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Investigation of the effects of single-nucleotide polymorphisms in DNA repair genes on the risk of glioma

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ABSTRACT. Several single-nucleotide polymorphisms (SNPs) in DNA repair gene have been shown to affect DNA repair and to modify susceptibility to cancer. In this study, to investigate the role of these SNPs in glioma, we examined the potential association of 14 SNPs in DNA repair genes with the glioma risk in a Chinese population. We included 326 glioma cases and 376 cancer-free controls. Genotyping of the 14 SNPs was performed on 384-well plates on the Sequenom MassARRAY platform. Of the 14 SNPs, rs1799782 and rs1799793 did not display the Hardy-Weinberg equilibrium in the control group. Moreover, the genotype distribution differed significantly between the two groups for the SNPs rs25487, rs3218536, and rs1799793. The rs25487 G/G genotype strongly and significantly increased the risk of glioma when compared with the rs25487 A/A genotype, indicated by an odds ratio (OR) = 2.23 [95% confidence interval (95%CI) = 1.36-3.87]. The rs25489 A/G genotype was also significantly associated with increased risk of glioma when compared with the A/A genotype (OR = 1.52; 95%CI = 1.03-2.35). In addition, rs1799782 increased the risk of glioma (OR = 1.89; 95%CI = 1.27-3.04), and a similar association was

found for rs1800067 (OR = 1.89; 95%CI = 1.21-3.07). In conclusion, the results of our study suggest that the rs25487, rs25489, rs1799793, and rs13181 SNPs are associated with an increased risk of glioma. These findings may be useful for identifying the genetic factors involved in the development of glioma to help devise more efficient strategies to prevent this disease.

Key words: DNA repair gene; Single-nucleotide polymorphisms; Glioma

INTRODUCTION

Glioma and meningioma are common tumors and account for almost 80% of all primary malignant brain tumors. Despite the advances in neurosurgery and adjuvant radiotherapy and chemotherapy, glioma and meningioma are generally associated with poor survival relative to other types of brain tumors (Bondy et al., 2008). To date, little is known about the etiology of glioma, which may involve interactions of multiple intrinsic and environmental factors (Connelly and Malkin, 2007; Bondy et al., 2008). Increasing evidence suggests that inheritance of risk factors plays some role in increased susceptibility of glioma, and most of this inherited risk is due to the coinheritance of multiple low-risk genetic variants. In normal cells, repair of damaged DNA is the main response to prevent the propagation of genetic errors and subsequent initiation and growth of tumors (Alberts et al., 2002; Vogelstein and Kinzler, 2004). Ionizing radiation is the only confirmed environmental risk factor for glioma because it produces several types of DNA damage, including oxidative damage to nucleotide bases, single- and double-strand breaks in DNA chains, and DNA-DNA or DNA-protein covalent cross links. The repair of these damage involves several molecular pathways for DNA repair such as base-excision repair, nucleotide excision repair, mismatch repair, double-strand break repair, and homologous recombination repair (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NR, 2006).

Previous studies have reported an association between glioma and several single-nucleotide polymorphisms (SNPs) in DNA repair genes (Wrensch et al., 2009; Shete et al., 2009; Liu et al., 2010). However, few studies have examined the association between DNA-repair genes and meningioma, and few reports have investigated the effects of gene-gene interactions on glioma risk. In this study, we performed a case-control study to assess the potential role of 14 SNPs in DNA repair genes in modifying the glioma risk in a Chinese population and investigated the role of gene-gene interactions in cancer risk.

MATERIAL AND METHODS

Study population

This case-control study included 326 subjects with glioma and 376 cancer-free subjects as a control group. Of the subjects with glioma, 358 were first diagnosed with intracranial glioma during 2008-2011 at the Beijing Tiantan Hospital, specialized in neurosurgery. Of these, 326 (91.06%) of the eligible brain tumor patients agreed to participate; 222 patients

were diagnosed with glioma and 104 with meningioma. The 376 control subjects had been admitted to our hospital for orthopedic injuries, digestive disorders, or musculoskeletal disorders. Of these, 341 (90.7%) were enrolled in our study. Controls with known central nervous system-related diseases, a history of any types of cancer, and chemotherapy for unknown disease conditions were excluded. All the control subjects were frequency-matched to the glioma patients by age and gender. All subjects were questioned with a structured questionnaire in face-to-face interviews conducted by doctors or nurses.

Our study was approved by the Beijing Tiantan Hospital, and all subjects were asked to provide 5 mL venous blood.

Genotyping

DNA was extracted from the buffy-coat blood fractions with the TIANamp Blood DNA kit (Tiangen Biotech, Beijing, China). Genotyping of the 14 SNPs was performed on 384-well plates on the Sequenom MassARRAY platform (Sequenom, San Diego, CA, USA). Primers for polymerase chain reaction (PCR) amplification and single-base extension assays were designed by using the Sequenom Assay Design 3.1 software (Sequenom) according to manufacturer instructions (Table 1). PCR was carried out in a reaction volume of 20 μL, containing 50 ng genomic DNA, 200 μM dNTPs, 2.5 U Taq DNA polymerase (Promega Corporation, Madison, WI, USA), and 200 μM primers. The thermal cycling protocol used was as follows: 94°C for 2 min, followed by 35 cycles of 94°C for 30 s, 64°C for 30 s, and 72°C for 1 min. The PCR products were fractionated by electrophoresis on a 1.0% agarose gel to identify desired products. For quality control, genotyping was performed without knowledge of the case/control status of the subjects, and a random sample of 5% of cases and controls was genotyped again by different researchers. The reproducibility was 100%.

Statistical analyses

Continuous variables are reported as means ± standard deviation, whereas categorical variables are shown as frequencies and percentages. Demographic characteristics were compared between cases and controls by χ^2 and Student *t*-tests. Hardy-Weinberg equilibrium (HWE) in the controls was assessed by using the χ^2 test. Multiple models of inheritance (i.e., codominant, dominant, and recessive models) were chosen to evaluate associations between each SNP and glioma and meningioma risks. For each polymorphism, unconditional logistic regression analysis was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) after adjusting for gender, age, ionizing radiation (IR), and family history of cancer. Statistical analyses were performed using the SPSS for Windows software (version 16.0 SPSS, Chicago, IL, USA). We analyzed the data using two-sided P values.

RESULTS

Study subjects

A total of 326 glioma and meningioma patients were included in our study, including 187 males and 139 females, with a mean age at diagnosis of 45.4 ± 14.3 years (Table 1). Of

these, 222 patients were diagnosed with glioma and 104 patients with meningioma. The 376 control subjects had a mean age of 47.2 ± 12.7 years and included 203 males and 173 females. No significant difference was found between patient and control subjects in smoking and drinking status ($P > 0.05$). It was noted that glioma and meningioma patients were more likely to have had a history of cancer and of higher IR exposure than the controls (8.28 *vs* 2.13%, respectively, $P < 0.05$, for history of cancer; 6.75 *vs* 0.53%, respectively, $P < 0.05$, for history of IR exposure).

Table 1. Frequencies of glioma and meningioma patients and controls with respect to selected characteristics.

Characteristics	Case (N = 326)	%	Control (N = 376)	%	χ^2	P value
Age (mean ± SD; years)	47.5 ± 8.5		48.6 ± 7.4			
<40	57	17.48	70	18.62	0.27	0.88
40-55	126	38.65	139	36.97		
>55	143	43.87	167	44.41		
Gender						
Male	194	59.51	224	59.57	0.00	0.99
Female	132	40.49	152	40.43		
Smoking status						
Never	220	67.48	234	62.35	2.11	0.15
Ever	106	32.52	142	37.65		
Drinking status						
Never	191	58.59	201	53.57	1.86	0.17
Ever	135	41.41	175	46.43		
Ionizing radiation exposure						
Never	304	93.25	374	99.47	20.44	<0.05
Ever	22	6.75	2	0.53		
History of cancer in the first relatives						
No	299	91.72	368	97.87	13.96	<0.05
Yes	27	8.28	8	2.13		
Histological types						
High-grade glioma	148	45.31				
Low-grade glioma	178	54.69				

Allele and genotype distributions of 14 SNPs and HWE

Twelve of the 14 SNPs tested were confirmed to have distributions within the parameters of HWE for the control population, whereas rs1799782 and rs1799793 did not display HWE in the control group (Table 2). The minor allele frequencies among healthy controls were consistent with those in the Chinese population as recorded in the NCBI dbSNP database. In accordance with the allelic associations, the genotype distribution differed significantly between the two groups for SNPs rs25487, rs3218536, and rs1799793. The minor allele frequencies of the SNPs rs25489, rs3734091, and rs1800067 were very low (i.e., frequencies of <10%).

Polymorphisms of 14 SNPs and their association with glioma risk

We further analyzed the effect of genotypes in different genetic models and on the different cancers (Table 3). The rs25487 G/G genotype was found to significantly increase the risk of glioma when compared with the rs25487 A/A genotype in the codominant model, indicated by an OR = 2.23 (95%CI = 1.36-3.87). Moreover, significant associations between rs25387 and risk of glioma were detected in both dominant and recessive models (OR = 1.50; 95%CI = 1.14-2.06 for the dominant model and OR = 1.91; 95%CI = 1.14-3.28 for the recessive model). Next,

Table 2. Genotype characteristics of the 14 single nucleotide polymorphisms (SNPs).

Genes	dbSNP	Used denotation	Major/Minor allele	Genotype frequency of cases			Genotype frequency of controls			P value	MAF from dbSNP		MAF	P for HWE in controls
				1/1	1/2	2/2	1/1	1/2	2/2		Case	Control		
XRCC1	rs25487	Gln399Arg	A/G	126	155	45	178	168	29	<0.05	0.2633	0.376	0.301	0.22
XRCC1	rs25489	Arg280His	A/G	250	66	10	313	57	6	0.08	0.0609	0.132	0.092	0.52
XRCC1	rs1799782	Arg194Trp	C/T	235	73	18	279	84	13	0.41	0.1296	0.167	0.146	<0.05
XRCC2	rs3218536	Arg188His	A/G	261	59	5	332	40	4	<0.05	0.0426	0.106	0.064	0.06
XRCC3	rs861539	Thr241Met	C/T	158	146	22	202	159	15	0.16	0.25	0.291	0.251	0.07
XRCC4	rs3734091	Ala247Ser	A/G	284	37	5	339	34	3	0.38	0.0371	0.072	0.053	0.09
XRCC4	rs6869366	Gln1394Trp	G/T	254	61	11	303	66	8	0.53	0.0952	0.127	0.109	0.06
ERCC1	rs11615	Asn118Asp	C/T	149	128	49	179	139	57	0.83	0.3439	0.347	0.336	0.06
ERCC1	rs3212986	Gln504Lys	G/T	163	129	33	197	140	39	0.80	0.2935	0.299	0.290	0.56
ERCC2	rs1799793	Asp312Asn	A/G	168	128	31	238	112	26	<0.05	0.1937	0.291	0.218	<0.05
ERCC2	rs13181	Lys751Gln	G/T	173	126	37	223	124	30	0.09	0.2367	0.307	0.245	0.20
ERCC4	rs1799801	Ser835Ser	C/T	192	112	21	225	127	24	0.98	0.2266	0.236	0.233	0.29
ERCC4	rs1800067	Arg415Gln	A/G	301	24	1	345	29	2	0.89	0.0311	0.040	0.044	0.12
ERCC5	rs17655	Asp1558His	C/G	168	119	59	165	146	65	0.40	0.3768	0.363	0.367	0.10

1 = Wide-type variant; 2 = Heterozygous variant; 3 = Homozygous variant; MAF = minor allele frequencies.

rs25489 A/G was identified as being significantly associated with an increased risk of glioma when compared with the rs25489 A/A genotype (OR = 1.52; 95%CI = 1.03-2.35) in the codominant model, and the dominant model analysis indicated that rs25489 was associated with the risk of glioma (OR = 1.56; 95%CI = 1.07-2.31). rs1799782 was significantly associated with a higher risk of glioma in both codominant and dominant models, indicated by OR = 1.89 (95%CI = 1.27-3.04) and OR = 1.86 (95%CI = 1.21-2.94), respectively. A similar association was found for rs1800067, with OR = 1.89 (95%CI =1.21-3.07) and OR = 1.86 (95%CI = 1.20-2.88) in codominant and dominant models, respectively.

Table 3. Genotype frequencies and OR (95%CI) for association between 14 SNPs and glioma risk.

Genes	Major/Minor allele	Case	Control	Genotype frequency of cases [OR (95%CI)]		
				Codominant[1]	Dominant[1]	Recessive[1]
XRCC1 Gln399Arg	A/A	126	178	-	-	-
rs25487	A/G	155	168	1.31 (0.93-1.81)	1.50 (1.14-2.06)	1.91 (1.14-3.28)
	G/G	45	29	2.23 (1.36-3.87)	-	-
XRCC1 Arg280His	A/A	250	313	-	-	-
rs25489	A/G	66	57	1.52 (1.03-2.35)	1.56 (1.07-2.31)	1.95 (0.63-6.60)
	G/G	10	6	2.12 (0.71-7.21)	-	-
XRCC1 Arg194Trp	C/C	235	279	-	-	-
rs1799782	C/T	73	84	1.03 (0.72-1.56)	1.15 (0.81-1.76)	1.63 (0.75-3.71)
	T/T	18	13	1.64 (0.75-3.81)	-	-
XRCC2 Arg188His	A/A	261	332	-	-	-
rs3218536	A/G	59	40	1.89 (1.27-3.04)	1.86 (1.21-2.94)	1.45 (0.31-7.39)
	G/G	5	4	1.61 (0.34-8.11)	-	-
XRCC3 Thr241Met	C/C	158	202	-	-	-
rs861539	C/T	146	159	1.19 (0.88-1.61)	1.26 (0.92-1.71)	1.75 (0.85-3.68)
	T/T	22	15	1.90 (0.91-4.07)	-	-
XRCC4 Ala247Ser	A/A	284	339	-	-	-
rs3734091	A/G	37	34	1.31 (0.78-2.24)	1.38 (0.85-2.29)	1.94 (0.38-12.57)
	G/G	5	3	2.03 (0.40-13.2)	-	-
XRCC4 Gln1394Trp	G/G	254	303	-	-	-
rs6869366	G/T	61	66	1.12 (0.76-1.69)	1.20 (0.81-1.71)	1.65 (0.61-4.73)
	T/T	11	8	1.64 (0.62-4.78)	-	-
ERCC1 Asn118Asp	C/C	149	179	-	-	-
rs11615	C/T	128	139	1.12 (0.86-1.65)	1.32 (0.98-1.83)	0.98 (0.64-1.53)
	T/T	49	57	1.06 (0.67-1.73)	-	-
ERCC1 Gln504Lys	G/G	163	197	-	-	-
rs3212986	G/T	129	140	1.12 (0.82-1.55)	1.12 (0.84-1.55)	0.98 (0.58-1.65)
	T/T	33	39	1.06 (0.63-1.75)	-	-
ERCC2 Asp312Asn	A/A	126	178	168	-	-
rs1799793	A/G	155	168	1.31 (0.95-1.83)	1.53 (1.14-2.06)	1.93 (1.15-2.31)
	G/G	45	29	2.22 (1.29-3.96)	-	-
ERCC2 Lys751Gln	G/G	250	313	173	-	-
rs13181	G/T	66	57	1.45 (0.96-2.19)	1.54 (1.07-2.31)	1.95 (0.64-6.61)
	T/T	10	6	2.18 (0.70-7.17)	-	-
ERCC4 Ser835Ser	C/C	235	279	192	-	-
rs1799801	C/T	73	84	1.05 (0.73-1.52)	1.13 (0.78-1.57)	1.64 (0.75-2.71)
	T/T	18	13	1.65 (0.76-3.74)	-	-
ERCC4 Arg415Gln	A/A	261	332	301	-	-
rs1800067	A/G	59	40	1.89 (1.21-3.07)	1.86 (1.20-2.88)	1.46 (0.32-7.40)
	G/G	5	4	1.61 (0.34-8.13)	-	-
ERCC5 Asp1558His	C/C	158	202	168	-	-
rs17655	C/G	146	159	1.27 (0.89-1.71)	1.24 (0.91-1.71)	1.75 (0.86-3.73)
	G/G	22	15	1.89 (0.90-4.05)	-	-

[1]Adjusted for gender, age, ionizing radiation exposure history, and history of cancer in the first relatives.

DISCUSSION

To the best of our knowledge, our study is the first that has evaluated potential associa-

tions between 14 SNPs in DNA repair genes and the risk of glioma and meningioma. We have shown that the rs25487, rs25489, rs1799793, and rs13181 SNPs are associated with increased risk of glioma. Although many studies have examined the association of DNA repair genes with the risk of glioma (Wang et al., 2012; Chen et al., 2012; Jacobs and Bracken, 2012), only 2 have comprehensively investigated the association of SNPs in DNA repair genes with glioma risk, and no study has shown such association in Chinese populations (Liu et al., 2009; Rajaraman et al., 2010). A study conducted on an American population with 373 Caucasian glioma cases and 365 cancer-free Caucasian controls assessed associations between glioma risk and 18 functional SNPs in DNA repair genes; 6 SNPs, including the *ERCC1* 3'-untranslated region (UTR), *XRCC1* R399Q, *APEX1* E148D, *PARP1* A762V, *MGMT* F84L, and *LIG1* 5'-UTR, were identified as having a significant association with glioma risk (Liu et al., 2009). Another study also conducted in Americans included 565 cases and 495 controls and investigated 36 SNPs in 26 genes; its results indicated that the *GLTSCR1* rs1035938, *ERCC4* rs1800067, *ERCC2* rs1799793, and *PARP1* rs1136410 polymorphisms significantly increase the risk of glioma, whereas *XRCC1* rs1799782 decreases the glioma risk (Rajaraman et al., 2010).

A strong association observed in our study of 14 SNPs in the DNA repair pathway was the 2.23-fold increased risk of glioma in subjects with the rs25487 G/G genotype. This association remained statistically significant even in dominant and recessive models after controlling for confounding factors. These results were consistent with several previous studies that have reported an association between polymorphisms in this SNP and glioma risk. In a recent study conducted in Americans, an association of the rs25487 polymorphism with increased risk of glioma was detected in a survey including 373 glioma patients and 365 controls (Liu et al., 2009). Another study reported that the carriers of the rs25487 G allele have a 3.5 times greater risk for glioma (Yosunkaya et al., 2010). The rs25487 polymorphism has been a particular research focus because of its location within the region of the BRCT1-binding domain. Mutations in the BRCT1 domain of BRCA1 have been implicated in the altered function of this tumor suppressor gene (Sterpone and Cozzi, 2010). A previous study that measured the expression of the *XRCC1* gene reported that the 399 variant allele is associated with increased gene expression in breast cancer (Zipprich et al., 2010).

In addition, the results of our study have shown that rs25489 was associated with glioma risk in codominant and dominant models. Although the previous 3 studies investigated the association between rs25487 and risk of glioma (Kiuru et al., 2008; Zhou et al., 2011; Wang et al., 2012), these studies did not find a significant association between rs25489 and the risk of glioma. Our study results also did not replicate previous reports of nonsignificant associations between rs25489 and glioma. These inconsistencies between our results and those of previous studies might be explained by differences in population background, source of control subjects, sample size, and also by chance. Confirmation of our observations is still needed and requires additional studies.

We have shown here that the rs3218536 SNP is significantly associated with glioma risk. The G allele of rs3218536, although not associated with glioma risk in previous studies, has been associated with a significant effect on risk of lung, colorectal, and breast cancer (Krupa et al., 2011; Romanowicz-Makowska et al., 2011, 2012), and it has been suggested that individuals carrying the G allele variant of this SNP are more susceptible to the effects of ionizing radiation. Further studies are strongly needed to validate the association between this SNP and glioma risk.

No previous study has investigated the association between rs1800067 and glioma risk. However, several studies have investigated the association between rs1800067 and other cancers such as breast cancer, non-small cell lung cancer, bladder cancer, prostate cancer, and head and neck cancer (Chiu et al., 2008; Mandal et al., 2011; Zhou et al., 2012; Yin et al., 2012; Mittal et al., 2012). These studies suggested that individuals with the T allele genotype are more susceptible to various cancers, and this genotype might decrease the effectiveness of anticancer treatments. It is hypothesized that the T allele of rs1800067 might lower the expression of XRCC4; thus, individuals with the T allele might be more impaired in double strand break-repair pathways increasing the susceptibility to cancer when compared with G/G genotypes.

Many approaches have aimed at identifying the genetic risk factors for glioma. In line with the rationale for this study, authors have suggested that some polymorphisms in genes of the DNA repair system are associated with various cancers (Kiuru et al., 2008; Chiu et al., 2008; Zhou et al., 2011; Mandal et al., 2011; Mittal et al., 2012). All of these findings strengthen the link between DNA repair systems and genome instability and carcinogenesis. Our study has comprehensively investigated the association of polymorphisms in genes of the DNA repair system and glioma. Its results suggested that rs25487, rs25489, rs1799793, and rs13181 are associated with an increased risk of glioma. Our findings may be useful for identifying the genetic conditions underlying glioma, to help devise more efficient strategies for preventing this disease.

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