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Investigation of the role of XRCC1 genetic polymorphisms in the development of gliomas in a Chinese population

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ABSTRACT. We conducted a study in a Chinese Han population to investigate the role of *XRCC1* gene polymorphisms (Arg399Gln and Arg194Trp) with a risk of susceptibility to gliomas. Samples from 115 patients with gliomas and 228 control subjects were consecutively collected between March 2012 and December 2014. Genotype analysis of *XRCC1* Arg399Gln and Arg194Trp was performed using polymerase chain reaction-restriction fragment length polymorphism assay. All the analyses were performed using the SPSS 17.0 software package. We observed that the *XRCC1* Arg399Gln and Arg194Trp genotype frequencies conformed to the Hardy-Weinberg equilibrium. We observed that the Trp/Trp genotype of *XRCC1* Arg194Trp was associated with an increased risk of glioma when compared to the

wild-type genotype (odds ratio (OR) = 2.14, 95% confidence interval (CI) = 1.14-3.86, P = 0.03). In the dominant model, we found that the Arg/Trp + Trp/Trp genotype of *XRCC1* Arg194Trp could significantly elevate the susceptibility of developing glioma (OR = 1.79, 95%CI = 1.07-0.94). However, we observed that the *XRCC1* Arg399Gln genetic polymorphism did not influence the risk of glioma. In summary, we suggest that the XRCC1 Arg194Trp genetic polymorphism could be a predictive biomarker for the susceptibility to glioma in a Chinese population.

Key words: XRCC1; Arg399Gln; Arg194Trp; Polymorphism; Glioma; Chinese population

INTRODUCTION

Malignant glioma is the most frequent form of primary brain tumors and is always accompanied by a poor prognosis. The etiology of gliomas remains poorly understood. Previous epidemiologic studies have reported that many environmental and lifestyle factors contribute to the development of gliomas (Ohgaki and Kleihues, 2005). However, increasing evidence has indicated that hereditary factors may be involved in modifying glioma susceptibility (Kinnersley et al., 2015). Genetic studies demonstrated that several genetic factors may play an important role in the development of gliomas, such as *CCDC26*, *CDKN2BAS*, *RTEL1*, and *TERT* genes (Adel Fahmideh et al., 2015; Wang et al., 2015a).

Polymorphisms in DNA repair genes leading to variation of DNA repair efficiency may be correlated with development of several kinds of cancers (De Gobbi et al., 2006; Nothnagel et al., 2009). *XRCC1* is located on chromosome 19q13.2-19q13.3, is 33 kb in length, and contains 17 exons. The *XRCC1* gene can combine with many other components and play an important role in facilitating base excision repair and single-strand break repair processes. Previous studies have reported that *XRCC1* gene polymorphisms contribute to the development of cancers, such as lung, colorectal, breast, and ovarian cancers (Guo et al., 2015; Malisic et al., 2015; Nissar et al., 2015; Wang et al., 2015b). Recently, several epidemiologic studies have assessed the association between *XRCC1* gene polymorphisms and susceptibility to glioma, but their findings are inconclusive (Feng et al., 2014; Li et al., 2014; Rodriguez-Hernandez et al., 2014; Wang et al., 2015a). In our study, we examined a Chinese Han population and investigated the role of *XRCC1* gene polymorphisms (Arg399Gln and Arg194Trp) with a risk for susceptibility to gliomas.

MATERIAL AND METHODS

Patients

Here, a hospital-based case-control study was performed. Samples from 115 patients with gliomas and 228 control subjects were consecutively collected from the People's Hospital of Xishuangbana Dai Nationality Autonomous Prefecture between March 2012 and December 2014. All the patients were newly diagnosed and confirmed to have gliomas with pathological examination. All the patients with gliomas were confirmed to be without history of other

malignant tumors and prior chemotherapy or radiochemotherapy.

The control subjects were enrolled from amongst individuals who came to receive regular health check-up examinations. All the patients with gliomas and the control subjects were of Han Chinese ethnicity. The control subjects were confirmed to be without malignant tumors, infectious diseases, or serious endocrine, metabolic, or nutritional disorders.

The demographic and lifestyle data were collected from a structured questionnaire or medical records, including age, gender, exposure to ionizing radiation, tobacco smoking, alcohol consumption, and family history of cancer. All the patients with gliomas and the control subjects gave their informed consent before enrolling in this study. This study was approved by the Ethics Committee of the People's Hospital of Xishuangbana Dai Nationality Autonomous Prefecture.

Genotyping methods

Five milliliters of peripheral blood was collected from patients with gliomas and the control subjects after recruitment into this study. The blood samples were stored at -20°C until use. The DNA extraction was performed using the TIANGEN blood mini kit (TIANGEN Co. Limited, Beijing, China). DNA (1 μL) was used as the template for each polymerase chain reaction (PCR) cycle. Genotype analysis of *XRCC1* Arg399Gln and Arg194Trp was performed using PCR-restriction fragment length polymorphism (PCR-RFLP) assay. The primers, restriction enzymes, and product sizes are shown in Table 1. The PCR products were digested with restriction enzymes, analyzed using electrophoresis on a 2% agarose gel, and observed under UV light.

Table 1. Primers, restriction enzymes, and product sizes of *XRCC1* Arg399Gln and Arg194Trp genes.

XRCC1	SNP	Primers (5'-3')	Restriction enzyme	PCR product (bp)
Arg399Gln	rs25487	TTGTGCTTTCTCTGTGTCCA (forward) TCCTCCAGCCTTTACTGATA (reverse)	*Msp*I	615
Arg194Trp	rs1799782	GTGAAGGAGGAGGATGAGAGC (forward) CCCCAGCCCCCTCTACCCT (reverse)	*Pvu*II	160

Statistical analysis

The categorical and quantitative data between the patients with gliomas and control subjects were compared using the Student *t*-test or the chi-square (χ^2) test. Before performing the association study, the Hardy-Weinberg equilibrium (HWE) for any deviation from expected allele frequencies was tested by using the χ^2 test. Genotype frequencies between the patients with gliomas and control subjects were compared using the χ^2 test. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression analysis and the results were adjusted for potential confounding factors. Three genetic models, including codominant, dominant, and recessive, were performed to assess the association between *XRCC1* Arg399Gln and Arg194Trp and glioma risk. All the analysis was performed using the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA). All P values used in this study were two-sided. A P value <0.05 at 95%CI was taken as statistically significant.

RESULTS

The mean age of patients and control subjects was 48.53 ± 10.34 and 46.65 ± 11.60 years, respectively (Table 2). Patients with gliomas were comparable with control subjects in terms of age, gender, tobacco smoking, alcohol consumption, and family history of cancer. However, a significant difference was observed between patients and controls with respect to exposure to ionizing radiation ($\chi^2 = 9.36$, P = 0.002).

Table 2. Demographic characteristics of patients with gliomas and control subjects.

Variables	Patients (N = 115)	%	Controls (N = 228)	%	*t*-test or χ^2 test	P value
Age (years)	48.53 ± 10.34		46.65 ± 11.60			
Gender						
Female	49	42.61	104	45.61		
Male	66	57.39	124	54.39	0.28	0.60
Tobacco smoking						
No	37	32.17	69	30.26		
Yes	78	67.83	159	69.74	0.13	0.72
Alcohol consumption						
No	29	25.22	50	21.93		
Yes	86	74.78	178	78.07	0.47	0.50
Family history of cancer						
No	106	92.17	212	92.98		
Yes	9	7.83	16	7.02	0.07	0.79
Exposure to ionizing radiation						
No	12	10.43	6	2.63		
Yes	103	89.57	222	97.37	9.36	0.002

The distributions of *XRCC1* Arg399Gln and Arg194Trp genes are presented in Table 3. For the *XRCC1* Arg399Gln polymorphism, 42 (36.52%), 51 (44.35%), and 22 (19.13%) glioma patients harbored the Arg/Arg, Arg/Gln, and Gln/Gln genotypes, respectively. For the control subjects, 92 (40.35%), 99 (43.42%), and 37 (16.23%) harbored the Arg/Arg, Arg/Gln, and Gln/Gln genotypes, respectively. For the *XRCC1* Arg194Trp polymorphism, 31 (26.96%), 58 (50.43%), and 26 (22.61%) glioma patients harbored the Arg/Arg, Arg/Trp, and Trp/Trp genotypes, respectively. For the control subjects, 82 (35.96%), 109 (47.81%), and 37 (16.23%) harbored the Arg/Arg, Arg/Trp, and Trp/Trp genotypes, respectively. There was no significant difference found in the genotype frequencies of *XRCC1* Arg399Gln ($\chi^2 = 0.68$, P = 0.71) and Arg194Trp ($\chi^2 = 3.69$, P = 0.16) between glioma patients and controls. We observed that *XRCC1* Arg399Gln and Arg194Trp genotype frequencies conformed to the HWE.

Table 3. Genotype distributions of *XRCC1* Arg399Gln and Arg194Trp genes.

XRCC1	Patients (N = 115)	%	Controls (N = 228)	%	χ^2 test	P value	P for HWE	
							Patients	Controls
Arg399Gln	42	36.52	92	40.35				
Arg/Arg	51	44.35	99	43.42				
Arg/Gln	22	19.13	37	16.23	0.68	0.71	0.36	0.24
Gln/Gln								
Arg194Trp								
Arg/Arg	31	26.96	82	35.96				
Arg/Trp	58	50.43	109	47.81				
Trp/Trp	26	22.61	37	16.23	3.69	0.16	0.91	0.94

We analyzed the correlation between *XRCC1* Arg399Gln and Arg194Trp genetic polymorphisms and glioma risk using codominant, dominant, and recessive models with unconditional multivariate logistic regression analysis (Table 4). We observed that the Trp/Trp genotype of *XRCC1* Arg194Trp was associated with an increased risk of glioma when compared to the wild-type genotype (OR = 2.14, 95%CI = 1.14-3.86, P = 0.03). In a dominant model, we found that the Arg/Trp + Trp/Trp genotype could significantly elevate the susceptibility of developing glioma (OR = 1.79, 95%CI = 1.07-0.94). However, we observed that *XRCC1* Arg399Gln genetic polymorphisms could not influence the risk of glioma.

Table 4. Association between *XRCC1* Arg399Gln and Arg194Trp genetic polymorphisms and susceptibility to glioma.

XRCC1	Patients	%	Controls	%	OR (95%CI)	P value
Arg399Gln						
Codominant						
Arg/Arg	42	36.52	92	40.35	1.0 (Ref.)	-
Arg/Gln	51	44.35	99	43.42	1.13 (0.67-1.92)	0.63
Gln/Gln	22	19.13	37	16.23	1.30 (0.65-2.59)	0.42
Dominant						
Arg/Arg	42	36.52	92	40.35	1.0 (Ref.)	-
Arg/Gln+Gln/Gln	73	63.48	136	59.65	1.18 (0.72-1.92)	0.49
Recessive						
Arg/Arg+ Arg/Gln	93	80.87	191	83.77	1.0 (Ref.)	-
Gln/Gln	22	19.13	37	16.23	1.22 (0.65-2.26)	0.50
Arg194Trp						
Codominant						
Arg/Arg	31	26.96	82	35.96	1.0 (Ref.)	-
Arg/Trp	58	50.43	109	47.81	1.41 (0.81-2.46)	0.20
Trp/Trp	26	22.61	37	16.23	2.14 (1.14-3.86)	0.03
Dominant						
Arg/Arg	31	26.96	82	35.96	1.0 (Ref.)	-
Arg/Trp +Trp/Trp	84	73.04	146	64.04	1.79 (1.07-.94)	0.04
Recessive						
Arg/Arg + Arg/Trp	89	77.39	191	83.77	1.0 (Ref.)	-
Trp/Trp	26	22.61	37	16.23	1.57 (0.93-2.60)	0.09

DISCUSSION

We conducted a hospital clinical study to investigate the association between *XRCC1* Arg399Gln and Arg194Trp genetic polymorphisms and susceptibility to glioma in a Chinese population, and we observed that individuals harboring the Trp/Trp and Arg/Trp + Trp/Trp genotypes were at an increased risk of glioma compared to individuals harboring the wild-type genotype. However, no significant correlation was found between the *XRCC1* Arg399Gln polymorphism and susceptibility to gliomas.

Previous studies have reported that *XRCC1* genetic polymorphisms may influence the development of several kinds of cancers, such as lung, colorectal, ovarian, thyroid, and esophageal squamous cell cancers (Han et al., 2015; Malisic et al., 2015; Nissar et al., 2015; Wang et al., 2015b,c,d; Yun et al., 2015). Wang et al. (2015b) conducted a study in a Chinese population and reported that the rs25487 genetic polymorphism contributed to the risk of development of lung cancer. Han et al. (2015) conducted a study in a Chinese population and revealed that the *XRCC1* Arg399Gln polymorphism correlated with an increased risk of non-small-cell lung cancer. Nissar et al. (2015) performed a study in an Indian population

and suggested that the *XRCC1* Arg194Trp polymorphism modulated the risk of developing colorectal cancer. Malisic et al. (2015) revealed that the *XRCC1* Arg399Gln polymorphism could be a predictive biomarker for developing ovarian cancer. However, Yun et al. (2015) did not find a significant association between the *XRCC1* Arg399Gln polymorphism and development of esophageal squamous cell carcinoma in a Chinese population.

Epidemiologic studies have reported the association of *XRCC1* genetic polymorphisms and susceptibility to glioma in a Chinese population, but their findings are inconclusive (Luo et al., 2013; Wang et al., 2013; Xu et al., 2014; Zhu et al., 2014). Luo et al. (2013) conducted a study in a Chinese population and showed that the *XRCC1* Arg399Gln and Arg194Trp polymorphisms could increase the risk of gliomas. Wang et al. (2013) suggested that the *XRCC1* Arg399Gln polymorphism was associated with a significantly increased risk for glioma in a Chinese population. Xu et al. (2014) indicated that the *XRCC1* Arg399Gln and Arg194Trp genetic variations had a higher risk of glioma in a Chinese population. Zhu et al. (2014) conducted a meta-analysis and reported that the *XRCC1* Arg399Gln polymorphism may affect the risk of glioma. However, our study only revealed a significant association of the *XRCC1* Arg194Trp polymorphism with glioma risk, but the *XRCC1* Arg399Gln polymorphism had no effective role in the risk of this cancer. The discrepancies of the above-mentioned studies may be caused by different ethnicities and sample size.

In summary, we suggest that the *XRCC1* Arg194Trp genetic polymorphism could be a predictive biomarker for the susceptibility to glioma in a Chinese population. Further large-scale studies are greatly warranted to confirm the association between *XRCC1* genetic polymorphisms and risk of development of glioma.

Conflicts of interest

The authors declare no conflict of interest.

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