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Original Article

Association of six SNPs in *SLC7A7* with glioma risk in a Chinese population

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Abstract: Glioma is the most common type of tumors in the central nervous system. We performed a case-control study in a Chinese population, and investigated the contributions of six SNPs (rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134) of *SLC7A7* to the susceptibility to glioma. We selected 159 patients with histological confirmed glioma and 319 healthy control subjects between March 2013 and March 2015. Genotyping of *SLC7A7* rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 was carried out in a 384-well plate format on the sequenom MassARRAY platform. We observed that the AG and AA genotypes of rs12433985 were associated with a higher risk of developing glioma in comparison to those harboring the GG genotype, and the adjusted ORs (95% CI) was 1.59 (1.02-2.48) and 1.98 (1.12-3.50), respectively. The CC genotypes of rs12888930 had 2.29 fold risk of developing glioma when compared with the TT genotype (adjusted OR=2.29, 95% CI=1.33-3.94). The *SLC7A7* rs12888930 polymorphism had correlation with radiation exposure (Trend of χ^2=4.84, P=0.03). The T-G-G-G-T-C and T-A-G-G-T-T haplotypes showed an increased risk in glioma risk, and the ORs (95% CI) were 6.74 (2.63-17.25) and 5.37 (1.89-15.30), respectively; while the T-G-G-G-T-T haplotype was associated with a reduced risk in glioma (OR=0.41; 95% CI=0.25-0.67; P < 0.001). In summary, we observed that the *SLC7A7* rs12433985 and rs12888930 genetic mutations ere significantly correlated with an elevated risk of developing glioma, and the development of glioma risk could be affected by the *SLC7A7* haplotype differences.

Keywords: Glioma, *SLC7A7*, polymorphism, haplotype

Introduction

Glioma is the most common type of tumor disease in the central nervous system, and this cancer is derived from the lesion of glial cells [1]. Glioma accounts for about 30% of all brain and center nerves system tumors, and 80% of glioma was malignant tumor of brain [2]. Without complete capsule, glioma intrusively grows in brain by an interlocking pattern with normal tissues [3]. Glioma tends to relapse because of its growth characteristics. Currently, the cause of glioma is still unknown and the etiology has been poorly understood, and may be multifactorial resulted from the interaction of intrinsic and environmental factors [4-7]. The only established environmental risk factor is the common exposure to therapeutic or high dose ionizing radiation [8, 9]. Additionally, high meat consumption and obesity have also been reported to play an important role in increasing glioma risk [10, 11]. Recently studies have indicated that many genetic factors play an important role in the risk of development of glioma, such as *TGF-β1*, *PTGS2*, *EGFR*, *CXCL12*, *VEGF*, *KDR*, *ABCG2* and *ABCB1* [12-17].

The solute-carrier (SLC) superfamily gene encodes in the second categories of tansmembrane protein family, and is mainly responsible for cells of the amino acid intake and exchange [18]. *SLC* superfamily genes contain 55 gene families and 362 functional genes for encoding proteins. *SLC7* is an important member of SLC superfamily genes, and is responsible for transporting cationic oxygen acids or glycoprotein [19, 20]. Previous studies have reported that over expression of *SLC7A7* is observed in glioblastoma [21]. Currently, only one previous study has reported the association between

SLC7A7 genetic polymorphisms and risk of glioma in a Chinese population [22]. Therefore, we performed a case-control study in a Chinese population, and investigated the contribution of two SNPs (rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134) in intros of *SLC7A7* in the susceptibility to glioma.

Subjects and methods

Subjects

This retrospective case-control study was performed between March 2013 and March 2015 at Guangzhou Zhujiang Hospital and Shenzhen Longgang central Hospital. Study subjects comprised of 159 patients with histological confirmed glioma and 319 healthy control subjects. The grade of glioma was diagnosed according to the pathological grading criteria established by World Health Organization (WHO) in 1997. All the patients with gliomas were confirmed to be without history of other malignant tumors and prior chemotherapy or radiochemotherapy.

The controls were recruited from the outpatients' clinics in our hospital, and all the controls were confirmed to be free of malignant tumors, drug allergy, cardiovascular diseases, nervous system diseases, cerebral diseases, end-stage liver or kidney diseases. The demographic, lifestyle and clinical variables were collected through a self-reported questionnaire. The demographic and lifestyle habits and clinical variables included age, sex, radiation exposure, tobacco smoking, alcohol consumption, family history of cancer, WHO grade of glioma and pathological types. Each study subject agreed to participate into our study and signed a consent form prior to enrollment. Our research was approved by the Research Ethics Committee of Guangzhou Zhujiang Hospital and Shenzhen Longgang central Hospital.

DNA extraction and genotyping

Blood samples were taken from all participants in EDTA-containing tube for total genomic DNA extraction. Genomic DNA was extracted using QIAamp DNA blood Mini Kit, according to manufacturer's instruction (Qiagen GmbH, Hilden, Germany). Genome DNA was preserved at -20°C for later. The SNPs of *SLC7A7* were selected according to the criteria of population and MAF > 5% with dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP). A total of six SNPs (rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134) in *SLC7A7* were selected for analysis.

Genotyping of *SLC7A7* rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 was carried out in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). PCR primers for polymerase chain reaction amplification and single base extension assays were designed using Sequenom Assay Design 3.1 software. For Sequenom genotyping, an initial PCR reaction for genotyping rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 was performed in 5 μL reaction, including 0.8 μl HPLC grade water, 0.5 μl of 10×PCR buffer with 20 mM $MgCl_2$, 0.4 μl of 25 mM $MgCl_2$, 0.1 μl of 25 mM dNTP mix, 1 μl of 0.5 μM primer mix, 0.2 μl Sequenom PCR enzyme and 2 μl of genomic DNA (5 ng/μl), following by the SAP and iPLEX reaction. The PCR products are then desalted, and dispensed to SpectroCHIP Arrays and analyzed using MALDI-TOF MS.

Statistical analysis

Student's *t*-test was used to determine differences in means, and Pearson Chi-square test or Fisher's exact test was used to assess intergroup significance. The Hardy-Weinberg equilibrium (HWE) of Genotype distributions of SLC7A7 rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 in the control population were tested using a Chi-square (χ^2)-test with one degree of freedom. Logistic regression analysis was performed in order to determine the odds ratios (OR) and 95% confidence intervals (95% CI) associated with the glioma risk, taking the wide-type genotype as the reference group. All analyses were carried out under co-dominant model, dominant and recessive models. Interaction between genetic polymorphisms of *SLC7A7* rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 was analyzed by Spearman correlation analysis. The linkage disequilibrium and haplotype analysis were analyzed by SHEs is software (http://analysis.bio-x.cn/myAnalysis.php) [23]. SPSS version 18.0 software (SPSS Inc. Chicago, USA) was used for

Table 1. Demographic and lifestyle habits and clinical variables of investigated patients and controls

Variables	Patients N=159	%	Controls N=319	%	Chi-square test	*P* value
Age, years	45.64±5.75		45.03±5.38		1.15	0.26
< 50	122	76.73	262	82.13		
≥ 50	37	23.27	57	17.87	1.96	0.16
Gender						
Female	72	45.28	131	41.07		
Male	87	54.72	188	58.93	0.77	0.38
Tobacco smoking						
Never	99	62.26	224	70.22		
Ever	60	37.74	95	29.78	3.07	0.08
Alcohol consumption						
Never	96	60.38	195	61.13		
Ever	63	39.62	124	38.87	0.03	0.87
Family history of cancer						
No	138	86.79	296	92.79		
Yes	21	13.21	23	7.21	5.77	0.02
Radiation exposure						
No	139	87.42	316	99.06		
Yes	20	12.58	3	0.94	31.38	< 0.001
WHO grade of glioma						
I-II	69	43.40				
III-IV	90	56.60				
Pathological types						
Glioblastoma	51	32.08				
Astrocytoma; oligodendroglioma and mixed glioma	108	67.92				

statistical analysis. Statistical significance was set at $P < 0.05$.

Results

The demographic and lifestyle habits and clinical variables of investigated patients and controls were presented in **Table 1**. The mean ages of glioma patients and controls were 46.44±6.55 and 45.06±5.39 years, respectively. There were 72 (45.28%) females and 87 (54.72%) males in glioma patients, and 131 (41.07%) females and 188 (58.93%) males in controls. In comparison to the controls, glioma patients were more likely to have a history of radiation exposure (χ^2=31.38, $P < 0.001$) and family history of cancer (χ^2=5.77, P=0.02). However, there were no significant differences between glioma patients and controls in terms of age, gender, tobacco smoking, alcohol consumption and family history of cancer. There were 69 (43.40%) patients with I-II WHO grade of glioma, and 90 (56.60%) cases with III-IV grade. The pathological types of 51 (32.08%) patients were glioblastoma, and 108 (67.92%) patients were astrocytoma, oligodendroglioma and mixed glioma.

The genotype distributions of *SLC7A7* rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 were presented in **Table 2**. Using chi-square test, we observed a significant difference in the genotype distributions of rs12433985 (χ^2=7.36, P=0.03) and rs12888930 (χ^2=9.95, P=0.01) between investigated glioma patients and controls, while no significant difference was found in the genotype distribution of rs7151065, rs12436190, rs12884337 and rs2065134. We observed that the genotype distributions of the six SNPs were in agreement with HWE through a Chi-square (χ^2)-test with one degree of freedom.

We observed that individuals harboring the AG and AA genotypes of rs12433985 were associ-

Table 2. Association between SLC7A7 rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134 polymorphisms and glioma risk

SLC7A7	Patients N=155	%	Controls N=314	%	χ^2 test	*P* value	χ^2 test for HWE	P for HWE	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)[1]	*P* value
rs12433985												
GG	53	33.33	146	45.77					1.0 (Ref.)	-	1.0 (Ref.)	-
AG	74	46.54	128	40.13					1.59 (1.02-2.48)	0.04	1.77 (1.11-2.82)	0.02
AA	32	20.13	45	14.11	7.36	0.03	3.73	0.06	1.98 (1.12-3.50)	0.02	2.11 (1.16-3.85)	0.02
rs12888930												
TT	54	33.96	145	45.45					1.0 (Ref.)	-	1.0 (Ref.)	-
CT	66	41.51	129	40.44					1.32 (0.85-2.06)	0.22	1.27 (0.80-2.23)	0.31
CC	39	24.53	45	14.11	9.95	0.01	3.39	0.07	2.29 (1.33-3.94)	0.003	2.01 (1.14-3.57)	0.02
rs7151065												
GG	82	51.57	164	51.41					1.0 (Ref.)	-	1.0 (Ref.)	-
AG	66	41.51	119	37.30					1.09 (0.72-1.65)	0.70	1.05 (0.68-1.63)	0.84
AA	11	6.92	36	11.29	2.54	0.28	3.82	0.06	0.60 (0.28-1.28)	0.19	0.67 (0.31-1.45)	0.31
rs12436190												
GG	53	33.33	106	33.23					1.0 (Ref.)	-	1.0 (Ref.)	-
AG	75	47.17	160	50.16					0.95 (0.61-1.47)	0.81	0.84 (0.53-1.34)	0.46
AA	31	19.50	53	16.61	0.70	0.71	0.32	0.57	1.16 (0.66-2.05)	0.61	1.08 (0.60-1.96)	0.80
rs12884337												
TT	74	46.54	148	46.39					1.0 (Ref.)	-	1.0 (Ref.)	-
CT	63	39.62	142	44.51					0.93 (0.61-1.41)	0.73	0.93 (0.60-1.44)	0.73
CC	22	13.84	29	9.09	2.83	0.24	0.37	0.54	1.62 (0.85-3.08)	0.14	1.26 (0.63-2.51)	0.52
rs2065134												
TT	138	86.79	282	88.40					1.0 (Ref.)	-	1.0 (Ref.)	-
GT	19	11.95	34	10.66					1.04 (0.56-1.94)	0.89	1.12 (0.58-2.15)	0.74
GG	2	1.26	3	0.94	0.29	0.86	2.77	0.10	1.27 (0.19-8.34)	0.81	1.32 (0.21-8.42)	0.77

[1]Adjusted for sex, age, tobacco smoking, radiation exposure.

Table 3. Interaction between *SLC7A7* rs12433985 and rs12888930 and demographic and lifestyle habits

Variables		rs12433985			Trend of χ^2	*P* value	rs12888930			Trend of χ^2	*P* value
		GG (%)	AG (%)	AA (%)			TT (%)	CT (%)	CC (%)		
Age, years	< 50	154	160	61			156	154	65		
	≥ 50	45	42	16	0.18	0.67	43	41	19	0.01	0.91
Gender	Female	76	91	36			97	73	33		
	Male	123	111	41	2.33	0.13	102	122	51	3.68	0.06
Tobacco smoking	Never	129	142	52			138	136	49		
	Ever	70	60	25	0.55	0.46	61	59	35	2.27	0.13
Alcohol consumption	Never	125	122	44			122	118	51		
	Ever	74	80	33	0.78	0.38	77	77	33	0.02	0.90
Family history of cancer	No	178	183	70			181	177	73		
	Yes	21	19	7	0.19	0.67	18	18	11	0.82	0.37
Radiation exposure	No	190	193	72			194	184	77		
	Yes	9	9	5	0.31	0.58	5	11	7	4.84	0.03

ated with a higher risk of developing glioma in comparison to those harboring the GG genotype, and the adjusted ORs (95% CI) was 1.59 (1.02-2.48) and 1.98 (1.12-3.50), respectively (**Table 2**). We observed that the CC genotypes of rs12888930 had 2.29 fold risk of developing glioma when compared with the TT genotype (adjusted OR=2.29, 95% CI=1.33-3.94). However, we observed no significant relationship between rs7151065, rs12436190, rs12884337 and rs2065134 polymorphisms and glioma risk.

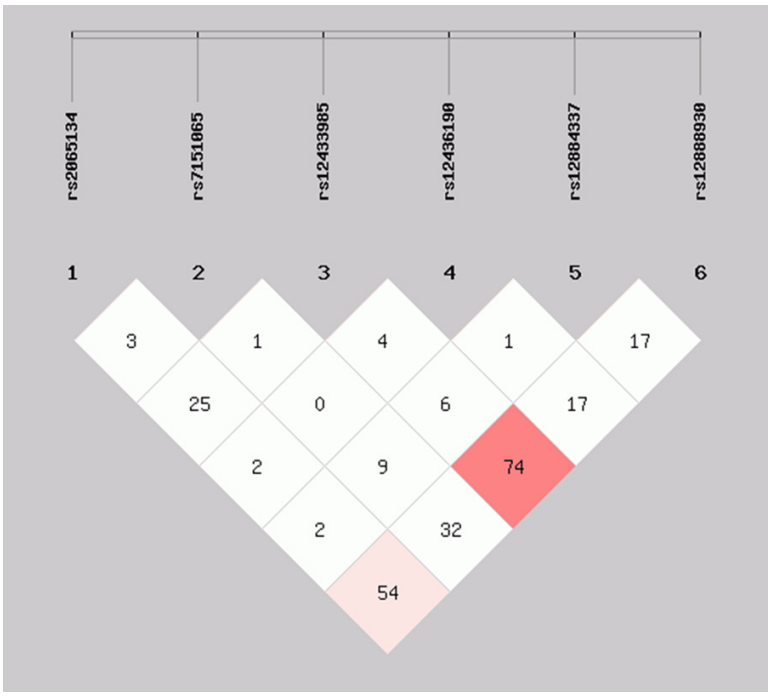

Figure 1. The linkage disequilibrium of SLC7A7 rs12433985, rs12888930, rs7151065, rs12436190, rs12884337 and rs2065134.

Using Spearman correlation analysis, the *SLC7A7* rs12888930 polymorphism had correlation with radiation exposure (Trend of χ^2=4.84, P=0.03). However, *SLC7A7* rs12433985 polymorphism had no significant correlation with age, gender, tobacco smoking, alcohol consumption, family history of cancer and radiation exposure (All *P* value for interaction > 0.05) (**Table 3**).

The haplotype analysis revealed that *SLC7A7* rs12433985 and rs12888930 showed linkage disequilibrium (D'=0.74, r^2=0.16), and rs2065134 and rs12888930 also revealed a linkage disequilibrium (D'=0.54, r^2=0.12) (**Figure 1**). The T-G-G-G-T-C (rs2065134-rs7151065-rs12433985-rs12436190-rs12884337-rs12888930) and T-A-G-G-T-T haplotypes showed an increased risk in glioma risk, and the ORs (95% CI) were 6.74 (2.63-17.25) and 5.37 (1.89-15.30), respectively; while the T-G-G-G-T-T haplotype was associated with a reduced risk in glioma (OR=0.41; 95% CI=0.25-0.67; P < 0.001).

Discussion

We carried out a hospital-based case-control study to evaluate the relationship between six SNPs of *SLC7A7* genetic polymorphisms and risk of developing glioma in a Chinese population, and we observed that the AG and AA genotype of *SLC7A7* rs12433985 were associated with a higher risk of developing glioma, and the CC genotypes of rs12888930 was related to the risk of glioma. However, no significant relationship was observed between other four SNPs in *SLC7A7* and risk of glioma.

Previous study reported that the abnormal gene expression of *SLC7A7* was observed in malignant tumors. Chen L et al. carried out a study in a China, and identified that *SLC7A7* showed over expression in ovarian cancer patients with chemotherapy resistance [24]. Xie L et al. carried out a study to new signaling pathways in the cellular response to ionizing radiation, and they revealed that up-regulated of *SLC7A7* is involve in acquired radioresistance of non-small cell lung cancer [25].

Genetic variation includes the transformation of a single base by transversion, insertion, or deletions, and the SNP is thought to result in susceptibility to human diseases [26-28]. Genetic polymorphisms of *SLC7A7* could influence the function and expression of proteins or result in abnormal cell proliferation, thus triggering cell transformation [29, 30].

Only three studies have reported the association between *SLC7A7* polymorphisms and risk of diseases [22, 31, 32]. Kashevarova AA et al. reported that the mutation in the SLC7A7 is associated with intellectual disability in Russian patients [31]. Fan S et al. carried out a case-control study with 736 glioma cases and 793 cancer-free controls, and found that rs12433985 and rs2065134 polymorphisms were significantly correlated with risk of glioma and glioblastoma in a Chinese population [22]. Font-Llitjós M et al. carried out a study in 11 patients from nine unrelated lysinuric protein intolerance families, and reported that *SLC7A7* plays an important role in lysinuric protein

intolerance [32]. A recent study carried out a study with 119 patients with pathologically confirmed glioblastoma, and reported that over expression of *SLC7A7* is associated with poor outcomes in patients with glioblastoma in a Chinese population [21]. Our study reported that the *SLC7A7* rs12433985 and rs128889-30 polymorphisms were associated with risk of developing glioma. However, the exact molecular mechanisms underlying the pathogenesis of glioma remain to be elucidated. Efforts to identify molecular markers for early detection of glioma and personalization of both patients' prognosis and therapy are of critical clinical significance.

Our finding also revealed that the T-G-G-G-T-C and T-A-G-G-T-T haplotypes showed an increased risk in glioma risk, whereas the T-G-G-G-T-T haplotype was associated with a reduced risk in glioma risk. These findings indicated that the development of glioma risk could be affected by SNP, as well as haplotype differences. Moreover, our finding revealed a correlation between *SLC7A7* rs12888930 polymorphism and radiation exposure. A previous study reported that the SLC gene suerfamily is involved in acquired radioresistance [25], which indicated that differentially expressed SLC genes may show different in radiation exposure.

There are two limitations involved in this study. First, the hospital-based case-control design and investigated subjects selected from only one hospital may cause selective bias. Second, the sample size of the included subjects is small, which may cause low statistical power in the determination of statistical differences between investigated groups.

In summary, we observed that the *SLC7A7* rs12433985 and rs12888930 genetic mutations were significantly correlated with an elevated risk of developing glioma, and the development of glioma risk could be affected by the *SLC7A7* haplotype differences. Further studies with larger sample sizes are required to elucidate the relationship between *SLC7A7* polymorphisms and risk of developing glioma.

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Disclosure of conflict of interest

None.

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