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Investigation of the Relationship between *CMYC* Gene Polymorphisms and Glioma Susceptibility in Chinese Children

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ABSTRACT

Glioma is a common central nervous system tumors in children. *CMYC* has a range of functions that are disrupted in various tumor cells, and may contribute to the occurrence and development of glioma. Two *CMYC* single nucleotide polymorphisms (rs4645943C>T and rs2070583 A>G) were genotyped in 190 cases and 248 controls from Wenzhou and Guangzhou hospitals. After adjusting for age and sex, odds ratio and 95% confidence interval values were calculated by logistic regression to evaluate the correlation between *CMYC* gene polymorphisms and glioma risk; no significant associations were detected. These results require future validation in a larger sample cohort.

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KEYWORDS
Child; single nucleotide polymorphism; glioma; central nervous system neoplasms; cohort studies

Introduction

Glioma is an intracranial tumor that originates from glial cells, and one of the most common malignant tumors in children, accounting for 45%–55% of pediatric intracranial tumors (1,2). The overall annual incidence of glioma is 3–8 per 100000, and varies according to glioma subtype, among which astrocytoma is the most common, accounting for 17.4%, with ependymoma accounting for 10.2%, and oligodendroglioma for 5.8%. Treatment and prognosis also differ according to glioma subtype (3). At present, the primary treatment for glioma is surgical resection, usually combined with radiotherapy and chemotherapy (4,5). In recent years, there has been remarkable progress in glioma diagnosis, imaging, radiotherapy, chemotherapy, and neurosurgery; however, because of high rates of tumor recurrence, the poor prognosis of patients with malignant glioma has not been substantially improved (6,7). The median survival time of patients with glioblastoma is less than 14 months, and the one-year cumulative survival rate is less than 30% (8,9).

At present, the etiology of glioma is unclear, with potential risk factors including genetic factors, or specific gene polymorphisms, ionizing radiation, carcinogens of the nervous system, and virus infection, among others (3). Previous studies demonstrated that, compared with patients with an ins/ins genotype at *GAS5*, those with ins/del or del/del genotypes have significantly increased glioma risk (10). Further, *EGF* (11), *CCND1* c.870G>A (12), *pre-mir-146a* (13), *microRNA-196a* (14), *IL-12* (3), and *ERCC1* (15) have clear effects on glioma risk. Zhang et al. identified a significant association between the *XRCC1* Arg399Gln polymorphism and glioma risk specific to the Asian population (16). Nevertheless, current knowledge cannot fully explain the causes of glioma, and further study of the effects of other gene polymorphisms on the risk of glioma is required (17).

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Supplemental data for this article can be accessed here.

The *CMYC* protooncogene encodes an important transcription factor, which contributes to regulation of approximately 15% of human genes; participates in fundamental processes, including cell proliferation, metabolism, and differentiation (18,19); and is significantly up-regulated in numerous types of tumor (20–22). *CMYC* is up-regulated in patients with cholangiocarcinoma (CCA), and this can increase the conversion of glucose to serine and reduce levels of mitochondrial oxidative phosphorylation, resulting in poor patient survival and prognosis (20). In patients with pancreatic cancer, *PRMT5* promotes the proliferation and aerobic glycolysis of pancreatic cancer cells by silencing the expression of the tumor suppressor, *FBW7*, thereby increasing levels of *CMYC* (23). Further, *CMYC* expression is crucial to the metabolism and functional responses of natural killer cells (24). In addition, the *CMYC/EMT* axis can inhibit nasopharyngeal carcinoma metastasis, under the regulation of *hsa-miR-24*, thus improving the survival rate and prognosis of patients with this type of cancer (25). *CMYC* is also related to thyroid cancer (26); however, the relationship between *CMYC* gene polymorphism and glioma risk has not been studied.

At present, the etiology of glioma is unclear, and the functional roles of single nucleotide polymorphisms (SNPs) in glioma pathogenesis have not been studied. Therefore, the molecular mechanisms underlying glioma require further study and more sensitive and specific early biomarkers are needed to improve the quality of life of patients with glioma. Considering the important role of *CMYC* in the carcinogenesis of many types of tumor, we explored the relationship between *CMYC* gene polymorphisms and susceptibility to glioma in Chinese children.

Materials and methods

Study subjects

A total of 190 patients with glioma and 248 healthy controls were included in this study. All subjects were treated at Guangzhou Women and Children's Medical Center and The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The inclusion and exclusion criteria for subjects were described in detail in our previous reports (27,28). The case and control groups were matched for age and sex, and subjects were not close relatives. Before collection of blood samples, we discussed the study with parents or guardians of all participants and obtained their written informed consent. This study was approved by the Institutional Review Board of the centers in Wenzhou and Guangzhou.

Polymorphism selection and genotyping

Two potential functional polymorphisms of *CMYC* (rs4645943 C>T and rs2070583 A>G) were selected from the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP) and SNPinfo (http://snpinfo.niehs.nih.gov/snpfunc.htm) (29–31). rs4645943 may be linked to multiple SNPs. rs2070583 may act as a miRNA binding site. Genomic DNA samples were extracted from venous blood, and a TaqMan SNP genotyping assay conducted on an Applied Biosystems 7900 real-time PCR system. More detailed SNP selection and genotyping criteria were described in our previous reports (32–34).

Statistical analysis

We used the χ^2 test to analyze differences in the distribution of characteristics between the case and control groups. A goodness-of-fit chi-squared test was used to evaluate Hardy-Weinberg equilibrium (HWE) in the control group. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression analysis to detect any association with glioma risk. In addition, we also conducted stratified analysis to evaluate correlations between age, sex, and clinical stage with the risk of glioma. $P < 0.05$ was considered to indicate a significant result. All analyses in this study were conducted using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

In this study, we genotyped 190 cases and 248 controls from Wenzhou and Guangzhou. Specific demographic characteristics are presented in detail in Table S1.

Association between CMYC gene polymorphisms and glioma susceptibility

Tables 1 and 2 summarizes the genotype and allele frequencies of the selected polymorphisms in this case-control study and their relationship with the risk of glioma. In the control group, the genotype frequencies of the selected polymorphisms were all in accordance with Hardy–Weinberg equilibrium (HWE = 0.528 and 0.678 for rs4645943 C>T and rs2070583 A>G, respectively). In single locus analysis, we did not observe any statistically significant association between the frequencies of the two SNPs and risk of glioma. For rs4645943, compared with CC genotype carriers, CT genotype carriers (OR = 0.92, 95% CI = 0.62–1.37 $p = 0.688$) or TT genotype carriers (OR = 0.76, 95% CI = 0.35–1.64, $p = 0.481$) had no significant correlation with glioma risk. In addition, there was no significant association between rs4645943 and glioma risk in

Table 1. Genotype frequencies of *CMYC* polymorphisms in cases and controls.

Model	Genotype	Control (*n*, %)	Case (*n*, %)	OR[a](95%CI)	*p* Value[a]
rs4645943 HWE: $p = 0.528$					
Co-dominant	CC	120 (48.4)	96 (50.5)	1.00	
Heterozygote	CT	108 (43.6)	82 (43.2)	0.95 (0.64–1.41)	0.794
Homozygote	TT	20 (8.1)	12 (6.3)	0.75 (0.35–1.61)	0.461
Dominant	CC	120 (48.4)	96 (50.5)	1.00	
Recessive	CT + TT	128 (51.6)	94 (49.5)	0.92 (0.63–1.34)	0.657
	CC + CT	228 (91.9)	178 (93.7)	1.00	
	TT	20 (8.1)	12 (6.3)	0.77 (0.37–1.61)	0.486
Overdominant	CC + TT	140 (56.5)	108 (56.8)	1.00	
	CT	108 (43.6)	82 (43.2)	0.98 (0.67–1.44)	0.935
Allele	C	348 (70.2)	274 (72.1)	1.00	
	T	148 (29.8)	106 (27.9)	0.91 (0.68–1.22)	0.530
rs2070583 HWE: p = 0.678					
Co-dominant	AA	177 (71.4)	139 (73.2)	1.00	
Heterozygote	AG	64 (25.8)	48 (25.3)	0.96 (0.62–1.48)	0.836
Homozygote	GG	7 (2.8)	3 (1.6)	0.55 (0.14–2.15)	0.386
Dominant	AA	177 (71.4)	139 (73.2)	1.00	
	AG + GG	71 (28.6)	51 (26.8)	0.92 (0.60–1.40)	0.679
Recessive	AA + AG	241 (97.2)	187 (98.4)	1.00	
	GG	7 (2.8)	3 (1.6)	0.55 (0.14–2.17)	0.394
Overdominant	AA + GG	184 (74.2)	142 (74.7)	1.00	
	AG	64 (25.8)	48 (25.3)	0.97 (0.63–1.50)	0.897
Allele	A	418 (84.3)	326 (85.8)	1.00	
	G	78 (15.7)	54 (14.2)	0.89 (0.61–1.29)	0.535

HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval.

Table 2. Association between *CMYC* gene polymorphisms and glioma susceptibility in Chinese children.

Genotype	Cases ($N = 190$)	Controls ($N = 248$)	P^a	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)[b]	P^b
rs4645943 C>T (HWE = 0.528)							
CC	96 (50.53)	120 (48.39)		1.00		1.00	
CT	82 (43.16)	108 (43.55)		0.95 (0.64–1.41)	0.794	0.92 (0.62–1.37)	0.688
TT	12 (6.32)	20 (8.06)		0.75 (0.35–1.64)	0.461	0.76 (0.35–1.64)	0.481
Additive			0.487	0.90 (0.66–1.22)	0.487	0.90 (0.66–1.22)	0.486
Dominant	94 (49.47)	128 (51.61)	0.657	0.92 (0.63–1.34)	0.657	0.91 (0.62–1.33)	0.608
Recessive	178 (93.68)	228 (91.94)	0.486	0.77 (0.37–1.61)	0.487	0.80 (0.38–1.69)	0.555
rs2070583 A>G (HWE = 0.678)							
AA	139 (73.16)	177 (71.37)		1.00		1.00	
AG	48 (25.26)	64 (25.81)		0.96 (0.62–1.48)	0.836	0.98 (0.63–1.52)	0.922
GG	3 (1.58)	7 (2.82)		0.55 (0.14–2.15)	0.386	0.62 (0.16–2.46)	0.495
Additive			0.514	0.88 (0.61–1.29)	0.514	0.91 (0.62–1.33)	0.631
Dominant	51 (26.84)	71 (28.63)	0.679	0.92 (0.60–1.40)	0.679	0.94 (0.62–1.44)	0.783
Recessive	187 (98.42)	241 (97.18)	0.388	0.55 (0.14–2.17)	0.394	0.61 (0.15–2.40)	0.477
Combined effect of protective genotypes[c]							
0	93 (48.95)	119 (47.98)	0.594	1.00		1.00	
1	49 (25.79)	59 (23.79)		1.06 (0.67–1.69)	0.798	1.00 (0.62–1.61)	0.991
2	48 (25.26)	70 (28.23)		0.88 (0.56–1.39)	0.575	0.94 (0.74–1.18)	0.571
0–1	142 (74.74)	178 (71.77)		1.00		1.00	
2	48 (25.26)	70 (28.23)	0.489	0.86 (0.56–1.32)	0.489	0.89 (0.58–1.36)	0.581

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]Protective genotypes were carriers with rs4645943 CT/TT, rs2070583 AG/GG genotypes.

additive (OR = 0.90, 95% CI = 0.66–1.22 $p = 0.486$), dominant (OR = 0.91, 95% CI = 0.62–1.33 $p = 0.608$), or recessive models (OR = 0.80, 95% CI = 0.38–1.69 $p = 0.555$). For rs2070583, compared with AA genotype carriers, AG genotype carriers (OR = 0.98, 95% CI = 0.63–1.52 $p = 0.922$) or GG genotype carriers (OR = 0.62, 95% CI = 0.16–2.46, $p = 0.495$) had no significant correlation with glioma risk. In addition, there was no significant association between rs4645943 and glioma risk in additive (OR = 0.91, 95% CI = 0.62–1.33 $p = 0.631$), dominant (OR = 0.94, 95% CI = 0.62–1.44 $p = 0.783$), or recessive models (OR = 0.61, 95% CI = 0.15–2.40 $p = 0.477$).

Stratified analysis

We also conducted stratified analyses according to age, sex, glioma subtype, and clinical stage (Table 3); however, no significant associations were detected.

Haplotype analysis

As shown in the Table 4, we can see that none of the results are statistically significant.

Discussion

In this case-control study, we analyzed the association between two potential functional polymorphisms of *CMYC* and glioma risk in children. No association of either selected SNP (rs4645943 C>T and rs2070583 A>G) and glioma risk was detected in either whole cohort or stratified analyses.

The *CMYC* oncogene encodes a helix-loop-helix leucine zipper transcription factor, which is dysregulated in numerous cancers, and has

Table 3. Stratification analysis of risk genotypes with glioma susceptibility.

	rs4645943 (cases/controls)				rs2070583 (cases/controls)				Protective genotypes (cases/controls)			
Variables	CC	CT/TT	AOR (95% CI)[a]	[a]*p* Value	AA	AG/GG	AOR (95% CI)[a]	[a]*p* Value	0–2	3	AOR (95% CI)[a]	[a]*p* Value
Age, month												
<60	50/64	47/62	0.99 (0.58–1.68)	0.957	69/91	28/35	1.08 (0.60–1.94)	0.810	71/92	26/34	1.01 (0.56–1.85)	0.967
≥60	46/56	47/66	0.86 (0.49–1.53)	0.616	70/86	23/36	0.98 (0.47–1.73)	0.755	71/86	22/36	0.88 (0.46–1.70)	0.705
Gender												
Females	42/55	46/49	1.15 (0.65–2.05)	0.637	68/77	20/27	0.82 (0.42–1.60)	0.562	70/77	18/27	0.71 (0.36–1.40)	0.318
Males	54/65	48/79	0.75 (0.45–1.25)	0.265	71/100	31/44	1.04 (0.59–1.80)	0.904	72/101	30/43	1.03 (0.59–1.81)	0.919
Subtypes												
Astrocytic tumors	70/120	66/128	0.86 (0.56–1.32)	0.492	103/177	33/71	0.83 (0.51–1.36)	0.464	103/178	33/70	0.85 (0.52–1.38)	0.503
Ependymoma	20/120	13/128	0.69 (0.32–1.47)	0.333	25/177	8/71	0.83 (0.35–1.95)	0.668	27/178	6/70	0.60 (0.24–1.53)	0.283
Neuronal and mixed	5/120	9/128	1.65 (0.53–5.13)	0.384	7/177	7/71	2.36 (0.79–7.05)	0.123	7/178	7/70	2.44 (0.82–7.29)	0.109
Embryonal tumors	1/120	6/128	3.48 (0.38–31.85)	0.269	4/177	3/71	1.73 (0.33–9.01)	0.518	5/178	2/70	0.94 (0.16–5.69)	0.945
Clinical stages												
I	53/120	57/128	1.00 (0.63–1.57)	0.985	79/177	31/71	1.02 (0.62–1.68)	0.949	79/178	31/70	1.03 (0.63–1.71)	0.898
II	26/120	14/128	0.54 (0.26–1.09)	0.085	31/177	7/71	0.56 (0.23–1.33)	0.186	31/178	7/70	0.57 (0.24–1.35)	0.202
III	9/120	8/128	0.93 (0.34–2.53)	0.878	11/177	6/71	1.39 (0.49–3.94)	0.535	13/178	4/70	0.81 (0.25–2.61)	0.727
IV	10/120	15/128	1.20 (0.50–2.89)	0.690	18/177	7/71	0.99 (0.38–2.60)	0.980	19/178	6/70	0.85 (0.31–2.34)	0.757
I + II	77/120	71/128	0.85 (0.57–1.29)	0.449	110/177	38/71	0.88 (0.55–1.40)	0.588	110/178	38/70	0.90 (0.56–1.42)	0.641
III + IV	19/120	23/128	1.06 (0.54–2.07)	0.868	29/177	13/71	1.15 (0.56–2.36)	0.706	32/178	10/70	0.82 (0.38–1.77)	0.605

AOR: adjusted odds ratio; CI: confidence interval.
[a]Adjusted for age and gender, omitting the corresponding stratify factor.

Table 4. The frequency of inferred haplotypes of *CMYC* gene based on observed genotypes and their association with the risk of Glioma.

Genotypes		Cases	Controls				
rs4645943	rs2070583	(*n* = 190)	(*n* = 248)	OR (95% CI)	*p* Value	AOR (95% CI)[a]	[a]*p* Value
CC	AA	93 (48.95)	119 (47.98)	1.00		1.00	
CC	AG	3 (1.58)	0 (0.00)	NA	NA	NA	NA
CT	AA	44 (23.16)	52 (20.97)	1.08 (0.67–1.76)	0.748	0.01 (0.62–1.67)	0.955
CT	AG	38 (20.00)	55 (22.18)	0.88 (0.54–1.45)	0.625	0.88 (0.53–1.45)	0.610
CT	GG	0 (0.00)	1 (0.00)	NA	NA	NA	NA
TT	AA	2 (0.01)	6 (0.02)	0.427 (0.08–2.16)	0.304	0.398 (0.08–2.10)	0.277
TT	AG	7 (0.04)	8 (0.03)	1.12 (0.39–3.20)	0.833	1.13 (0.39–3.29)	0.818
TT	GG	3 (0.02)	6 (0.02)	0.64 (0.12–2.63)	0.535	0.68 (0.16–2.84)	0.597

[a]Obtained in logistic regression models with adjustment for age and gender.

differing effects on the growth, proliferation, metastasis, and angiogenesis of cancer cells (35,36). CMYC protein levels are strictly regulated by amino acids, and the transcription factor is very important for the metabolic and functional responses induced by *IL-2*/*IL-12* [24]. Liu et al. found that *CMYC* and *TIP110* can regulate the expression of one another, thereby playing an important role in hematopoiesis regulation (37). Chen et al. reported that *CMYC* can regulate *miR-200c*, to inhibit the tumor suppressor gene, *PTEN*, leading to cancer occurrence and progression (35). Further, Zhong et al. determined that *CMYC* can interact with SREBP2 and synergistically activate the expression of *HMGCR*, thus promoting the growth and migration of esophageal squamous cell carcinoma cells (38), while Luo et al. found that CMYC protein levels in human CCA cells were significantly higher than those in normal bile duct epithelial cells, and that expression of *CMYC* in human CCA cells could eliminate contact inhibition and promote their invasion and migration (39). Moreover, Zaharieva et al. discovered that changes in *CMYC* are related to low survival rate in patients with bladder cancer, with increased expression and amplification of *CMYC* closely related to development of late stage bladder cancer (40).

In our previous research, we determined that, compared with patients carrying the CT/TT genotypes of rs4645943 in *CMYC*, those with the CC genotype had a significantly reduced risk of neuroblastoma (30); however, no significant association was found between *CMYC* gene polymorphism and Wilms tumor risk (29).

Berberich et al. reported that CMYC can increase the resistance of glioblastoma cells to alectinib (41), while Odia et al. found that the CMYC protein has an adverse prognostic role in malignant glioma expressing mutant *IDH1* (42); however, there are no reported investigations of the relationship between *CMYC* gene polymorphisms and glioma risk. As the *CMYC* gene has important roles in various cancers, we collected blood samples from glioma cases and healthy controls to study the association between *CMYC* gene polymorphisms and glioma risk. Our results did not detect any significant association between *CMYC* polymorphisms and glioma risk, although this may be attributable to the low sample size included in this study.

Although we are the first group to study the association between *CMYC* gene polymorphisms and glioma risk, there remains scope for more comprehensive investigations. Further, while this was a multi-center study, due to the low incidence of glioma and the small number of cooperating hospitals, the sample size we collected was far from sufficient, potentially leading to some anomalies in our results. In addition, all subjects were from Wenzhou and Guangzhou; hence it may be inappropriate to apply our conclusions to patients from other regions and ethnic groups. Moreover, only two SNPs were analyzed in our research, and some important potentially functional SNPs may have been omitted. Finally, we did not investigate the relationships of gene-gene or gene-environment interactions with glioma risk. Nevertheless, our data indicate that *CMYC* may not be an independent factor influencing the risk of glioma.

Conclusions

In summary, our study did not find a significant correlation between *CMYC* gene polymorphisms and glioma risk. In the future, we will conduct further research based on a larger sample collection.

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Disclosure statement

The authors declare no conflicts of interest.

Data availability statement

All the data used to support the findings of this study are available from the corresponding author upon request.

Supplementary materials

Supplemental Table 1: frequency distribution of selected variables for Glioma cases and cancer-free controls. (Supplementary Materials)

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