Original Article

The correlation between polymorphisms in the *XPC* gene and glioma susceptibility in a Chinese pediatric population

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Background: A previous study revealed that single nucleotide polymorphisms (SNPs) in coding genes play a key role in tumorigenesis, genetic disorders, and drug resistance. Xeroderma pigmentosum group C (*XPC*) protein is a key DNA damage recognition factor that is required for maintaining the genomic stability. However, the correlation between *XPC* polymorphisms and glioma susceptibility is still unclear. Hence, this study aimed to investigate the correlation between *XPC* polymorphisms and pediatric glioma susceptibility.

Methods: A total of 399 participants (171 glioma patients and 228 controls) were enrolled to evaluate the correlation between *XPC* polymorphism and pediatric glioma susceptibility. The count data of two groups was analyzed by chi-squared (χ^2) test. Moreover, logistic regression was used to assess the strength of *XPC* polymorphisms associated with glioma susceptibility.

Results: We identified that *XPC* rs1870134 G>C reduced pediatric glioma susceptibility. Compared to participants with rs1870134 GG/GC genotypes, those with rs1870134 CC genotype had a significantly lower risk for glioma [adjusted odds ratio (AOR) =0.10, 95% confidence interval (CI): 0.01 to 0.78, P=0.028]. Patients with 4–5 genotypes have higher risk of glioma than those with 0–3 genotypes (AOR =1.59, 95% CI: 1.04 to 2.43, P=0.031). The stratified analysis showed that the risky effects of rs2228000 CT/TT genotypes and rs2229090 GC/CC genotypes were more predominant among children aged ≥60 months, astrocytic tumors, and clinical stage I.

Conclusions: We found for the first time that *XPC* polymorphisms had a statistically significant correlation with pediatric glioma susceptibility in a Chinese population. The *XPC* rs2228000 CT/TT and rs2229090 GC/CC genotypes could both increase the risk of pediatric glioma in subgroups with females, astrocytic tumors, and clinical stage I. The *XPC* polymorphism has potential to be a useful adjunct method to screen pediatric glioma.

Keywords: Pediatric glioma; xeroderma pigmentosum group C (*XPC*); susceptibility; polymorphism.

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Introduction

Brain glioma is a common type of primary malignant tumor accounting for 40–50% of central nervous system (CNS) tumors in adults and children (1). The average incidence rate of glioma is 6.6 per 100,000 individuals (2), and the incidence is even higher in children. Unfortunately, from 2005 to 2018, the incidence and mortality of glioma in China showed an upward trend (3,4). Although diagnosis and treatment levels have been improved to some extent, the prognosis of glioma patients is still not satisfactory (5,6), especially for diffuse midline gliomas (7). To date, pediatric high-grade glioma is the main cause of cancer death in children, with a 5-year survival rate of less than 20% (8). Therefore, exploration of the related risk factors of pediatric glioma is of great significance for improving the prognosis of glioma.

Tumor susceptibility refers to the tendency of different populations and individuals to suffer from certain malignant tumors under the influence of external environment due to different genetic structure. Single nucleotide polymorphism (SNP), the most common type of DNA polymorphism, is the substitution of a single nucleotide in a genome (9). Increasing studies have shown that SNPs are involved in the occurrence of various diseases, such as type 2 diabetes mellitus (T2DM) and tumors (10,11). They have been used in the early diagnosis of a variety of tumors, such as tumor necrosis factor-α (TNF-α) (11,12). Moreover, SNPs can also be used as an important indicator to identify tumor-genetically susceptible populations.

Previous studies have confirmed that the DNA repair system plays a key role in maintaining the integrity of the cellular genome (13). In DNA repair pathways, nucleotide excision repair (NER) functions through a "cut-and-patch" mechanism by excising and removing a short fragment of DNA of about 24–32 nucleotides containing the damaged nucleotides. The DNA damage repair pathway can maintain the stability of the cell genome and prevent gene mutation and tumorigenesis (14). The xeroderma pigmentosum group C (*XPC*) gene is located on chromosome 3p25 and codes for a 940 amino acid protein. It plays a key role in initiating the NER pathway by associating with HR23B to form a complex that recognizes sites of damaged DNA (15). The *XPC* gene may also actively participate in base excision repair (BER) by ablating G/T mismatches to suppress spontaneous mutations. This DNA repair is an important way of maintaining the stability of genetic information in the human body (16). There have been great concerns that an association between *XPC* polymorphisms and risk of diseases including chronic myeloid leukemia advanced non-small cell lung cancer (17,18). Previous studies have reported about the correlation between polymorphisms in the XPC gene and genetic susceptibility (19), but there is no research on the relationship between XPC gene and genetic susceptibility of glioma. Especially, the correlation between *XPC* polymorphisms and pediatric glioma is still unclear. Thus, this case-control study predominantly focused on analyzing the correlation between *XPC* gene polymorphism and glioma susceptibility in Chinese children through a population of 339 patients. We present the following article in accordance with the STREGA reporting checklist (available at https://dx.doi.org/10.21037/tp-21-301).

Methods

Study subjects

In this study, a total of 171 glioma patients and 228 tumor-free controls from South China were enrolled. Healthy children were included in the study as the controls and matched with contemporaneous cases by age and gender. We collected clinical information including patients' age, gender, and clinical stages. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (No. 2016021650) and informed consent was taken from all the patients.

Polymorphism analysis

Firstly, the functional *XPC* gene polymorphisms were retrieved from dbSNP database (https://www.ncbi.nlm.nih.gov/snp/) and SNPinfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html). The screening criteria were as the previous study described (20). Notably, we selected SNPs from noncoding region, UTR (5' and 3') and introns regions, and finally obtained five SNPs including rs2228001 A>C, rs2228000 C>T, rs2607775 C>G, rs1870134 G>C, and rs2229090 G>C.

Secondly, 2 mL of peripheral blood was drawn from each participant, and genomic DNA was isolated using the TIANamp Blood DNA Kit (TianGen Biotech Co., Ltd., Beijing, China). The *XPC* genotyping was conducted by TaqMan real-time quantitative polymerase chain reaction (qPCR). In addition, to make the results reliable, another

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10% of patients' samples were randomly selected for secondary testing to ensure that the results of all samples were consistent.

Statistical analysis

All data were analyzed using SAS software (version 9.4 SAS Institute Inc., Cary, NC, USA). The Hardy-Weinberg equilibrium (HWE) of all SNPs in the controls was tested by the goodness-of-fit chi-squared (χ^2) test, and the count data of two groups was analyzed by χ^2 test. Logistic regression was further used to analyze the correlation between *XPC* genotypes and glioma susceptibility. The odds ratio (OR), 95% confidence interval (CI), and the P value were corrected for age and gender. A two-sided P<0.05 was deemed statistically significant.

Results

Baseline characteristics

In this case-control study, a total of 399 age/gender-matched participants (171 cases with glioma and 228 non-tumor controls) were enrolled. The clinicopathological characteristics are summarized in Table S1. The mean ages of cases with glioma and controls were 63.40±47.72 and 52.41±32.65 months, respectively. There were more males in this study than female participants (56.4% *vs.* 43.6%). However, there were no statistical differences in age (P=0.623) and gender (P=0.190). Among the 171 participants with glioma, there were 131 (76.6%) cases of glioma grade I–II. The two groups did not statistically differ in age (P=0.623) and gender (P=0.190).

The correlation between XPC polymorphisms and glioma susceptibility in Chinese pediatric population

All participants were genotyped. The genotype frequency and percentage of *XPC* polymorphism are shown in *Table 1*. The genotype distributions of five SNPs were consistent with HWE in controls (P=0.845 for rs2228001 A>C, P=0.764 for rs2228000 C>T, P=0.583 for rs2607775 C>G, P=0.121 for rs1870134 G>C, P=0.215 for rs2229090 G>C). From the single-locus analysis, we found that *XPC* rs1870134 G>C was significantly correlated with low risk glioma susceptibility. Compared to participants with rs1870134 GG/GC genotypes, those with rs1870134 CC genotype had a remarkably lower risk for glioma [adjusted OR (AOR) =0.10, 95% CI: 0.01 to 0.78, P=0.028]. The distribution of *XPC* rs1870134 genotype was different between the cases and the control group. In the cases group, participants with GG, GC, and CC genotypes were 116 (67.84%), 54 (31.58%), and 1 (0.58%). However, participants with GG, GC, and CC genotypes were 146 (64.04%), 68 (29.82%), and 14 (6.14%) in the control group. The proportions of CC genotype in the two groups were significantly different. The above results suggested that *XPC* rs1870134 CC genotype may reduce the risk of pediatric glioma in recessive models.

Next, we further assessed the combined effect of the five genotypes of *XPC* on glioma susceptibility. The results revealed that patients with 4–5 genotypes were at remarkably higher risk of developing glioma than those with 0–3 genotypes (AOR =1.59, 95% CI: 1.04 to 2.43, P=0.031).

Stratification analysis

We also further assessed the effects of rs2228000 C>T polymorphism, rs2229090 G>C polymorphism, and combined risk genotypes on the glioma risk in different subgroups. *Table 2* summarizes the genotypes frequencies in different subgroups. After adjustment for potential confounders, we observed that rs2228000 C>T polymorphism increased the risk of glioma susceptibility in several subgroups (females subgroup: CC *vs.* CT/TT: AOR =1.93, 95% CI: 1.01 to 3.67, P=0.047; astrocytic tumors subgroup: CC *vs.* CT/TT: AOR =1.73, 95% CI: 1.07 to 2.80, P=0.026; clinical stage I subgroup: CC *vs.* CT/TT: AOR =1.96, 95% CI: 1.16 to 3.29, P=0.012). In addition, similar results were obtained in rs2229090 G>C polymorphism (females subgroup: GG *vs.* GC/CC: AOR =2.13, 95% CI: 1.10 to 4.11, P=0.025; astrocytic tumors subgroup: GG *vs.* GC/CC: AOR =2.05, 95% CI: 1.24 to 3.38, P=0.005; clinical stage I subgroup: GG *vs.* GC/CC: AOR =2.31, 95% CI: 1.34 to 3.98, P=0.003; clinical stage II subgroup: GG *vs.* GC/CC: AOR =1.63, 95% CI: 1.02 to 2.61, P=0.041).

When the risk genotypes were combined, we found that patients with 4–5 risk genotypes had higher risk of glioma than those with 0–3 risk genotypes among the following subgroup: age ≥60 months (AOR =1.86, 95% CI: 1.02 to 3.38, P=0.043), females (AOR =2.34, 95% CI: 1.22 to 4.50, P=0.011), astrocytic tumors (AOR =2.07, 95% CI: 1.27 to 3.37, P=0.004), clinical stage I (AOR =2.38, 95% CI: 1.40 to 4.05, P=0.002) and clinical stage I + II group

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Table 1 Association between *XPC* gene polymorphisms and glioma susceptibility in Chinese children

Genotype	Cases (n=171), n (%)	Controls (n=228), n (%)	P value[a]	Crude OR (95% CI)	P value	AOR (95% CI)[b]	P value[b]
rs2228001 A>C (HWE =0.845)							
AA	62 (36.26)	89 (39.04)		1.00		1.00	
AC	87 (50.88)	108 (47.37)		1.16 (0.75–1.78)	0.508	1.10 (0.71–1.70)	0.672
CC	22 (12.87)	31 (13.60)		1.02 (0.54–1.92)	0.954	0.94 (0.49–1.79)	0.849
Additive			0.764	1.05 (0.78–1.41)	0.763	1.00 (0.74–1.35)	0.989
Dominant	109 (63.74)	139 (60.96)	0.571	1.13 (0.75–1.70)	0.571	1.06 (0.70–1.61)	0.773
Recessive	149 (87.13)	197 (86.40)	0.831	0.94 (0.52–1.69)	0.832	0.89 (0.49–1.62)	0.702
rs2228000 C>T (HWE =0.764)							
CC	57 (33.33)	92 (40.35)		1.00		1.00	
CT	88 (51.46)	104 (45.61)		1.37 (0.88–2.11)	0.161	1.36 (0.87–2.11)	0.176
TT	26 (15.20)	32 (14.04)		1.31 (0.71–2.42)	0.387	1.36 (0.73–2.53)	0.339
Additive			0.237	1.19 (0.89–1.59)	0.237	1.21 (0.90–1.62)	0.215
Dominant	114 (66.67)	136 (59.65)	0.152	1.35 (0.90–2.05)	0.152	1.36 (0.89–2.06)	0.154
Recessive	145 (84.80)	196 (85.96)	0.743	1.10 (0.63–1.92)	0.742	1.14 (0.65–2.01)	0.653
rs2607775 C>G (HWE =0.583)							
CC	164 (95.91)	212 (92.98)		1.00		1.00	
CG	6 (3.51)	16 (7.02)		0.49 (0.19–1.27)	0.139	0.47 (0.18–1.24)	0.125
GG	1 (0.58)	0 (0.00)		–	–	–	–
Additive			0.352	0.67 (0.29–1.56)	0.355	0.67 (0.28–1.57)	0.354
Dominant	7 (4.09)	16 (7.02)	0.215	0.57 (0.23–1.41)	0.220	0.56 (0.22–1.40)	0.211
Recessive	170 (99.42)	228 (100.00)	0.248	–	–	–	–
rs1870134 G>C (HWE =0.121)							
GG	116 (67.84)	146 (64.04)		1.00		1.00	
GC	54 (31.58)	68 (29.82)		1.00 (0.65–1.54)	0.998	1.01 (0.65–1.56)	0.984
CC	1 (0.58)	14 (6.14)		0.09 (0.01–0.69)*	0.021*	0.10 (0.01–0.78)*	0.028*
Additive			0.098	0.74 (0.51–1.06)	0.099	0.75 (0.52–1.09)	0.129
Dominant	55 (32.16)	82 (35.96)	0.429	0.84 (0.56–1.28)	0.429	0.86 (0.56–1.31)	0.473
Recessive	170 (99.42)	214 (93.86)	0.004	0.09 (0.01–0.69)*	0.021*	0.10 (0.01–0.78)*	0.028*
rs2229090 G>C (HWE =0.215)							
GG	51 (29.82)	88 (38.60)		1.00		1.00	
GC	88 (51.46)	100 (43.86)		1.52 (0.97–2.38)	0.068	1.55 (0.99–2.44)	0.058
CC	32 (18.71)	40 (17.54)		1.38 (0.77–2.46)	0.275	1.43 (0.79–2.56)	0.236
Additive			0.165	1.22 (0.92–1.62)	0.166	1.24 (0.93–1.65)	0.138
Dominant	120 (70.18)	140 (61.40)	0.069	1.48 (0.97–2.26)	0.069	1.52 (0.99–2.33)	0.057
Recessive	139 (81.29)	188 (82.46)	0.764	1.08 (0.65–1.81)	0.763	1.10 (0.66–1.86)	0.712

Table 1 (*continued*)

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Table 1 (*continued*)

Genotype	Cases (n=171), n (%)	Controls (n=228), n (%)	P value[a]	Crude OR (95% CI)	P value	AOR (95% CI)[b]	P value[b]
Combined effect of risk genotypes[c]							
0–3	54 (31.58)	95 (41.67)		1.00		1.00	
4–5	117 (68.42)	133 (58.33)	0.039	1.55 (1.02–2.35)*	0.040*	1.59 (1.04–2.43)*	0.031*

[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 rs2228001 AC/CC, rs2228000 CT/TT, rs2607775 GG, rs1870134 GC/GG, rs2229090 GC/CC genotypes; *, P<0.05. *XPC*, xeroderma pigmentosum group C; OR, odds ratio; CI, confidence interval; AOR, adjusted OR; HWE, Hardy-Weinberg equilibrium.

(AOR =1.73, 95% CI: 1.09 to 2.75, P=0.020).

Discussion

Glioma is the most common intracranial malignant tumor, and the incidence of gliomas is rising worldwide (21-23). Increasing studies have revealed that mutations in different genes in glioma patients are closely correlated with gliomagenesis (24). Among them, SNP is the most common type of genetic mutation which alters single base pair in alleles either in or between individuals (25). There are only 0.1% differences between individual genomes, known as SNP, and these small differences between genomes determine the differences between individuals and are the main cause of genetic variation between individuals. The associations between genetic polymorphisms in *XPC* and glioma susceptibility remain largely unknown.

In this case-control study, we firstly assessed the correlation between *XPC* polymorphisms and glioma susceptibility in a Chinese pediatric glioma population. We found that *XPC* rs1870134 G>C was correlated with pediatric glioma susceptibility in recessive models. The *XPC* rs1870134 CC genotype could reduce the risk of pediatric glioma. Additionally, rs2228000 CT/TT and rs2229090 GC/CC genotypes could increase the risk of pediatric glioma in subgroups with females, astrocytic tumors, and clinical stage I. These results suggest that *XPC* polymorphisms may potentially act as biomarker for pediatric glioma diagnosis.

The *XPC* gene contains 16 exons and 15 introns, is located on the long arm of chromosome 3, and encodes a 940-amino acid protein (26), which is also the DNA recognition molecule of the NER-repair pathway. Previous studies have shown that *XPC* protein forms a stable complex with HHR23b protein and is mainly involved in the identification of DNA damage sites, and further initiates the repair of the NER pathway (27). Thus, *XPC* gene mutation could reduce its ability to repair. Increasing studies have shown that *XPC* polymorphism is correlated with susceptibility to prostate cancer, non-small cell lung cancer, colorectal cancer, and other diseases (28,29). However, Hua *et al.* (30) reported that *XPC* gene rs1870134 G>C was not correlated with gastric cancer susceptibility in a southern Chinese population, which did not concur with our results. The inconsistent biological function of *XPC* rs1870134 G>C locus may be caused by different population types and kinds of tumor. In addition, genetic factors and living environment are also potential reasons. Lakkireddy reported that *XPC* Ala499Val (rs2228000 C>T) correlate is a high-risk polymorphism of chronic myeloid leukemia susceptibility, which was consistent with our results (18). Gil *et al.* found that the *XPC* rs279017 (i11C/A) genotype is associated with an increased risk of sporadic colorectal cancer, and the possible cause is that polymorphism at the *XPC* intron 11 splicing receptor site increased the jump frequency of exon 12, leading to reduced DNA repair ability (31). Mathew *et al.* found that the Gln allele at Lys939Gln (rs2228001 A>C) is associated with Hepatocellular carcinoma susceptibility (32). The possible reason is that *XPC* rs2228001 A>C is located on the protein-coding areas, and the A/C transversions potentiate the change of encoded amino acid from lysine to glutamate (33). Notably, mutations that cause disease are not concentrated in the *XPC* gene (34), a single amino acid change is enough to have a significant effect on the function of *XPC* (35). Khan *et al.* found that genotype A/A can reduce the repair ability of *XPC* protein by about 50% (36).

This study had some considerable limitations. Firstly, was a case-control study based on a hospital population, and there may have been some participant selection bias. Secondly, only 399 participants were included in this study, so the sample size was not sufficiently large. It is necessary

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Table 2 Stratification analysis of risk genotypes with glioma susceptibility

Variables	rs2228000				rs2229090				Risk genotypes			
	Cases/controls		AOR (95% CI)[a]	P value[a]	Cases/controls		AOR (95% CI)[a]	P value[a]	Cases/controls		AOR (95% CI)[a]	P value[a]
	CC	CT/TT			GG	GC/CC			0–3	4–5		
Age, months												
<60	29/49	56/70	1.34 (0.75–2.39)	0.322	26/45	59/74	1.37 (0.76–2.48)	0.296	28/47	57/72	1.32 (0.74–2.36)	0.353
≥60	28/43	58/66	1.37 (0.75–2.48)	0.305	25/43	61/66	1.62 (0.88–2.97)	0.121	26/48	60/61	1.86 (1.02–3.38)*	0.043*
Gender												
Females	23/40	58/53	1.93 (1.01–3.67)*	0.047*	21/39	60/54	2.13 (1.10–4.11)*	0.025*	22/42	59/51	2.34 (1.22–4.50)*	0.011*
Males	34/52	56/83	1.04 (0.60–1.80)	0.895	30/49	60/86	1.17 (0.66–2.05)	0.596	32/53	58/82	1.19 (0.68–2.08)	0.538
Subtypes												
Astrocytic tumors	36/92	89/136	1.73 (1.07–2.80)*	0.026*	31/88	94/140	2.05 (1.24–3.38)*	0.005*	34/95	91/133	2.07 (1.27–3.37)*	0.004*
Ependymoma	13/92	12/136	0.67 (0.29–1.54)	0.342	12/88	13/140	0.71 (0.31–1.63)	0.415	12/95	13/133	0.78 (0.34–1.80)	0.559
Neuronal and mixed neuronal-glial tumors	5/92	9/136	1.19 (0.38–3.71)	0.760	5/88	9/140	1.07 (0.35–3.33)	0.904	5/95	9/133	1.20 (0.39–3.74)	0.749
Embryonal tumors	3/92	4/136	1.26 (0.23–6.83)	0.786	3/88	4/140	1.25 (0.23–6.78)	0.795	3/95	4/133	2.19 (0.36–13.57)	0.398
Clinical stage												
I	27/92	76/136	1.96 (1.16–3.29)*	0.012*	23/88	80/140	2.31 (1.34–3.98)*	0.003*	25/95	78/133	2.38 (1.40–4.05)*	0.002*
II	14/92	14/136	0.67 (0.31–1.48)	0.326	14/88	14/140	0.63 (0.28–1.38)	0.243	14/95	14/133	0.71 (0.32–1.56)	0.394
III	8/92	7/136	0.61 (0.21–1.76)	0.361	6/88	9/140	0.95 (0.32–2.77)	0.920	6/95	9/133	1.04 (0.36–3.05)	0.937
IV	8/92	17/136	1.78 (0.68–4.64)	0.237	8/88	17/140	1.74 (0.67–4.56)	0.256	9/95	16/133	1.81 (0.70–4.69)	0.220
I + II	41/92	90/136	1.49 (0.94–2.36)	0.087	37/88	94/140	1.63 (1.02–2.61)*	0.041*	39/95	92/133	1.73 (1.09–2.75)*	0.020*
III + IV	16/92	24/136	1.04 (0.52–2.09)	0.918	14/88	26/140	1.25 (0.61–2.57)	0.544	15/95	25/133	1.32 (0.65–2.70)	0.444

[a], adjusted for age and gender, omitting the corresponding stratify factor; *, P<0.05. AOR, adjusted odds ratio; CI, confidence interval.

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to further expand the sample size and involve different medical centers to verify the results. Thirdly, in the future, we should consider a broader range of risk factors that affect glioma susceptibility, such as environmental factors and ionizing radiation.

Conclusions

We found for the first time that *XPC* polymorphisms were statistically significantly correlated with pediatric glioma susceptibility in a Chinese population. The *XPC* rs1870134 CC genotype could reduce the risk of pediatric glioma. However, the rs2228001 A>C, rs2607775 C>G, rs2229090 G>C polymorphisms of *XPC* were not correlated with the risk of pediatric glioma. Additionally, rs2228000 CT/TT and rs2229090 GC/CC genotypes could both increase the risk of pediatric glioma in subgroups with females, astrocytic tumors, and clinical stage I.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (No. 2016021650) and informed consent was taken from all the patients.

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Supplementary

Table S1 Frequency distribution of selected variables in glioma patients and cancer-free controls (37)

Variables	Cases (n=171)		Controls (n=228)		P[a]
	No.	%	No.	%	
Age, months					0.623
Range	4.00–168.00		4.00–168.00		
Mean ± SD	63.40±47.72		52.41±32.65		
<60	85	49.71	119	52.19	
≥60	86	50.29	109	47.81	
Gender					0.190
Female	81	47.37	93	40.79	
Male	90	52.63	135	59.21	
Subtypes					
Astrocytic tumors	125	73.10	–	–	
Ependymoma	24	14.62	–	–	
Neuronal and mixed neuronal-glial tumors	14	8.19	–	–	
Embryonal tumors	7	4.09	–	–	
WHO stages					
I	103	60.23	–	–	
II	28	16.37	–	–	
III	15	8.77	–	–	
IV	25	14.62	–	–	

[a], two-sided χ^2 test for distributions between glioma patients and cancer-free controls. SD, standard deviation.

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