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ORIGINAL RESEARCH

Association of *HMGA2* Polymorphisms with Glioma Susceptibility in Chinese Children

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Background: Glioma is a malignant central nervous system tumor in children, with poor outcomes and prognosis. *HMGA2* is a proto-oncogene with increased expression in various malignancies.

Methods: We explored the association of *HMGA2* polymorphisms with glioma susceptibility in Chinese children using a case-control study (191 cases, 248 controls). *HMGA2* single nucleotide polymorphisms (rs6581658 A>G; rs8756 A>C; rs968697 T>C) were genotyped using PCR-based TaqMan.

Results: Increased glioma susceptibility was associated with rs6581658 A>G; AG (adjusted odds ratio (OR) = 1.71, 95% confidence interval (CI) = 1.13–2.58, P = 0.010) or GG (adjusted OR = 3.12, 95% CI = 1.26–7.74, P = 0.014) genotype carriers had significantly raised glioma risk compared with AA genotype carriers. The rs6581658 AG/GG (adjusted OR = 1.85, 95% CI = 1.25–2.73, P = 0.002) and AA/GG (adjusted OR = 2.58, 95% CI = 1.05–6.33, P = 0.038) genotypes were associated with an increased risk of glioma relative to the AA genotype. Subjects with 2–3 risk genotypes had a significantly elevated risk (adjusted OR = 1.93, 95% CI = 1.31–2.84, P = 0.001) relative to those with 0–1 risk genotype.

Conclusion: *HMGA2* rs6581658 A>G is associated with glioma susceptibility in Chinese children.

Keywords: *HMGA2*, polymorphism, susceptibility, glioma

Introduction

Glioma is an intracranial tumor, that can be categorized into subtypes, as follows: diffuse astrocytic and oligodendroglial, other astrocytic, ependymal, or other glioma.[1] Brain cancer is the leading cause of cancer deaths in children.[2] From 2001 to 2010, the incidence of intracranial and intraspinal tumors in British children under the age of 15 was 1/1678, among which astrocytoma accounted for 40%.[3] The most common type of glioma in children is pilocytic astrocytoma. The 5-year survival rates for patients with many glioma subtypes are relatively high; however, the 5-year survival rate for specific types of glioma, such as glioblastoma (GBM), is only 14%.[3] Glioma occurrence can be influenced by ionizing radiation, allergic disease, and gene mutation. Although glioma can currently be treated using surgery, radiotherapy, and chemotherapy, its heterogeneity and invasiveness make it prone to drug resistance and recurrence. Hence, future prospects for treatment of pediatric brain tumors tend more towards molecularly targeted therapy.[4,5] Some genetic loci have been identified as associated with increased susceptibility to adult glioma, including *RTEL1*,[6] *CDKN2A/B*,[6] *PHLDB1*,[6] *CCDC26*[7] and *TERT*;[7] however, these risk loci cannot fully explain the molecular genetic contribution to glioma. Further,

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pediatric glioma has molecular and genetic differences from adult glioma.[8,9] Therefore, identification of suitable gene markers for application in pediatric glioma is increasingly important, and the influence of other genes on susceptibility to pediatric glioma warrants further study.

HMGA2 is a 160 kb gene located on chromosome 12. As an architectural transcription factor, *HMGA2* has three AT-hook domains that interact with AT-rich sequences in DNA minor grooves, leading to alteration of the chromatin architecture and modulation of the maintenance and assembly of enhancer complexes.[10] Although it is widely expressed in embryos, HMGA2 is not present in adults, except in stem cells. Further, it is expressed in tumor cells, including colon cancer,[11] lung cancer,[12] liver cancer,[13] thyroid tumor[14] and prostate cancer.[15] Therefore, *HMGA2* is considered to be a proto-oncogene that promotes the occurrence and development of tumors.[16]

HMGA2 expression is also increased in glioma.[17] Genomic single nucleotide polymorphisms (SNPs) are closely related to disease susceptibility and prognosis;[18,19] however, few studies have focused on the relationship between *HMGA2* SNPs and glioma. Our research explored the association of *HMGA2* polymorphisms with glioma susceptibility in Chinese children.

Materials and Methods

Patients and Controls

We selected participants from Guangzhou and Wenzhou, including 191 cases histopathologically diagnosed with glioma and a control group of 248 healthy children with no family history of cancer, who were matched for sex and age with those in the experimental group. The Institutional Review Board of two hospitals approved the study protocol (the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Guangzhou Women and Children's Medical Center). In accordance with the Declaration of Helsinki, all subjects or their guardians signed informed consent forms.

Polymorphism Selection and Genotyping

We investigated the potentially functional *HMGA2* polymorphisms and selected three *HMGA2* polymorphisms (rs6581658 A>G, rs8756 A>C, and rs968697 T>C) based on data obtained in the SNPinfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html) and dbSNP database (https://www.ncbi.nlm.nih.gov/snp/). The rs8756 A>C was located in 3′ untranslated region (UTR) of the *HMGA2* gene. It may affect microRNA binding affinity and subsequently affects expression and stabilization of *HMGA2* gene. The rs6581658 A>G and rs968697 T>C were located in the 5′ near gene region. Binding of transcription factors may be affected, which may influence the transcription of *HMGA2*. There was no significant linkage disequilibrium among the selected SNPs ($r^2 < 0.8$). All SNPs had minor allele frequencies > 5% and potential biological function. Genomic DNA was extracted from venous blood samples and genotyped by TaqMan real-time PCR. The principle of tagging SNP selection and the genotyping methods used were described in our previous publications.[20–22]

Statistical Analysis

Distributions of demographic characteristics and genotype frequencies in both groups and appropriate intergroup comparisons were assessed by chi-square analysis. Hardy-Weinberg equilibrium (HWE) was evaluated in the control group using the goodness-of-fit chi-square test, whereas the association between the *HMGA2* SNPs and glioma susceptibility was assessed by univariate and multivariate unconditional logistic regression analysis, to generate odds ratio (OR) and 95% confidence interval (CI) values. We performed stratified analysis, according to age, sex, glioma subtype, and clinical grade. The criterion for statistical significance was $P < 0.05$. All two-sided statistical analyses were performed using SAS version 9·1 (SAS Institute, Cary, NC, USA).

Results

Participant Characteristics

The general characteristics of subjects are presented in Table 1. All participants were < 168 months old, with mean ages of patients (n = 191) of 62.74 ± 47.28 months and of controls (n = 248) of 53.90 ± 33.47 months. The majority of tumors were of the astrocytic subtype. In the case group, 57.59%, 19.90%, 8.90%, and 13.09% of patients were at clinical grades I–IV, respectively; clinical grade data were unavailable for 0.52% of patients.

Relationship Between *HMGA2* SNPs and Glioma Risk

The detailed results are shown in Table 2. In analysis of the entire cohort, carriers of the rs6581658 AG genotype (adjusted OR = 1.71, 95% CI = 1.13–2.58, $P = 0.010$) or GG genotype (adjusted OR = 3.12, 95% CI = 1.26–7.74, $P = 0.014$) were found to have a significantly elevated risk

Table 1 Frequency Distribution of Selected Variables in Glioma Patients and Cancer-Free Controls

Variables	Cases (N=191)		Controls (N=248)		P^a
	No.	%	No.	%	
Age range, month	2.60–168.00		4.00–168.00		0.997
Mean ± SD	62.74 ± 47.28		53.90 ± 33.47		
<60	97	50.79	126	50.81	
≥60	94	49.21	122	49.19	
Gender					0.329
Female	89	46.60	104	41.94	
Male	102	53.40	144	58.06	
Subtypes					
Astrocytic tumors	136	71.20	/	/	
Ependymoma	33	17.28	/	/	
Neuronal and mixed neutonal-glial tumours	14	7.33	/	/	
Embryonal tumors	7	3.66	/	/	
NA	1	0.52	/	/	
WHO grades					
I	110	57.59	/	/	
II	38	19.90	/	/	
III	17	8.90	/	/	
IV	25	13.09	/	/	
NA	1	0.52	/	/	

Note: [a]Two-sided χ^2 test for distributions between glioma patients and cancer-free controls.
Abbreviations: SD, standard deviation; NA, not available.

of developing glioma compared with those with the AA genotype. Further investigation indicated that subjects with rs6581658 AG/GG (adjusted OR = 1.85, 95% CI = 1.25–2.73, P = 0.002) or AA/GG (adjusted OR = 2.58, 95% CI = 1.05–6.33, P = 0.038) genotypes had an increased risk of glioma relative to those with AA genotype. Moreover, we observed that individuals with 2–3 risk genotypes had a significantly elevated risk relative to those with 0–1 risk genotype (adjusted OR = 1.93, 95% CI = 1.31–2.84, P = 0.001).

Stratification Analysis

We next explored the effects of rs6581658 genotype and joint risk genotypes on glioma susceptibility following further stratification, according to age, sex, tumor subtype, and clinical grade. The results are presented in Table 3. The rs6581658 AG/GG genotypes significantly increased glioma susceptibility in children > 60 months old (adjusted OR = 2.07, 95% CI = 1.19–3.59, P = 0.010), males (adjusted OR = 2.07, 95% CI = 1.23–3.50, P = 0.007), patients with astrocytic tumor subtype (adjusted OR = 1.70, 95% CI = 1.10–2.64, P = 0.017), and those with ependymoma subtype (adjusted OR = 2.47, 95% CI = 1.17–5.21, P = 0.018), clinical grade I (adjusted OR = 1.77, 95% CI = 1.11–2.81, P = 0.016), grade IV (adjusted OR = 3.16, 95% CI = 1.29–7.69, P = 0.012), grade I+II (adjusted OR = 1.67, 95% CI = 1.10–2.55, P = 0.017) and grade III+IV (adjusted OR = 2.72, 95% CI = 1.38–5.33, P = 0.004).

On analysis of combination risk genotypes, we found that subjects with 2–3 risk genotypes had an increased glioma risk relative to those with 0–1 risk genotype, among the following subgroups: age < 60 months (adjusted OR = 1.97, 95% CI = 1.15–3.38, P = 0.014), age ≥ 60 months (adjusted OR = 2.01, 95% CI = 1.15–3.51, P = 0.014), males (adjusted OR = 1.70, 95% CI = 1.01–2.86, P = 0.046), patients with astrocytic tumors (adjusted OR = 1.89, 95% CI = 1.22–2.92, P = 0.004), patients with ependymoma (adjusted OR = 2.18, 95% CI = 1.01–4.68, P = 0.046) and children at clinical grade I (adjusted OR = 1.76, 95% CI = 1.10–2.79, P = 0.017), grade III (adjusted OR = 4.11, 95% CI = 1.29–13.15, P = 0.017), grade I+II (adjusted OR = 1.74, 95% CI = 1.15–2.64, P = 0.009), and grade III+IV (adjusted OR = 3.00, 95% CI = 1.43–6.29, P = 0.004).

Discussion

Here, we studied the association of *HMGA2* polymorphisms with glioma susceptibility in Chinese children. The relationship between these three gene polymorphisms and glioma susceptibility has not been studied previously. We found that rs6581658 AG/GG was associated with a significantly increased risk of susceptibility to glioma.

HMGA2 promotes cancer progression through several functions: promoting cell proliferation and metastasis, influencing the cell cycle, inhibiting apoptosis, and conferring stem cell characteristics.[23] HMGA2 overexpression can promote the migration and invasion of pancreatic cancer cells,[24] and HMGA2 can inhibit apoptosis and promote cell proliferation in breast cancer, as well as conferring stem cell-like features, whereas knocking out HMGA2 led to cell cycle arrest at G2/M, reducing tumor invasiveness.[25] Further, HMGA2 overexpression reduced the sensitivity of pancreatic cancer cells to the standard first-line drug, gemcitabine.[26] *HMGA2* is regulated as a downstream target of many miRNAs and is involved in progression of various tumors. *HMGA2* can also promote epithelial-mesenchymal transition of esophageal squamous

Table 2 *HMGA2* Gene Polymorphisms and Glioma Susceptibility in Chinese Children

Genotype	Cases (N=191)	Controls (N=248)	*P* [a]	Crude OR (95% CI)	*P*	Adjusted OR (95% CI) [b]	*P* [b]
rs6581658 A>G (HWE=0.933)							
AA	101 (52.88)	168 (67.74)		1.00		1.00	
AG	76 (39.79)	72 (29.03)		**1.76 (1.17–2.64)**	**0.007**	**1.71 (1.13–2.58)**	**0.010**
GG	14 (7.33)	8 (3.23)		**2.91 (1.18–7.18)**	**0.020**	**3.12 (1.26–7.74)**	**0.014**
Additive			0.0008	**1.73 (1.25–2.40)**	**0.0009**	**1.73 (1.25–2.41)**	**0.001**
Dominant	90 (47.12)	80 (32.26)	0.002	**1.87 (1.27–2.76)**	**0.002**	**1.85 (1.25–2.73)**	**0.002**
Recessive	177 (92.67)	240 (96.77)	0.051	2.37 (0.97–5.78)	0.057	**2.58 (1.05–6.33)**	**0.038**
rs8756 A>C (HWE=0.513)							
AA	161 (84.29)	214 (86.29)		1.00		1.00	
AC	29 (15.18)	32 (12.90)		1.21 (0.70–2.07)	0.501	1.25 (0.72–2.16)	0.427
CC	1 (0.52)	2 (0.81)		0.67 (0.06–7.39)	0.740	0.62 (0.06–6.88)	0.693
Additive			0.638	1.13 (0.69–1.85)	0.638	1.15 (0.70–1.90)	0.582
Dominant	30 (15.71)	34 (13.71)	0.557	1.17 (0.69–2.00)	0.557	1.21 (0.71–2.07)	0.490
Recessive	190 (99.48)	246 (99.19)	0.721	0.65 (0.06–7.19)	0.723	0.60 (0.05–6.68)	0.676
rs968697 T>C (HWE=0.707)							
TT	141 (73.82)	191 (77.02)		1.00		1.00	
TC	47 (24.61)	54 (21.77)		1.18 (0.75–1.84)	0.471	1.17 (0.75–1.84)	0.492
CC	3 (1.57)	3 (1.21)		1.36 (0.27–6.81)	0.713	1.28 (0.25–6.51)	0.767
Additive			0.430	1.18 (0.79–1.76)	0.430	1.16 (0.78–1.74)	0.467
Dominant	50 (26.18)	57 (22.98)	0.440	1.19 (0.77–1.84)	0.440	1.18 (0.76–1.83)	0.469
Recessive	188 (98.43)	245 (98.79)	0.747	1.30 (0.26–6.53)	0.747	1.23 (0.24–6.25)	0.801
Combined effect of risk genotypes [c]							
0–1	69 (36.13)	131 (52.82)		1.00		1.00	
2–3	122 (63.87)	117 (47.18)	0.0005	**1.98 (1.35–2.91)**	**0.0005**	**1.93 (1.31–2.84)**	**0.001**

Notes: The results were in bold, if the 95% CI excluded 1 or *p*-values less than 0.05; [a]χ^2 test for genotype distributions between glioma patients and cancer-free controls; [b]Adjusted for age and gender; [c]Risk genotypes were carriers with rs6581658 AG/GG, rs8756 AC/AA, rs968697 TC/CC genotypes.
Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

cell carcinoma, which can be targeted by binding of *miR490-3p* to its 3′ untranslated region.[27] In addition, *HMGA2* can be regulated via the *miR-503-5p*/*HMGA2* and *miR-150-5p*/*HMGA2* axes, to promote the progression of gastric and breast cancers, respectively.[28,29] *HMGA2* can also be targeted by *miR-493* to inhibit tongue squamous cell carcinoma.[30]

In addition to the cancers mentioned above, HMGA2 is also associated with glioma. HMGA2 expression is up-regulated in glioma,[31] which is associated with tumorigenicity, since increased HMGA2 in vivo can promote the glioma growth, and the increased clonogenicity in vitro also supports the role of HMGA2 in tumor initiation.[32] Further, *HMGA2* expression, a target gene of *miR-107*, could be enhanced by the long non-coding RNA LINC00152 through regulation of *miR-107* expression and promotion of glioma occurrence.[33] Moreover, HMGA2 expression level is associated with glioma grade. Compared with diffuse astrocytoma, HMGA2 expression is higher in glioblastoma multiforme and anaplastic astrocytoma[34] and increased HMGA2 expression suggests worse prognosis. HMGA2 is also associated with glioma malignant degree. In GBM cell lines, HMGA2 increased GBM cell invasion, clonogenicity, and tumorigenicity.[32] HMGA2 may also activate *MMP2*, which can increase glioma invasion.[35] In contrast, *HMGA2* suppression inhibits glioma growth. *HMGA2* is suppressed by *let-7g-5p* and down-regulation of HMGA2 expression can promote GBM tumor cell apoptosis and inhibit their invasion, indicating that *HMGA2* is a potential novel target gene in GBM.[36] In addition, *HMGA2* can be targeted by *miR-370-3p*, which inhibits glioma cell growth and

Table 3 Stratification Analysis of Risk Genotypes with Glioma Susceptibility

Variables	rs6581658 (Cases/Controls)		AOR (95% CI) [a]	*P* [a]	Risk Genotypes (Cases/Controls)		AOR (95% CI) [a]	*P* [a]
	AA	AG/GG			0–1	2–3		
Age, month								
<60	55/87	42/39	1.72 (0.99–3.00)	0.054	37/69	60/57	**1.97 (1.15–3.38)**	**0.014**
≥60	46/81	48/41	**2.07 (1.19–3.59)**	**0.010**	32/62	62/60	**2.01 (1.15–3.51)**	**0.014**
Gender								
Females	50/71	39/33	1.60 (0.88–2.89)	0.123	31/58	58/46	2.26 (1.25–4.07)	0.007
Males	51/97	51/47	**2.07 (1.23–3.50)**	**0.007**	38/73	64/71	**1.70 (1.01–2.86)**	**0.046**
Subtypes								
Astrocytic tumors	74/168	62/80	**1.70 (1.10–2.64)**	**0.017**	49/131	87/117	**1.89 (1.22–2.92)**	**0.004**
Ependymoma	16/168	17/80	**2.47 (1.17–5.21)**	**0.018**	12/131	21/117	**2.18 (1.01–4.68)**	**0.046**
Neuronal and mixed	6/168	8/80	2.87 (0.95–8.64)	0.061	5/131	9/117	2.07 (0.67–6.43)	0.208
Embryonal tumors	4/168	3/80	1.59 (0.31–8.16)	0.577	2/131	5/117	1.83 (0.32–10.68)	0.500
Clinical stages								
I	59/168	51/80	**1.77 (1.11–2.81)**	**0.016**	42/131	68/117	**1.76 (1.10–2.79)**	**0.017**
II	23/168	15/80	1.36 (0.67–2.75)	0.390	15/131	23/117	1.71 (0.85–3.44)	0.134
III	8/168	9/80	2.56 (0.94–6.98)	0.066	4/131	13/117	**4.11 (1.29–13.15)**	**0.017**
IV	10/168	15/80	**3.16 (1.29–7.69)**	**0.012**	7/131	18/117	2.49 (0.97–6.39)	0.058
I+II	82/168	66/80	**1.67 (1.10–2.55)**	**0.017**	57/131	91/117	**1.74 (1.15–2.64)**	**0.009**
III+IV	18/168	24/80	**2.72 (1.38–5.33)**	**0.004**	11/131	31/117	**3.00 (1.43–6.29)**	**0.004**

Notes: The results were in bold, if the 95% CI excluded 1 or *p*-values less than 0.05; [a]Adjusted for age and gender, omitting the corresponding stratify factor.
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

invasion[37] and is, therefore, a potential target for glioma therapy.

Many researchers have focused on the relationship between *HMGA2* gene SNPs and susceptibility to different conditions. For example, *HMGA2* SNPs are related to height. *HMGA2* rs1042725 influences height variability in European populations, and the association is more pronounced in individuals with small size for gestational age (SGA).[38] Further, *HMGA2* rs7968902 is significantly correlated with the height of the Japanese population.[39] We previously explored the effect of *HMGA2* SNPs on susceptibility to different diseases and found that *HMGA2* polymorphisms weakly influence Wilms tumor.[40] In addition, the *HMGA2* SNPs, rs8756A>C and rs968697T>C, are associated with lower susceptibility to neuroblastoma[41] and hepatoblastoma,[42] respectively.

This is the first study to investigate the relationship between *HMGA2* SNPs and glioma susceptibility. We found that the relationship is highly significant. Nevertheless, this study has limitations. First, the prevalence of glioma is low, and the sample size was relatively moderate, which may affect the statistical power of the analysis. Second, we only selected three *HMGA2* SNPs, while other *HMGA2* SNPs may also be related to glioma susceptibility. Third, the sample was from Chinese children alone, therefore, the results may not be relevant to other populations. Fourth, this study was retrospective; therefore, selection bias cannot be avoided. Finally, environmental factors, which can also influence glioma susceptibility, were not taken into consideration.

Conclusion

We analyzed *HMGA2* SNPs and the risk of gliomas in the Chinese Han population. Our study is the first to identify a role for *HMGA2* gene polymorphisms in glioma susceptibility. The results contribute to understanding of glioma etiology; however, further studies with a larger sample size, increased representation of other ethnic groups, and that consider interactions between the environment, genetics, and other factors, are required.

Abbreviations

OR, odds ratio; CI, confidence interval; GBM, glioblastoma; SNP, genomic single nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium.

Ethics Approval and Informed Consent

The Institutional Review Board of two hospitals approved the study protocol (the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Guangzhou Women and Children's Medical Center). All subjects or their guardians signed informed consent forms.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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