		GT	**1.52 (1.04–2.23)[g]**	1.40 (0.76–2.42)	1.44 (0.96–2.17)	1.50 (0.91–2.49)
		GG	0.77 (0.21–2.73)	NA	0.90 (0.20–4.00)	1.07 (0.15–7.65)
		Dominant	**1.45 (1.00–2.08)[h]**	1.40 (0.79–2.49)	1.40 (0.94–2.08)	1.48 (0.90–2.41)

NA: not available. OR 95%CI and *P* value are calculated from unconditional logistic regression analyses. ORs and 95% CIs are indicated in bold because their P-values are less than 0.05.
[a]$P = 0.012$; [b]$P = 0.025$; [c]$P = 0.004$; [d]$P = 0.021$; [e]$P = 0.004$; [f]$P = 0.013$; [g]$P = 0.03$; [h]$P = 0.049$.

highlight the potentially important role of this SNP in the aetiology of glioma. Besides, our data also indicates the genetic risk profiles of glioma differ by histology.

To the best of our knowledge, this is the first study that has comprehensively investigated whether the genetic variants of SLC7A7 were associated with risk of glioma. Consistent and convincing results were observed for rs12433985 and allowed us to assign functional candidate variant to a smaller region flanking rs12433985 of SLC7A7. Based on our investigation, further work annotating the pathological mechanisms of glioma via resequencing of this region and performing corresponding bio-functional studies would be greatly admired.

Author contributions: SF provided the study design and performed the data analysis section. YZ wrote and revised the manuscript. XL, XS, FZ and YZ collected the blood samples and extracted genomic DNA. HC and GC conducted the genotyping section. YM and QL jointly directed the work.

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