RESEARCH COMMUNICATION

Polymorphisms of DNA Repair gene XRCC1 and Risk of Glioma: a Case-control Study in Southern China

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Abstract

Objective: This study aimed to examine associations between polymorphisms in the X-ray cross-complementing group 1 (XRCC 1) gene and risk of glioma in a Chinese population. Methods: We performed a hospital-based case-control study with 271 cases and 289 controls in Guangdong province, China. Cases were patients newly diagnosed with pathologically confirmed glioma in two hospitals between June 2006 and May 2010. Controls were individuals without cancer, frequency matched by sex and age. Three SNPs in XRCC1 gene, Arg399Gln (rs25487), Arg194Trp (rs1799782) and Arg280His (rs25489), were analyzed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) based method. Unconditional logistic regression was used to estimate the odds ratios (ORs) of polymorphisms in XRCC1 gene for glioma. Results: The Arg399Gln polymorphism was significantly associated with risk of glioma. Individuals with the Gln/Gln genotype had a significantly increased likelihood of developing glioma compared with those with the Arg/Arg genotype (adjusted OR = 1.93, 95% CI: 1.04 - 3.58), especially among males and individuals aged 50 years or older. Conclusion: The XRCC1 Arg399Gln polymorphism may be a useful susceptibility biomarker for glioma. Further studies in Chinese populations with larger sample sizes are now warranted.

Key words: Glioma - DNA repair - XRCC1 - polymorphism - risk - China

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Introduction

Glioma is the most common type of primary brain malignancy in adults. Currently, the etiology of glioma has been poorly understood (Ohgaki and Kleihues, 2005). The only established environmental risk factor for glioma is ionizing radiation, which could only explain a small proportion of glioma because the exposure is generally rare (Ron et al., 1988; Wrensch et al., 1997; Little et al., 1998; Bondy et al., 2001). In addition, only a minority of those exposed to ionizing radiation eventually develop glioma, suggesting individual susceptibility may play a role in modifying the risk of glioma (Kyritsis et al., 2010).

DNA damage is considered to be an important mechanism in the development of glioma caused by ionizing radiation. Ionizing radiation produces several kinds of DNA damage, including oxidative DNA damage, single- and double- strand breaks in DNA chains, and DNA-DNA or DNA-protein cross links. Such damages, if not repaired, may cause errors during DNA synthesis leading to mutations that increase cancer risk (Rajaraman et al., 2010). Thus, polymorphisms of DNA repair genes are plausible candidates which can modify the risk of human cancers. Previous studies have also reported that a number of single nucleotide polymorphisms (SNPs) in DNA repair genes may modify glioma risk (Wrensch et al., 2005; Kiuru et al. 2008; Liu et al., 2009; Zhou et al., 2009; Rajaraman et al., 2010).

The X-ray cross-complementing group 1 (XRCC1) gene, which locates at chromosome 19q13.2, encodes an enzyme involved in the base excision repair (BER) pathway (Tudek 2007). Polymorphisms in XRCC1 gene have been reported to be associated with altered risk of several types of cancers (Qian et al., 2011; Hao et al., 2004; Zhang et al., 2005; Zhai et al., 2009). Associations between polymorphisms in XRCC1 gene and glioma risk have also been examined in American and European populations but the results remained inconsistent (Wang et al., 2004; Felini et al., 2007; Kiuru et al., 2008; Liu et al., 2009; Rajaraman et al., 2010; Yosunkaya et al., 2010). In contrast, evidence from Chinese populations is still lacking. Therefore,

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we conducted a hospital-based case-control study in Guangdong, a province in Southern China, to evaluate the association between polymorphisms in XRCC1 gene and the risk of glioma.

Materials and Methods

Study population and data collection

This case-control study was conducted in two hospitals in Guangdong, a province in Southern China. All Chinese cases with newly diagnosed gliomas between June 2006 and May 2010 in these hospitals were invited participate within two months after diagnosis. All cases recruited in this study were histologically confirmed. Among a total of 328 eligible cases, 271 were successfully interviewed and donated blood samples with a participation rate of 82.6%. Controls were randomly selected from people who requested general health examinations in the same hospital during the same period. Controls were required to be without any history of any type of cancer and frequency matched by five-year age groups. Among a total of 354 eligible controls, 289 were successfully interviewed and donated blood samples with a participation rate of 81.6%. Informed consent was obtained before each interview and blood taking. Trained interviewers conducted face-to-face interviews using a structured questionnaire to collect information on sociodemographic characteristics, tobacco smoking, alcohol use, radiation exposure, family history of cancer, and other potential confounders. Approval to conduct this study was granted by the Ethics Committee of Southern Medical University and the Ethics Committee for Clinical Research of Longgang Central Hospital. All interviews and blood samples collection were conducted after obtaining signed informed consent from participants.

Genotyping

Genomic DNA was extracted from whole-blood samples using the Qiagen Blood Kit (Qiagen, Chastworth, CA). Genotyping was conducted using TaqMan assays (Applied Biosystems, Foster City, CA). Primer and probe sets were designed and manufactured using Applied Biosystems 'Assay-by-Design' custom service (Applera, Austria). General TaqMan reaction conditions were as described previously (Hao, Wang et al. 2004). We also performed the genotyping of internal positive control samples, use of no template controls, and use of replicates for 10% samples for quality control.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software 13.0 for windows. Chi square or t tests were used to test differences of sociodemographic factors and potential confounders between the cases and controls. Deviation of genotype frequency distribution in controls from those expected under Hardy-Weinberg Equilibrium (HWE) was assessed using chi square tests. Unconditional logistic regression was used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for each polymorphism. The associations between each polymorphism and risk of glioma were further examined after adjusting for potential confounders using multivariate logistic regression models. Inclusion of potential confounders was based on biological and statistical considerations. Variables entered into the final model included: age, sex, smoking, and ionizing radiation exposure history.

Results

The distribution basic characteristics among cases and controls are shown in Table 1.The mean age was 47.8 years among cases and 46.9 years among controls. There were no significant differences between cases and controls in age, sex distribution, smoking status, and family history and cancer. More cases than controls had occupational ionizing radiation histories (P=0.026). The 271 glioma cases consisted of 97 (35.8%) glioblastoma, 91 (33.6%) anaplastic astrocytoma or diffuse astrocytoma or other astrocytoma, and 83 (30.6%) other gliomas. The distributions of the three genotype frequencies were in agreement with those expected from the HWE model at the 0.05 level for controls (P=0.963, 0.138, and 0.085 for Arg399Gln, Arg194Trp, and Arg280His, respectively).

Table 2 shows the genotype frequencies of the three polymorphisms in cases and controls and the corresponding ORs with CIs. Polymorphisms in Arg194Trp and Arg280His showed no statistically significant difference between glioma cases and controls. However, the genotype distribution of Arg399Gln differed between glioma cases and controls. Individuals with the Gln/Gln genotype had a significantly increased risk of developing giloma compared with those with the Arg/Arg genotype (adjusted OR = 1.93, 95% CI: 1.04 -

Table 1. Selected Characteristics of Cases and Controls N (%)

Variable	Cases (N=271)	Controls (N=289)	P value*
Age, years, mean ± SD	47.8 ± 7.3	46.9 ± 6.4	0.12
Sex			
Male	168 (62.0)	180 (62.3)	0.94
Female	103 (38.0)	109 (37.7)	
Smoking status			
Smokers	176 (64.9)	175 (60.6)	0.28
Non-smokers	95 (35.1)	114 (39.4)	
Occupational IR exposure history			
Yes	12 (4.4)	3 (1.0)	0.03
No	259 (95.6)	286 (99.0)	
Family history of cancer			
Yes	51 (18.8)	44 (15.2)	0.26
No	220 (81.2)	245 (84.8)	

SD, Standard Deviation; *Two-sided chi square test or t test

Table 2. Associations Between Polymorphisms in XRCC1 Gene and the Risk of Glioma

Genotype	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI) *
XRCC1 Arg399Gln				
Arg/Arg	121 (44.6)	147 (50.9)	Reference	Reference
Gln/Arg	113 (41.7)	118 (40.8)	1.16 (0.82, 1.66)	1.21 (0.78, 1.88)
Gln/Gln	37 (13.7)	24 (8.3)	1.87 (1.06, 3.30)	1.93 (1.04, 3.58)
Gln/Arg + Gln/Gln	150 (55.4)	142 (49.1)	1.28 (0.92, 1.79)	1.34 (0.91, 1.97)
XRCC1 Arg194Trp				
Arg/Arg	145 (53.5)	159 (55.0)	Reference	Reference
Arg/Trp	112 (41.3)	117 (40.5)	1.05 (0.74, 1.48)	1.03 (0.69, 1.54)
Trp/Trp	14 (5.2)	13 (4.5)	1.18 (0.54, 2.60)	1.09 (0.52, 2.28)
Arg/Trp + Trp/Trp	126 (46.5)	130 (45.0)	1.06 (0.76, 1.48)	1.04 (0.72, 1.50)
XRCC1 Arg280His				
Arg/Arg	218 (80.4)	240 (83.0)	Reference	Reference
Arg/His	45 (16.6)	44(15.2)	1.13 (0.71, 1.77)	1.24 (0.73, 2.11)
His/His	8 (3.0)	5 (1.7)	1.76 (0.57, 5.47)	1.64 (0.45, 5.98)
Arg/His + His/His	53 (19.6)	49 (16.9)	1.19 (0.78, 1.83)	1.30 (0.81, 2.09)

Table 3. Stratified Analyses Between XRCC1 Arg399Gln Polymorphism and the Risk of Glioma

Variables		No[a].	Adjusted OR (95% CI)*		
			Arg/Arg	Gln/Gln	Gln/Gln + Gln/Arg
Age	< 50 years	144/153	Reference	1.82 (0.78, 4.25)	1.29 (0.77, 2.16)
	≥ 50 years	127/136	Reference	2.17 (0.84, 5.61)	1.41 (0.80, 2.49)
Sex	Male	168/180	Reference	1.98 (0.91, 4.31)	1.37 (0.81, 2.29)
	Female	103/109	Reference	1.72 (0.69, 4.29)	1.28 (0.75, 2.18)
Histological types	Glioblastoma	97/289	Reference	1.92 (0.63, 5.85)	1.35 (0.67, 2.72)
	Astrocytomas[b]	83/289	Reference	1.89 (0.57, 6.27)	1.30 (0.64, 2.64)

*Adjusted for age, sex, smoking, and ionizing radiation exposure history; [a]Number of cases/controls; [b]including diffuse astrocytomas, anaplastic astrocytomas and other astrocytomas

3.58).

We further performed subgroup analyses stratified by age, sex and histological subtype for Arg399Gln polymorphism. Because of the low number of subjects with homozygous variant genotype in some subgroups, we only analyzed variant allele carriers. Results of subgroup analyses are shown in Table 3. The increased risk associated with the Arg399Gln polymorphism seemed more evident among males (adjusted OR for Gln/Gln genotype vs. Arg/Arg = 1.98, 95% CI: 0.91 – 4.31) than females (adjusted OR = 1.72, 95% CI: 0.69 – 4.29). The increased risk was also more evident among individuals aged 50 years or older (adjusted OR for Gln/Gln genotype vs. Arg/Arg = 2.17, 95% CI: 0.84 – 5.61) than those aged less than 50 years (adjusted OR = 1.82, 95% CI: 0.78 - 4.25). The increased risk associated with Arg399Gln polymorphism not varied significantly across different histological subtypes.

Discussion

To our knowledge, the present study was the first one which examined associations between polymorphisms in XRCC1 gene and the risk of glioma in a Chinese population in China. The observed significant association between Arg399Gln polymorphism and the risk of glioma suggested that Arg399Gln might be a useful susceptibility biomarker for glioma. Such a finding was in line with those of previous studies that 399Gln allele was associated with increased risk of glioma (Liu et al., 2009; Yosunkaya et al., 2010). However, several previous studies did not find significant association between the between Arg399Gln polymorphism and the risk of glioma (Wang et al., 2004; Kiuru et al., 2008; Rajaraman et al., 2010). We did not find significant association of polymorphisms in Arg194Trp and Arg280His with the risk of glioma, which were consistent with some but not all previous studies (Kiuru et al., 2008; Liu et al., 2009; Rajaraman et al., 2010). The inconsistency of these studies may be explained by differences in population background, source of control subjects, sample size, and also by chance. Further confirmation of existing findings is still needed in future studies.

The observed association between XRCC1 gene polymorphism and the risk of glioma in our study is biologically plausible. The human XRCC1 gene is an important component of the BER pathway and fixes base damage and DNA single-strand breaks caused by IR exposure (Tudek 2007). The Arg399Gln is located at the carboxylic acid terminal side of the polyadenosine diphosphate-ribose polymerase interacting domain and the variant Gln allele has been shown to reduce DNA repair capacity, and thereby, increased the risk of developing glioma (Lunn et al., 1999; Duell et al., 2000).

This study has several major limitations. First, we selected controls from hospital visitors, which may be

a threat to the validity of the results. Since it was not a random sample of the general population, there was still a certain risk of selection bias if they had any difference in terms of the studied exposures. However, all control subjects in our study were those who came to hospitals for routine health examination but not hospitalized patients with specific diseases, probably making the controls more representative of the general population. Second, because of the rarity of glioma, we only had limited number of cases. Increasing the number of controls to a control-case ratio of 2 or more can, at least to some extent, increase the study power, which needs consideration in future studies. Further, we only have a small number of participants with IR exposure, and thus, were not able to examine the potential interaction between genetic polymorphisms and IR exposure. Obviously, studies with larger sample size are still needed.

In summary, as the first study to investigate the association between polymorphisms in XRCC1gene and the risk of glioma in a Chinese population, this study found suggestive evidence that XRCC1 Arg399Gln polymorphism might be a useful susceptibility biomarker for glioma. Further studies in Chinese populations with larger sample sizes are still warranted.

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