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Association between XPG gene polymorphisms and development of gastric cancer risk in a Chinese population

Y.B. Feng[1], D.Q. Fan[2], J. Yu[2] and Y.K. Bie[1]

[1]Department of General Surgery, Ankang City Central Hospital, Ankang, China
[2]Department of General Surgery,
Nuclear Industry 215 Hospital of Shaanxi Province, Xianyang, China

Corresponding author: D.Q. Fan
E-mail: fandeqings@163.com

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ABSTRACT. We conducted a case-control study to investigate the role of three common single nucleotide polymorphisms (SNPs) in the xeroderma pigmentosum complementation group G (*XPG*) gene (rs2094258, rs751402 and rs17655) in the development of gastric cancer in a Chinese population. Between January 2012 and December 2014, samples from a total of 177 patients with gastric cancer and 237 control subjects were collected from the Ankang City Central Hospital. *XPG* rs2094258, rs751402 and rs17655 polymorphisms were genotyped using polymerase chain reaction-restriction fragment length polymorphism. Using logistic regression analysis, we found that the CC genotype of rs17655 was associated with an elevated risk of gastric cancer, and the adjusted odds ratio (OR) and 95% confidence intervals (95%CI) were 1.91 and 1.07-3.41, respectively. Moreover, individuals carrying the GC + CC genotype of rs17655 had an increased susceptibility to gastric cancer (OR = 1.61, 95%CI = 1.03-2.54). However, we did not observe a significant association between *XPG* rs2094258 and rs751402

polymorphisms and development of gastric cancer. In conclusion, our study suggests that the rs17655 polymorphism in *XPG* is associated with an increased risk of gastric cancer. The results of our findings should be further validated by further large sample size studies.

Key words: XPG; Polymorphism; Gastric cancer; Chinese population

INTRODUCTION

Gastric cancer is one of the most common types of malignancies in the world, and its morbidity and mortality rank fifth in all the tumors (International Agency for Research on Cancer, 2012). The International Agency for Research on Cancer has reported that there were 952,000 new gastric cancer cases in 2012 (International Agency for Research on Cancer, 2012). The root causes of gastric cancer are still unclear. Epidemical studies have revealed that *Helicobacter pylori* infection, alcohol consumption, obesity, and a high salt diet contribute to the development of gastric cancer (Alberts et al., 2003). However, not all individuals will develop gastric cancer even though they are exposed to the same risk factors. Moreover, some heritable factors may play an important role in the susceptibility to gastric cancer.

Xeroderma pigmentosum complementation group G (*XPG*) is an important nucleotide excision repair (NER) gene and it plays an important role in the DNA repair mechanism. Previous studies have reported that *XPG* gene polymorphisms are associated with different kinds of cancers (Liu et al., 2014; Mirecka et al., 2014; Steck et al., 2014; Xu et al., 2014; Paszkowska-Szczur et al., 2015). In this paper, we conducted a case-control study to investigate the role of three common single nucleotide polymorphisms (SNPs) in the *XPG* gene (rs2094258, rs751402 and rs17655) in the development of gastric cancer in a Chinese population.

MATERIAL AND METHODS

Patients

Between January 2012 and December 2014, samples from a total of 177 patients with gastric cancer were collected from the Ankang City Central Hospital, and all cases of gastric cancer were independently confirmed by two pathologists. Patients who had a history of other malignant tumors, recurrent cancers, or serious renal and liver diseases were excluded from the patient group. Samples from a total of 237 healthy subjects were also collected from individuals who underwent a regular health check-up in the Ankang City Central Hospital between January 2012 and December 2014. The exclusion criteria for control subjects were a history of any cancers and any digestive system disorders.

Detailed lifestyle and clinical characteristics, including sex, age, a family history of cancer in first-degree relatives, tobacco use, alcohol consumption, *H. pylori* infection, tumor-node-metastasis (TNM) stage, and Lauren classification, were collected from medical records or a self-designed questionnaire. The *H. pylori* infection was determined by a rapid urea breath test. All the individuals voluntarily participated in the study and signed an informed consent form before enrollment. This study was approved by the Ethics Committee of the Ankang City Central Hospital.

DNA extraction and SNP genotyping

Each patient and control was asked to provide a 5-mL peripheral blood sample, which was collected using ethylene diamine tetra-acetic acid (EDTA)-coated tubes. The DNA was extracted from patients and controls using the TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to manufacturer instructions. *XPG* rs2094258, rs751402 and rs17655 polymorphisms were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The primers for *XPG* rs2094258 were: forward, 5'-AGCCTCGCCTTTGCCGAT-3' and reverse, 5'-CTTCTGACCCATGCCCACC-3'. For rs751402, the primers were: forward, 5'-GGGCTTCCAGAACTCACT-3' and reverse, 5'-GTGTCTGTAATCGCCCTAC-3'. For rs17655, the primers were: forward, 5'-TTACGTCTTTGCGACAAATTCATT-3' and reverse, 5'-CATTAAAGATGAACTTTCAGCAT-3'. The PCR conditions were performed as follows: an initial denaturation at 95°C for 5 min; 30 cycles of denaturation at 94°C for 60 s, annealing at 60°C for 60 s, and extension at 72°C for 60 s; and a final extension at 72°C for 10 min. Digestion of products was confirmed by electrophoresis on ethidium bromide-stained agarose gels.

Statistical analysis

The demographic, lifestyle, and clinical data between patients with gastric cancer and control subjects were compared using chi-square test (χ^2). Chi-square test was used to assess whether the genotype distributions of *XPG* rs2094258, rs751402 and rs17655 deviated from the Hardy-Weinberg equilibrium (HWE). Unconditional regression analysis was used to analyze the association between *XPG* rs2094258, rs751402, and rs17655 polymorphisms and risk of gastric cancer, and the odds ratios (ORs) and 95% confidence intervals (CIs) were used to describe the results. The main homozygous genotypes of *XPG* rs2094258, rs751402, and rs17655 were considered as reference groups for analysis. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS, Chicago, IL, USA), and a P value less than 0.05 was considered to be statistically significant.

RESULTS

The demographic, lifestyle, and clinical data of patients with gastric cancer and control subjects are shown in Table 1. There were 61 (34.46%) females and 116 (65.54%) males with gastric cancer, and 110 (46.41%) females and 127 (53.59%) males as healthy controls. Compared with controls, patients with gastric cancer were more likely to be males (OR = 1.65, 95%CI = 1.08-2.51), have cancer history in first-degree relatives (OR = 2.87, 95%CI = 1.18-7.42), and consume alcohol (OR = 1.57, 95%CI = 1.04-2.37). Of all gastric cancer patients, 80 (45.20%) patients were at TNM stage I-II and 97 (54.80%) were at TNM stage III-IV. For the Lauren classification, 87 (49.15%) were intestinal type and 90 (50.85%) were diffuse type.

The genotype distributions of *XPG* rs2094258, rs751402, and rs17655 polymorphisms in gastric cancer patients and control groups are shown in Table 2. The genotype distributions of *XPG* rs2094258, rs751402, and rs17655 polymorphisms were in Hardy-Weinberg equilibrium in gastric cancer patients and controls (P values in gastric cancer patients were 0.84, 0.94 and 0.60, respectively; P values in controls were 0.58, 0.97 and 0.26, respectively). By the chi-square test, there was a significant difference in the genotype distributions of rs17655 between gastric cancer patients and controls (χ^2 = 4.38, P value = 0.11). However, no significant

difference was found in *XPG* rs2094258 (χ^2 = 1.11, P value = 0.57) and rs751402 (χ^2 = 0.54, P value = 0.76) between gastric cancer patients and controls.

Table 1. Demographic, lifestyle, and clinical data between patients with gastric cancer and control subjects.

Variables	Patients	%	Controls	%	χ^2test	OR(95% CI)	P value
Mean age(years)							
<50	77	43.50	91	38.40		1.0 (Ref.)	-
≥50	100	56.50	146	61.60	1.10	0.81(0.53-1.23)	0.30
Gender							
Female	61	34.46	110	46.41		1.0 (Ref.)	-
Male	116	65.54	127	53.59	5.97	1.65(1.08-2.51)	0.02
Familial cancer history in first-degree relatives							
No	159	89.83	228	96.20		1.0 (Ref.)	-
Yes	18	10.17	9	3.80	6.75	2.87(1.18-7.42)	0.01
Alcohol consumption							
No	84	47.46	139	58.65		1.0 (Ref.)	-
Yes	93	52.54	98	41.35	5.11	1.57(1.04-2.37)	0.02
Tobacco use							
No	104	58.76	125	52.74		1.0 (Ref.)	-
Yes	73	41.24	112	47.26	1.48	0.78(0.52-1.18)	0.22
TNM stage at diagnosis							
I-II	80	45.20					
III-IV	97	54.80					
Lauren classification							
Intestinal	87	49.15					
Diffuse	90	50.85					

Table 2. Distribution of XPG rs2094258, rs751402 and rs17655 polymorphisms between gastric cancer patients and control group.

XPG	Patients	%	Controls	%	χ^2 test	P value	P for HWE	
							In cases	In controls
rs2094258								
AA	87	49.15	127	53.59				
AG	75	42.37	96	40.51				
GG	15	8.47	15	6.33	1.11	0.57	0.84	0.58
rs751402								
CC	70	39.55	101	42.62				
CT	83	46.89	107	45.15				
TT	24	13.56	28	11.81	0.54	0.76	0.94	0.97
rs17655								
GG	47	26.55	84	35.44				
GC	85	48.02	107	45.15				
CC	45	25.42	46	19.41	4.38	0.11	0.60	0.26

Using logistic regression analysis, we found that the CC genotype of rs17655 was associated with an elevated risk of gastric cancer, and the adjusted OR and 95%CI was 1.91 and 1.07-3.41, respectively (Table 3). Moreover, individuals carrying the GC + CC genotype of rs17655 had an increased susceptibility to gastric cancer (OR = 1.61, 95%CI = 1.03-2.54). However, we did not observe a significant association between *XPG* rs2094258 and rs751402 polymorphisms and development of gastric cancer.

Table 3. Association between XPG rs2094258, rs751402 and rs17655 gene polymorphisms and risk of gastric cancer.

Variables	Patients	%	Controls	%	OR (95% CI)[1]	P value
rs2094258						
AA	87	49.15	127	53.59	1.0 (Ref.)	-
AG	75	42.37	96	40.51	1.14(0.74-1.75)	0.53
GG	15	8.47	15	6.33	1.46(0.63-3.38)	0.33
AG+GG	90	50.85	111	46.84	1.18(0.79-1.78)	0.40
rs751402						
CC	70	39.55	101	42.62	1.0 (Ref.)	-
CT	83	46.89	107	45.15	1.12(0.72-1.74)	0.60
TT	24	13.56	28	11.81	1.24(0.63-2.42)	0.50
CT+TT	107	60.45	135	56.96	1.14(0.75-1.74)	0.51
rs17655						
GG	45	25.42	84	35.44	1.0 (Ref.)	-
GC	85	48.02	107	45.15	1.48(0.91-2.42)	0.09
CC	47	26.55	46	19.41	1.91(1.07-3.41)	0.02
GC+CC	132	74.58	153	64.56	1.61(1.03-2.54)	0.03

[1]Adjusted for age, gender, familial cancer history in first-degree relatives, and alcohol consumption.

DISCUSSION

Polymorphisms in the *XPG* gene plays an important role in correcting the excision repair deficiency, resulting in a lower DNA repair capacity of the NER pathway and influencing cancer susceptibility (Mudgett and MacInnes, 1990; Takahashi et al., 1992). In our study, we assessed whether the *XPG* rs2094258, rs751402, and rs17655 gene polymorphisms could influence the development of gastric cancer, and we found that the rs17655 GC and CC genotypes were associated with an increased risk of this cancer.

Previous studies have reported that the *XPG* gene polymorphisms play an important role in the development of several kinds of cancers, such as colorectal cancer, breast cancer, lung cancer, laryngeal cancer, oral squamous cell carcinoma, and esophageal squamous cell carcinoma (Zavras et al., 2012; Zhu et al., 2012; Liang et al., 2014; Lu et al., 2014; Na et al., 2015; Zeng et al., 2015). Zeng et al. (2015) conducted a meta-analysis with 5102 gastric cancer and 6326 controls and reported that the excision repair cross-complementation group 5 (*ERCC5*) rs17655 polymorphism may contribute to susceptibility to colorectal cancer. Na et al. (2015) conducted a case-control study in a Chinese population and found that the *XPG* rs2094258 polymorphism was associated with risk of breast cancer. Liang et al. (2014) conducted a meta-analysis with nine case-control studies and reported that the *ERCC5* rs17655 polymorphism may not be correlated with the development of lung cancer. Zavras et al. (2012) reported that the *ERCC*5 rs751402 CC genotype was correlated with a decreased risk of oral squamous cell carcinoma. The discrepancies between the above mentioned studies may be caused by differences in cancer types, populations, selection of patients and controls, and sample size.

Several previous studies have reported the association between *XPG* gene polymorphisms and development of gastric cancer (Hussain et al., 2009; Duan et al., 2012; He et al., 2012; Yang et al., 2012). He et al. (2012) conducted a case-control study with 125 gastric cancer and 1196 cancer-free controls and reported that the *XPG* polymorphisms may contribute to the risk of gastric cancer. Yang et al. (2012) conducted a study in a Chinese population and suggested that the *XPG* rs2296147T > C, rs2094258C > T, and rs873601G > A polymorphisms may contribute to the development of gastric cancer. Duan et al. (2012) suggested that the *XPG*

rs751402 and rs2296147 polymorphisms might contribute to risk of gastric cancer in a Chinese population. Hussain et al. (2009) reported that the *XPG* rs1047768, rs17655, and rs2227869 polymorphisms may be correlated with reduced gastric cancer risk. In our study, we found that the rs17655 gene polymorphism in *XPG* was associated with an increased risk of gastric cancer. Further studies are greatly needed to confirm the results of our study.

In conclusion, our study suggests that the *XPG* rs17655 GC and CC genotypes are associated with an increased risk of gastric cancer, but there is no association between *XPG* rs2094258 and rs751402 polymorphisms and development of gastric cancer in a Chinese population. The results of our findings should be further validated by further large sample size studies.

Conflicts of interest

The authors declare no conflict of interest.

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