CASC15 Gene Polymorphisms and Glioma Susceptibility in Chinese Children*

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[Abstract] Objective: Gliomas are the most common tumors in the central nervous system. The cancer susceptibility candidate 15 (*CASC15*) gene has been reported to be a susceptibility gene for several types of cancer. No studies have been carried out on the predisposing effect of *CASC15* gene single nucleotide polymorphisms (SNPs) on glioma risk. **Methods:** In order to determine whether *CASC15* gene SNPs are involved in glioma susceptibility, the first association study in a relatively large sample, which consisted of 171 patients and 228 healthy controls recruited from China, was performed. The contribution of SNPs (rs6939340 A>G, rs4712653 T>C and rs9295536 C>A) to the risk of glioma was evaluated by multinomial logistic regression, based on the calculation of the odds ratio (OR) and 95% confidence interval (CI). **Results:** In the single locus and combined analysis, it was revealed that the genetic risk score had no significant associations between *CASC15* gene SNPs and glioma risk. However, in the stratified analysis, a significant decrease in risk of glioma was observed in subjects of <60 months old with the rs4712653 TT genotype, when compared to those with the CC/CT genotype (OR=0.12, 95% CI=0.02–0.91, *P*=0.041). **Conclusion:** The present study provides referential evidence on the association between the genetic predisposition of the *CASC15* gene and glioma risk in Chinese children. However, more well-designed case-control studies and functional experiments are needed to further explore the role of *CASC15* gene SNPs.

Key words: cancer susceptibility candidate 15; polymorphisms; glioma; susceptibility; Chinese

Glioma, the most common primary brain tumor, represents approximately 30% of all brain tumors[1–3]. Gliomas mainly arise from the neuroglial stem or progenitor cells[4, 5]. Furthermore, gliomas greatly vary in histology, from benign tumors that rarely undergo a malignant transformation with excellent overall survival to aggressive gliomas that rapidly progress. According to the World Health Organization (WHO) in 2010, low-grade gliomas (LGGs) are defined as WHO grade Ⅰ or Ⅱ, while high-grade gliomas (HGGs) are defined as WHO grade Ⅲ or Ⅳ[6]. Despite the multimodal treatment, patients with HGGs merely have 5-year survival rates of <20%[7].

Intensive attempts have been made to better understand the etiology of glioma. Various environmental factors, including excessive cell phone usage, some occupations, tobacco and ionizing radiation exposure, may be linked to the risk of glioma. Among these, ionizing radiation exposure is the only recognized causative factor for the risk of glioma[8–10]. However, merely a fraction of individuals exposed to ionizing radiation develop glioma, suggesting that

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glioma may be partially influenced by hereditary factors. Genome-wide association studies have by far discovered several glioma risk-associated susceptibility genes, including CCDC26, PHLDB1, TP53, EGFR, STK38L, RAB27A and CDKN2A-CDKN2B[11–15]. However, these identified genetic variants do not fully explain the genetic landscape of glioma. Much remains to be understood regarding the identity and relative contributions of genetic variants to the risk of glioma.

Long non-coding RNAs (lncRNAs) are a class of non-protein-coding transcripts that are longer than 200 nucleotides[16]. LncRNAs regulate diverse physiological and pathological processes through different mechanisms, including transcriptional and epigenetic regulation, genome rearrangement, genetic imprinting, and chromatin remodeling. LncRNAs and the polymorphisms are highly implicated in human disorders, especially in cancer[17, 18]. Cancer susceptibility candidate 15 (*CASC15*) is a highly active lncRNA. The *CASC15* gene was initially identified as a neuroblastoma susceptibility gene by a genome-wide association study (GWAS), and this was later assessed in other cancers. However, it has not been adequately investigated whether *CASC15* gene single nucleotide polymorphisms (SNPs) are associated with the risk of glioma. The present study aimed at determining the impact of *CASC15* gene SNPs on the risk of glioma.

1 MATERIALS AND METHODS

1.1 Sample Selection

The present study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. The entire work was carried out in strict compliance with the tenets of the Declaration of Helsinki. The associated clinicopathological information and samples were collected after receiving the written informed consent. The diagnosis of glioma of patients was confirmed by histopathology. All patients had no history of previous radiotherapy or chemotherapy before enrollment. The controls were comprised of healthy children who visited the hospital for health examination, and they were frequency-matched to the cases by age and gender. Controls that had other tumors, neurological diseases, congenital genetic diseases, and infectious diseases were excluded. All controls were selected from the same region, similar to the cases, during the same period. A total of 171 glioma cancer patients and 228 healthy controls, who attended the Guangzhou Women and Children's Medical Center and Sun Yat-sen University Cancer Center between 2005 and 2019, were enrolled for the present study. None of the study subjects had a blood relationship. All analyses were restricted to participants of genetically defined Chinese descent[19, 20].

1.2 Polymorphism Selection and Genotyping

Three *CASC15* gene SNPs (rs6939340 A>G, rs4712653 T>C and rs9295536 C>A) were chosen for the genotyping, which were previously identified using the GWAS approach[21]. The three selected SNPs in *CASC15* were previously identified to be associated with neuroblastoma susceptibility. Among the various detected SNPs in the GWAS, merely three selected SNPs (rs6939340, rs4712653, rs9295536) had a highly close linkage disequilibrium (LD) at chromosome 6p22, when compared to other SNPs. The close LD confers the potential of the three selected SNPs to alter cancer susceptibility. Thus, due to the close LD of these three SNPs, these were selected in *CASC15* to determine its association with glioma risk. Genomic DNA was isolated from peripheral blood using the TIANamp Blood DNA Kit (TianGen Biotech, China), according to the manufacturer's instructions. Subsequently, the DNA purity and concentration were evaluated using the Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). The primers and fluorescently labeled probes were purchased from Applied Biosystems (USA) to detect both wild-type and variant alleles. The SNP was genotyped using the TaqMan predesigned assay (Applied Biosystems, USA). Laboratory technicians were blinded to the sample information, including the identity of the replicate aliquots. PCR was performed for the genotyping, and the instrument was programmed with the following conditions: pre-read stage at 60°C for 30 s, holding stage at 95°C for 10 min, repeated 45 cycles each of denaturation at 95°C for 15 s, and annealing and extension at 60°C for one min. Then, standard run mode was selected, and the reaction volume (5 μL for each-well in the 384-well reaction plate) was added into the instrument. Finally, the reaction plate was loaded, and the run was initiated. For quality control, the case and control statuses were blinded during the genotyping process. In order to obtain a high accuracy rate for the genotyping results, strict quality control procedures were applied. Positive controls and negative controls (water) were used for each of the 384-well plates. A 100% concordant rate was achieved for the re-genotyping results of 10% of the randomly selected samples.

1.3 Statistical Analysis

In order to test the Hardy-Weinberg equilibrium (HWE) of SNPs, a goodness-of-fit χ^2-test was adopted based on the allele frequencies of the control subjects. A two-sided χ^2-test was used to compare the differences in the distribution of the demographic variables and SNP genotypes between cases and controls. The associations between the SNPs and risk of glioma and its subgroups were estimated using the odds ratio (OR) and 95% confidence interval (CI) calculated from unconditional logistic regression analyses. The adjusted ORs were calculated after the adjustment of

age and gender. A genotype that could decrease glioma risk was regarded as a protective genotype. In the present study, there were three protective genotypes: rs6939340 GA/AA, rs4712653 CT/TT, and rs9295536 CC. The carriers with one protective genotype indicate those that carried one protective genotype of the three SNPs, while carriers with 0–2 protective genotypes indicate those that carried zero, one, or two protective genotypes. Stratification analysis was further performed by age, gender, subtype and clinical stage, in order to determine whether the confounders impacted the distribution of genotypes on glioma risk. The statistical analyses were performed using the SAS statistical software package version 9.1 (SAS Institute Inc., USA), and significant differences were considered when $P<0.05$.

2 RESULTS

2.1 Population Characteristics

The age ($P=0.623$) and gender ($P=0.190$) distributions were similar between cases and controls, suggesting the adequate matching on these factors. The mean age was 63.40±47.72 months old for cases and 52.41±32.65 months old for controls. Among the cases, there were 125 (73.10%) astrocytic tumor cases, 24 (14.62%) ependymoma cases, 14 (8.19%) neuronal and mixed neuronal-glial tumor cases, and 7 (4.09%) embryonal tumor cases. According to the WHO staging system, 103 (60.23%) glioma cases were classified as stage Ⅰ, 28 (16.37%) glioma cases as stage Ⅱ, 15 (8.77%) glioma cases as stage Ⅲ, and 25 (14.62%) glioma cases were classified as stage Ⅳ (table S1).

2.2 Effect of *CASC15* Gene SNPs on Glioma Risk

The genotypes of *CASC15* SNPs in 171 cases and 228 controls, and their associations with glioma after adjusting for age and gender are presented in table 1. All three SNPs (rs6939340 A>G, rs4712653 T>C and rs9295536 C>A) were in HWE, and each had a value of 0.428, 0.890 and 0.890, respectively. None of the three SNPs was associated with glioma risk in the single locus analysis. Next, the rs6939340 GA/AA, rs4712653 CT/TT and rs9295536 CC genotypes were treated as protective genotypes. Compared to carriers with zero protective genotypes, carriers with 1, 2 and 3 protective genotypes failed to provide

Table 1 The *CASC15* gene polymorphisms and glioma susceptibility in Chinese children

Genotype	Cases (n=171)	Controls (n=228)	P^a	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P^b
rs6939340 G>A (HWE=0.428)							
GG	75 (43.86)	94 (41.23)		1.00		1.00	
GA	81 (47.37)	109 (47.81)		0.93 (0.61–1.42)	0.739	0.88 (0.57–1.34)	0.537
AA	15 (8.77)	25 (10.96)		0.75 (0.37–1.53)	0.430	0.67 (0.33–1.38)	0.277
Additive			0.462	0.89 (0.66–1.21)	0.462	0.84 (0.61–1.15)	0.274
Dominant	96 (56.14)	134 (58.77)	0.599	0.90 (0.60–1.34)	0.599	0.84 (0.56–1.26)	0.391
Recessive	156 (91.23)	203 (89.04)	0.470	0.78 (0.40–1.53)	0.471	0.72 (0.36–1.43)	0.347
rs4712653 C>T (HWE=0.890)							
CC	94 (54.97)	122 (53.51)		1.00		1.00	
CT	70 (40.94)	89 (39.04)		1.02 (0.68–1.54)	0.922	0.95 (0.62–1.44)	0.801
TT	7 (4.09)	17 (7.46)		0.54 (0.21–1.34)	0.182	0.50 (0.20–1.26)	0.141
Additive			0.434	0.88 (0.63–1.22)	0.433	0.83 (0.59–1.16)	0.270
Dominant	77 (45.03)	106 (46.49)	0.772	0.94 (0.63–1.40)	0.772	0.88 (0.58–1.31)	0.520
Recessive	164 (95.91)	211 (92.54)	0.162	0.53 (0.22–1.31)	0.168	0.51 (0.20–1.27)	0.147
rs9295536 A>C (HWE=0.890)							
AA	90 (52.63)	122 (53.51)		1.00		1.00	
AC	73 (42.69)	89 (39.04)		1.11 (0.74–1.68)	0.614	1.03 (0.68–1.57)	0.880
CC	8 (4.68)	17 (7.46)		0.64 (0.26–1.54)	0.319	0.60 (0.25–1.47)	0.263
Additive			0.759	0.95 (0.69–1.32)	0.759	0.90 (0.65–1.26)	0.536
Dominant	18 (47.37)	106 (46.49)	0.862	1.04 (0.70–1.54)	0.862	0.96 (0.64–1.44)	0.858
Recessive	163 (95.32)	211 (92.54)	0.258	0.61 (0.26–1.45)	0.261	0.59 (0.25–1.42)	0.240
Combined effect of protective genotypes							
0	69 (40.35)	91 (39.91)	0.500	1.00		1.00	
1	30 (17.54)	34 (14.91)		1.16 (0.65–2.08)	0.610	1.16 (0.65–2.10)	0.614
2	65 (38.01)	86 (37.72)		1.00 (0.64–1.56)	0.989	0.90 (0.57–1.43)	0.664
3	7 (4.09)	17 (7.46)		0.54 (0.21–1.38)	0.200	0.53 (0.21–1.35)	0.182
0–2	164 (95.91)	211 (92.54)		1.00		1.00	
3	7 (4.09)	17 (7.46)	0.162	0.53 (0.22–1.31)	0.168	0.53 (0.22–1.33)	0.178

OR: odds ratio; CI: confidence interval; HWE: Hardy-Weinberg equilibrium. [a]χ^2-test for genotype distributions between glioma patients and cancer-free controls; [b]adjusted for age and gender; [c]The protective genotypes were carriers with the rs6939340 GA/AA, rs4712653 CT/TT and rs9295536 CC genotypes.

protection against glioma. Furthermore, carriers with three protective genotypes failed to decrease the risk of glioma, when compared to carriers with 0–2 protective genotypes (supplemental fig. S1–S2, fig. 1).

2.3 Stratification Analysis

The relationship among SNP rs4712653, the protective genotypes and glioma risk was further explored by performing a stratified analysis, in terms of age, gender, subtype and clinical stage subgroups (table 2). Compared to the CC/CT genotype, rs4712653 TT was significantly associated with decreased risk of glioma (OR=0.12, 95% CI=0.02–0.91, *P*=0.041) in subjects of <60 months old. Compared to carriers with 0–2 protective genotypes, the three protective genotypes did not have an impact on the risk of glioma under any subgroup.

3 DISCUSSION

Candidate gene-based association studies have successfully mapped the susceptibility for various types of cancer. Accumulating evidence has indicated that various genes contribute to glioma susceptibility, but this could still not unearth the full pathogenesis of glioma. The present case-control study explored whether *CASC15* gene SNPs can modify the glioma risk in the Han Chinese population. The main findings of the present study were as follows: (1) individual or combined variants in the *CASC15* gene could not impact the glioma risk; (2) individuals with rs4712653 TT were significantly associated with decreased risk of glioma in the <60 months old subgroup.

The *CASC15* gene, which is also referred to as the

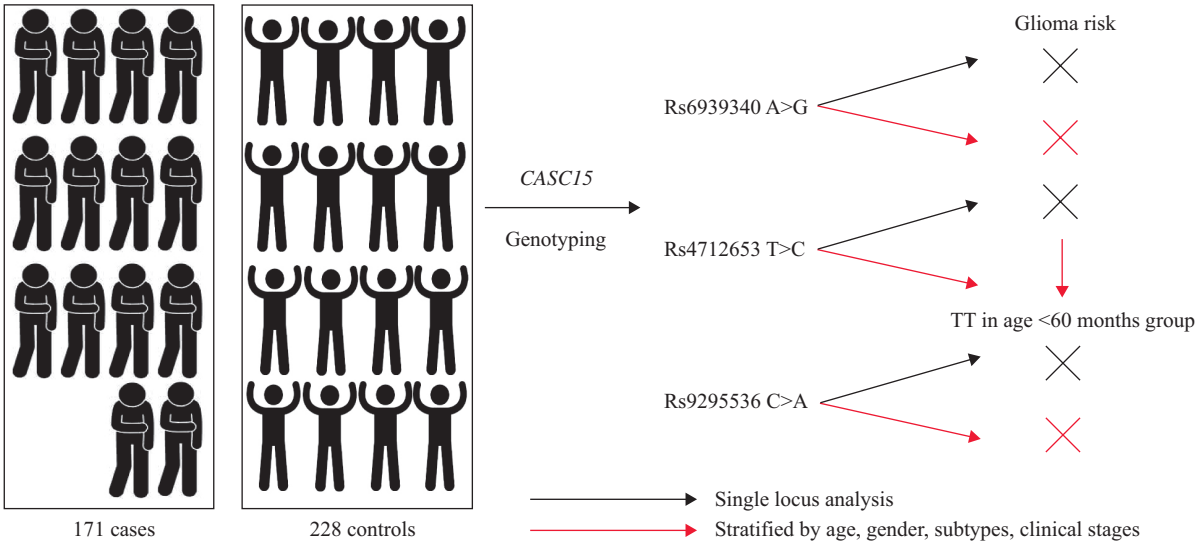

Fig. 1 Main results for the risk effects

Three *CASC15* gene SNPs (rs6939340 A>G, rs4712653 T>C and rs9295536 C>A) were genotyped from 171 glioma cases and 228 healthy controls. The only positive result was from stratification by age, gender, subtypes, clinical stages and implied that rs4712653 TT attenuated glioma risk in the subgroup of <60 months when compared to the CC/CT genotype

Table 2 Stratification analysis of risk genotypes with glioma susceptibility

Variables	rs4712653 (cases/controls)		AOR (95% CI)[a]	*P*[a]	Protective genotypes (cases/controls)		AOR (95% CI)[a]	*P*[a]
	CC/CT	TT			0–2	3		
Age (months)								
<60	84/108	1/11	0.12 (0.02–0.91)	0.041	83/108	2/11	0.23 (0.05–1.07)	0.062
≥60	80/103	6/6	1.35 (0.42–4.37)	0.619	81/103	5/6	1.13 (0.33–3.88)	0.841
Gender								
Females	78/86	3/7	0.45 (0.11–1.87)	0.272	78/86	3/7	0.52 (0.13–2.14)	0.364
Males	86/125	4/10	0.56 (0.17–1.85)	0.338	86/125	4/10	0.56 (0.17–1.85)	0.338
Subtypes								
Astrocytic tumors	119/211	6/17	0.58 (0.22–1.57)	0.286	120/211	5/17	0.51 (0.18–1.46)	0.211
Ependymoma	24/211	1/17	0.47 (0.06–3.74)	0.474	24/211	1/17	0.47 (0.06–3.74)	0.474
Neuronal and mixed	14/211	0/17	/	/	13/211	1/17	0.95 (0.12–7.83)	0.962
Embryonal tumors	7/211	0/17	/	/	7/211	0/17	/	/
Clinical stages								
Ⅰ+Ⅱ	124/211	7/17	0.67 (0.27–1.68)	0.396	124/211	7/17	0.70 (0.28–1.75)	0.448
Ⅲ+Ⅳ	40/211	0/17	/	/	40/211	0/17	/	/

AOR: adjusted odds ratio; CI: confidence interval. [a]Adjusted for age and gender, but the corresponding stratification factor was omitted

LINC00340 or FLJ22536 gene, spans approximately 530 kilobases on chromosome 6p22. The first GWAS for neuroblastoma conducted in 2008[21] identified a susceptibility locus at chromosome 6p22 in the newly identified lncRNA, and this was annotated as the *CASC15* gene[22]. This was predisposed to neuroblastoma development, specifically the more aggressive high-risk subset. The potential importance of *CASC15* gene SNPs in the etiology of cancer is supported by several avenues of research, other than the GWAS. This significant relationship was also verified in other populations, including Italian[23] and African-American[24] populations. Further investigation revealed that the interaction of *CASC15* and NBAT1 demonstrated to favor differentiation through regulatory interactions with important cancer-associated SOX9 and USP36 genes located on chromosome 17q, which is a region that often gains a high risk of neuroblastoma[25]. Gao *et al*[26] genotyped six SNPs (rs1555529, rs7740084, rs1928168, rs12212674, rs4712653 and rs9393266) in 494 cervical cancer cases and 504 unrelated controls from China. They found that the *CASC15* variant rs12212674, the A allele, was significantly associated with cervical cancer.

The *CASC15* expression was significantly upregulated in glioma samples, when compared to that in adjacent samples. The knockdown of *CASC15* has been shown to lead to the inhibition of cell proliferation, invasion and migration in glioma. Further experiments demonstrated that *CASC15* exerts its function via targeting miR-130b-3p[27]. Considering the implications of *CASC15* gene SNPs on the risk of other types of cancer, and the implications of *CASC15* on glioma, it is of significance to determine whether *CASC15* gene SNPs also impact glioma risk. In the present study, no significant relationships were detected between glioma risk and *CASC15* gene SNPs in the single or combined locus analysis (rs6939340 A>G, rs4712653 T>C and rs9295536 C>A) of 171 cases and 228 controls. However, when compared to the CC/CT genotype, rs4712653 TT was significantly associated with a decreased risk of glioma in subjects of <60 months old. It was assumed that such negative relationships might be due to the following reasons: (1) weak impact of SNPs; (2) relatively small sample size; (3) the phenotype was greatly modified by environmental factors. The investigators have carried out several studies on the role of *CASC15* gene SNPs in cancer risk. It was found that *CASC15* gene rs6939340 A>G, rs4712653 T>C and rs9295536 C>A are associated with significantly altered neuroblastoma susceptibility in Southern Chinese children, which comprised of 256 cases and 531 controls recruited from Guangdong province. Furthermore, the meta-analysis of the rs6939340 G>A polymorphism in 3302 neuroblastoma cases and 8279 controls revealed that carrying the rs6939340 A allele was associated with decreased neuroblastoma risk[28]. It was further verified that the rs6939340 G>A variant homozygote AA was associated with decreased neuroblastoma risk in 373 cases and 812 controls recruited from Henan and Guangdong provinces[29]. Therefore, the difference in cancer type cannot be neglected, when considering the exact role of *CASC15* gene SNPs in cancer risk.

There were several limitations in the present study. In order to achieve the power of 0.8, the investigators planned to collect 332 cases and 664 controls. As observed in the study, the sample size was relatively small, especially in the stratification analysis, which to some extent limited the ability to detect the associations with certain SNPs. The investigators are presently inviting more centers to collaborate with the present study, in order to enlarge the sample size. Furthermore, even though the confounding efforts of age and gender were taken into account in assessing the genetic factors to glioma risk, other potential confounders, such as dietary intake, living environment and cell phone exposure, were not considered. Thus, the conclusion should be interpreted with caution, and additional external validation is needed. Furthermore, the in-depth mechanism on how *CASC15* functions needs to be further explored in the future, and focus should be given on more polymorphisms, particularly potential functional genetic variations in *CASC15*, instead of only three SNPs. Selection bias also plagues the present hospital-based case-control study. That is, the enrolled subjects may not well-represent the population in the same region. Meanwhile, the conclusion obtained from Chinese participants may not be applied to other ethnicities due to the allele frequency variants among different populations. Finally, relevant biological experiments, such as the validation of related protein and RNA expression levels, should be further investigated.

In summary, the present study demonstrated that in the <60 months old subgroup, the *CASC15* gene polymorphisms were associated with decreased risk of developing glioma in the Chinese population. The present study reports a comprehensive analysis that sheds new light on the molecular basis of genetic risk for common cancer, greatly increasing the number of known *CASC15* gene risk SNPs. With the growing epidemiological evidence that links *CASC15* gene risk SNPs to glioma susceptibility, studies need to investigate the potential biological mechanisms by which *CASC15* gene risk SNPs contribute to the development of glioma.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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