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Association of polymorphisms of the xeroderma pigmentosum complementation group F gene with increased glioma risk

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ABSTRACT. We aimed to investigate the role of 4 single nucleotide polymorphisms of the xeroderma pigmentosum complementation group F (XPF) gene (rs3136038, rs1799798, rs1800067, and rs2276466) in glioma, and the roles of gene-gene interactions in the risk of developing this type of cancer. We collected samples from 225 glioma cases and 262 controls and genotyped the rs3136038, rs1799798, rs1800067, and rs2276466 polymorphisms using a 384-well plate format with the Sequenom MassARRAY platform. Individuals carrying the rs1800067 GG genotype were more likely to have an increased risk of glioma when compared with carriers of the A/A genotype in a co-dominant model, with an odds ratio (OR) [95% confidence interval (CI)] of 2.85 (1.14-7.76). However, we did not find an association with increased risk of glioma for the polymorphisms rs3136038, rs1799798, and rs2276466

in *XPF*. The combination genotype of the rs1800067 G allele and the rs2276466 G allele was associated with a moderate risk of glioma (OR = 1.71, 95%CI = 1.02-2.87). Our study suggests that the rs1800067 genetic variant of *XPF* functions in the development of glioma.

Key words: Xeroderma pigmentosum complementation group F; Polymorphisms; Glioma

INTRODUCTION

Glioma is the most common primary brain tumor in adults and is exceptionally difficult to treat. To date, only a few factors have been conclusively shown to affect glioma risk, including family history, rare genetic syndromes, and exposure to ionizing radiation. However, these factors only account for a fraction of glioma cases (Schwartzbaum et al., 2006; Bondy et al., 2008; Ostrom and Barnholtz-Sloan, 2011). Therefore, glioma carcinogenesis might be driven by the accumulation of genetic alterations that allow cells to escape from the normal growth-regulatory mechanisms (Liu et al., 2010).

Nucleotide excision repair (NER) is the most versatile DNA repair mechanism pathway, which is responsible for removing a wide variety of DNA lesions, such as bulky adducts, cross links, oxidative DNA damage, alkylating damage, and thymidine dimers (Wood et al., 2001). *Xeroderma pigmentosum complementation group F* (*XPF*) is one of the NER genes and is located on chromosome 16p13.12. It contains 11 exons that span approximately 28.2 kb, and is a key component involved in making the 5'-incision during NER (Liu et al., 1993; Wood et al., 2001). The XPF protein consists of 916 amino acids and contains an XPF nuclease domain, which is known to be a critical domain in essential meiotic endonuclease 1 (EME1) that acts with MUS81 in a Holliday junction resolvase complex (Tsodikov et al., 2005). Previously, only one study has explored the connection of two single nucleotide polymorphisms (SNPs) in ERCC4 with the risk of glioma. Therefore, we aimed to investigate the potential correlation of 4 *XPF* SNPs (rs3136038, rs1799798, rs1800067, and rs2276466) with the risk of glioma, and the role of gene-gene interactions in glioma risk.

MATERIAL AND METHODS

Study population

We identified 239 adults with newly diagnosed gliomas from November 2008 to May 2012 at Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. Ultimately, 225 patients agreed to participate in our study (94.2%). Patients who had a previous history of other cancers, prior chemotherapy, or radiotherapy were excluded.

A random sample of 319 healthy individuals was selected between January 2009 and May 2012 at Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. Subjects with chronic, brain, severe endocrinological, metabolic, or nutritional diseases were excluded from our study. A total of 262 healthy patients met our requirements and agreed to participate in our study (82.1%). Demographic and clinical data were collected from patient medical records or a self-designed questionnaire.

SNP selection and genotyping

The SNPs predicted to affect transcription factor binding site (TFBS) activity in the putative *XPF* promoter region and microRNA (miRNA) binding site activity were examined. From these SNPs, we chose 4 *XPF* SNPs according to our inclusion criteria, including rs3136038, rs1799798, rs1800067, and rs2276466. Genotyping of the 4 SNPs was performed in a 384-well plate format on the Sequenom MassARRAY RS1000 platform with a standard protocol that was recommended by the manufacturer (Sequenom; San Diego, CA, USA). Polymerase chain reaction (PCR) products were verified by 1.0% agarose gel electrophoresis and visualized via ethidium bromide staining under ultraviolet light. Genotyping was performed without knowledge of the glioma status of the subjects, and reproducibility was confirmed by repeat analysis of a randomly chosen subgroup of 5% of the study participants.

Statistical analyses

We analyzed Hardy-Weinberg equilibrium and intra-group genotype distributions using the chi-squared (χ^2) test. Allele frequencies and genotype frequencies of each SNP between glioma cases and controls were compared by means of the chi-squared test and the Student's *t*-test. Dominant and recessive genetic models were used to evaluate associations between each SNP and glioma risk. For each polymorphism, an odds ratio (OR) and 95% confidence interval (CI) were calculated by unconditional logistic regression analysis adjusted for potential risk factors. A P value < 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software, version 11.0 for Windows (SPSS Inc.; Chicago, IL, USA).

RESULTS

Our patient cohort included 225 patients with glioma (145 males and 80 females, mean age 52.7 ± 12.7 years) and 262 controls (142 males and 120 females, mean age 51.8 ± 12.9). The baseline clinical characteristics of the study population are shown in Table 1. Patients with glioma were significantly more likely to be male, to have an infrared radiation (IR) exposure history, and to have a history of brain cancer in first relatives ($P < 0.05$).

Table 1. Clinical and demographic characteristics of the study population.

Characteristics	Cases	%	Controls	%	χ^2	P
	N = 225		N = 262			
Age (mean ± SD) (years)	52.7 ± 12.7		51.8 ± 12.9		0.77	0.21
Gender						
Male	145	64.4	142	54.2	5.25	0.02
Female	80	35.6	120	45.8		
Smoking status						
Never	122	54.2	161	61.4		
Former	31	13.7	20	7.7	5.50	0.06
Current	72	32.1	81	30.9		
IR exposure history						
Never	195	86.7	255	97.4		
Ever	30	13.3	7	2.6	19.60	<0.001
History of brain cancer in the first relatives						
No	208	92.5	261	99.5		
Yes	17	7.5	1	0.5	17.50	<0.001

Genotype distributions of the 4 SNPs are shown in Table 2. In control subjects, the minor allele frequencies (MAFs) were consistent with published MAFs (available at http://www.ncbi.nlm.nih.gov/snp/) and were in Hardy-Weinberg equilibrium (Table 2).

Table 2. Association between the four XPF polymorphisms and glioma risk.

dbSNP	Major/minor allele	MAF From dbSNP	MAF	P for HWE in controls
			Control	
rs3136038	C/T	0.3324	35.8	0.17
rs1799798	A/G	0.0975	11.1	0.26
rs1800067	A/G	0.0311	11.9	0.49
rs2276466	C/G	0.2248	32.7	0.07

Multivariate logistic regression analysis was conducted to evaluate the effect of the 4 SNPs on glioma risk (Table 3). Individuals with the rs1800067 GG genotype were more likely to develop glioma than carriers of the A/A genotype in a co-dominant model, with an OR (95%CI) of 2.85 (1.14-7.76). However, we did not find an association with increased risk of glioma for the rs3136038, rs1799798, or rs2276466 polymorphisms in *XPF*.

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

dbSNP	Major/minor allele	Case	%	Control	%	Codominant model		Dominant model	
						OR (95%CI)[1]	P	OR (95%CI)	P
rs3136038	CC	94	41.7	111	42.5	-	-		
	CT	100	44.5	114	43.5	1.04 (0.69-1.55)	0.86		
	TT	31	13.8	34	14	1.08 (0.59-1.96)	0.80	1.02 (0.70-1.49)	0.90
rs1799798	AA	177	78.6	210	80.1	-	-	-	
	AG	38	16.8	46	17.6	0.98 (0.59-1.62)	0.93		
	GG	10	4.6	6	2.3	1.98 (0.64-6.74)	0.19	1.10 (0.69-1.74)	0.69
rs1800067	AA	164	72.8	208	79.4	-	-	-	
	AG	43	19.1	46	17.5	1.19 (0.73-1.93)	0.47		
	GG	18	8.1	8	3.1	2.85 (1.14-7.76)	0.01	1.43 (0.92-2.23)	0.09
rs2276466	CC	94	41.8	127	48.5	-	-	-	
	CG	87	38.7	99	37.7	1.19 (0.79-1.79)	0.39		
	GG	44	19.5	36	13.8	1.66 (0.97-2.86)	0.06	1.31 (0.90-1.91)	0.14

[1]Adjusted for gender, age, infrared radiation exposure history and history of brain cancer.

We analyzed the effect of interactions of rs1800067 and rs2276466 on glioma risk. The combination genotype of the rs1800067 G allele and the rs2276466 G allele was associated with a moderately increased risk of glioma (OR = 1.71, 95%CI = 1.02-2.87) (Table 4), but we did not find a statistically significant interaction between them (P = 0.36).

Table 4. Combination effect of rs1800067 and rs2276466 on glioma risk.

dbSNP		Cases	%	Controls	%	OR (95%CI)[1]	P
		N = 225		N = 262			
rs1800067	rs2276466						
AA	CC	88	39.1	115	43.9	-	-
G allele	CC	6	2.7	12	4.6	65 (0.19-1.97)	0.48
AA	G allele	76	33.8	93	35.5	1.07 (0.69–1.64)	0.82
G allele	G allele	55	24.4	42	16.0	1.71 (1.02–2.87)	0.03

[1]Adjusted for gender, age, infrared radiation exposure history and history of brain cancer.

DISCUSSION

In our study, we found that rs1800067 was strongly associated with increased glioma cancer risk, both individually and in combination with the rs2276466 polymorphism. Several previous studies have indicated that DNA repair gene polymorphisms play a role in the susceptibility to glioma (Wang et al., 2012; Chen et al., 2012; Jacobs and Bracken, 2012), but the association between polymorphisms in *XPF* SNPs and glioma risk has not yet been studied in a Chinese population. Our results suggest that the rs1800067 polymorphism may be used as a genetic susceptibility marker for glioma and as an identification index for high-risk individuals.

Currently, identification of novel genetic variants for assessing the early risk of glioma is attracting great interest across the global research community (Silva et al., 2013; Zhao et al., 2013; Hu et al., 2013). Based on genetic information, we may soon be able to determine the genetic etiology of glioma, identify high-risk individuals, and perform targeted therapy according to the genetic characteristics of an individual.

Studies have found that the rs1800067 variant was associated with an increased risk of developing various cancers, such as breast, larynx, and head and neck cancer (Rajaraman et al., 2008; Krupa et al., 2011; Yu et al., 2012; Shi et al., 2012). However, such results have been inconsistent. One study conducted in China did not find that rs1800067 could increase the susceptibility to head and neck cancer (Yu et al., 2012). Similarly, Krupa and colleagues reported that the rs1800067 polymorphism might not be associated with smoking and alcohol consumption-related larynx cancer in a Polish population (Krupa et al., 2011). Another meta-analysis suggested a lack of statistical evidence for the association between the rs1800067 polymorphism and the overall risk of developing various cancers (Shi et al., 2012). In this study, we found that the GG genotype of rs1800067 increased susceptibility to glioma. The main reason might be that this polymorphism of rs1800067 reduces the function of XPF, thereby reducing the efficiency of repairing double-strand breaks.

There were three limitations to our study. First, all cases and controls were selected from one hospital, and these subjects may not best represent the general population or glioma cases in China. Second, approximately 15% of the controls did not agree to participate in our study; therefore, the high non-participation rate might have introduced selection bias. Third, we did not find an association between the rs3136038, rs1799798, and rs2276466 alleles and glioma risk. The lack of statistical significance could have resulted from the small sample size that limited the statistical power available to detect an association.

Therefore, this case-control study indicated that rs1800067 SNPs were associated with glioma risk in a Chinese population. Our study suggests that the rs1800067 genetic variant of *XPF* impairs a biological function, which can lead to the development of glioma. Our study offers important insights into the molecular etiology of glioma.

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