Am J Transl Res 2019;11(2):1020-1029
www.ajtr.org /ISSN:1943-8141/AJTR0089280

Original Article

XPG Asp1104His polymorphism increases colorectal cancer risk especially in Asians

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Received December 2, 2018; Accepted December 24, 2018; Epub February 15, 2019; Published February 28, 2019

Abstract: Xeroderma pigmentosum group G (XPG) protein is a pivotal element of the nucleotide excision repair pathway. *XPG* gene single nucleotide polymorphisms (SNPs) have been shown to confer colorectal cancer (CRC) susceptibility. In this study, we further investigated the role of Asp1104His (rs17655 G > C) in *XPG* on CRC risk. We genotyped the rs17655 G > C polymorphism in Chinese population comprising 1019 CRC cases and 1036 cancer-free controls. We also performed a meta-analysis to further assess the association. Overall, no significant association was detected between the rs17655 G > C and the risk of CRC. Stratified analysis also revealed no significant association. To further elucidate the association of the rs17655 with CRC susceptibility, we conducted a meta-analysis by including qualified publications and the current study. The meta-analysis results demonstrated that rs17655 G > C was associated with an increased CRC risk (CG vs. GG: OR = 1.14, 95% CI = 1.01-1.28; CC/CG vs. GG: OR = 1.12, 95% CI = 1.01-1.24; C vs. G: OR = 1.06, 95% CI = 1.01-1.11). In subgroup analysis, the significant association between the rs17655 C allele and CRC risk was found in Asians and hospital-based subgroups. Taken together, our results suggested that the *XPG* rs17655 G > C polymorphism is a low-penetrance susceptibility locus for CRC. Further studies are warranted to validate these findings.

Keywords: Colorectal cancer, *XPG,* Asp1104His, polymorphism, susceptibility

Introduction

Colorectal cancer (CRC) is considered as the third most common cancer and the fourth leading cause of cancer-related death in the world [1]. In China, CRC ranks the top five both in new cancer cases and the cancer-related cause death [2]. The etiology of CRC is highly complicated, involving the interaction between genetic and environmental factors [3]. The discovery of risk factors would help to identify high-risk individuals and develop prevention strategies. Previous epidemiological studies have led to the findings of numerous polymorphisms predisposing to CRC.

DNA repair systems play an indispensable role in protecting genome from endogenous and exogenous damages [4]. Nucleotide excision repair (NER) is the most versatile DNA repair mechanism among the five known DNA repair systems [5, 6], which mainly takes the responsibility to get rid of bulky DNA adducts and UV-induced DNA damage [7]. Aberrant function of NER pathway is tightly associated with Xeroderma pigmentosum (XP), an unusual autosomal recessive disease; affected individuals are extremely vulnerable to sunlight-induced skin cancer [8]. NER pathway is composed of a number of core protein molecules, including XPA to XPG [9]. *XPG* [alias *excision repair cross-complementation group 5* (*ERCC5*)] [10] is mapped to chromosome 13q22-q23 and encodes a protein of 1186-amino acid residues. XPG protein participates in the initial step of DNA repair process by recognizing the DNA damage loci [11-13]. XPG also mediates mutagenesis and cell death by influencing RNA transcription [14, 15].

Single nucleotide polymorphisms (SNPs) in the *XPG* gene are reported to predispose to the

Table 1. Demographic characteristics of the colorectal cancer patients and controls

Variables	Cases (n = 1019)		Controls (n = 1036)		*P*[a]
	No.	%	No.	%	
Age range, year	23-87		24-85		0.508
Mean ± SD	56.58 ± 12.69		57.25 ± 11.82		
≤ 58	546	53.58	650	52.12	
> 58	473	46.42	496	47.88	
Gender					0.230
Female	389	38.17	369	35.62	
Male	630	61.83	667	64.38	
BMI					< 0.0001
< 18.0	90	8.83	9	0.87	
18-24.9	717	70.36	606	58.49	
25.0-29.9	193	18.94	362	34.94	
> 30.0	19	1.86	59	5.69	
Smoking status					< 0.0001
Never	726	71.25	565	54.54	
Ever	293	28.75	471	45.46	
Pack-year					< 0.0001
0	726	71.25	565	54.54	
≤ 30	151	14.82	294	28.38	
> 30	142	13.94	177	17.08	
Drinking status					< 0.0001
No	847	83.12	763	73.65	
Yes	172	16.88	273	26.35	
Tumor locations					
Colon	477	46.81	/	/	
Rectal	542	53.19	/	/	
Duke stages					
A	46	4.51	/	/	
B	314	30.81	/	/	
C	380	37.29	/	/	
D	279	27.38	/	/	

SD, standard deviation; BMI, body mass index. [a]Two-sided Chi-square test for the distributions between patients and controls.

susceptibility of several cancers, including gastric cancer [16-18], prostate cancer [19], breast cancer [20], as well as colorectal cancer [21]. Among cancer predisposing *XPG* SNPs, the Asp1104His polymorphism (rs17655 G > C) is most frequently investigated [22, 23]. Asp1104His polymorphism is a nonsynonymous polymorphism commonly regarded as a tagger. It can result in an amino acid alteration within the protein sequence. Several studies have been performed to investigate the association between the *XPG* rs17655 G > C polymorphism and CRC risk, but yielded conflicting results. Therefore, further replication studies are needed to solve these discrepancies. Here, we conducted a case-control study, followed by a meta-analysis, to provide a precise evaluation of the association of interest.

Materials and methods

Study population

We recruited 1019 cases with histologically confirmed CRC in the Department of Colorectal and Anal Surgery, The First Affiliated Hospital of Zhengzhou University in the last four year. We also enrolled 1036 cancer-free controls in the same region during the same period. All the enrolled participants were unrelated ethnic Han Chinese population. Each participant provided a written informed consent. The demographic characteristics were obtained from the participants by using a self-administered questionnaire. Each participant donated 5 ml of venous blood sample on a voluntary basis. The study was approved by the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University.

Genotyping

We first adopted the Qiagen Blood DNA Mini Kit (Qiagen Inc., Valencia, CA) to extract genomic DNA, according to the standard procedures. Then Taqman assay was chosen for genotyping with Applied Biosystems (Foster City, CA). We also set four duplicated positive controls and four negative controls (without DNA) in each of 384-well plates for quality control. Moreover, 10% of the samples were randomly chosen to be analyzed for a second time, and 100% concordant results were obtained.

Statistical analysis

Differences in demographic characteristics among cases and controls were tested using chi-square test. Goodness-of-fit X^2 test was applied to check whether the genotype fre-

Table 2. Association between *XPG* rs17655 G > C polymorphism and colorectal cancer risk

Genotype	Cases		Controls		P^a	OR (95% CI)	*P*	AOR (95% CI)[b]	P^b
	No.	%	No.	%					
rs17655 (HWE = 0.854)									
GG	248	24.34	265	25.58		1.00		1.00	
CG	510	50.05	515	49.71		1.06 (0.86-1.31)	0.601	0.99 (0.79-1.24)	0.947
CC	261	25.61	256	24.71		1.09 (0.85-1.39)	0.492	1.10 (0.85-1.43)	0.461
Additive					0.781	1.04 (0.92-1.18)	0.493	1.05 (0.92-1.20)	0.459
Dominant	771	75.66	771	74.42	0.515	1.07 (0.88-1.31)	0.516	1.03 (0.83-1.27)	0.797
Recessive	758	74.39	780	75.29	0.637	1.05 (0.86-1.28)	0.637	1.11 (0.90-1.37)	0.342

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; HWE, Hardy-Weinberg equilibrium. [a]Chi-square test for genotype distributions between patients and controls. [b]Adjusted for age, gender, BMI, smoking and drinking status.

quency distribution of rs17655 G > C in controls was deviated from Hardy-Weinberg equilibrium (HWE). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from multivariate logistic regression, and then used to estimate the associations between rs17655 G > C and CRC risk. We also performed stratification analysis by age, gender, body mass index (BMI), smoking status, pack-years, drinking status, tumor location, and Duke stage. All statistical analysis was performed using SAS system (version 9.1; SAS Institute, Cary, NC). Statistical significance was set on the basis of two-sided *P*-values < 0.05.

Meta-analysis

We further evaluated the association between rs17655 G > C and CRC risk using meta-analysis. PubMed, EMBASE, and MEDLINE databases were used to conduct systematic literature searches. The search terms were as follows: "colorectal cancer or colorectal tumor or colorectal carcinoma or colorectal neoplasm or CRC", "Xeroderma pigmentosum group G or *XPG* or rs17655 or Asp1104His", and "polymorphism or SNP or variant or variation". Literature searches were updated to July 1, 2018. Between-study heterogeneity was determined by a chi-square-based *Q*-Test. The random-effects model (the DerSimonian and Laird method) would be performed in the presence of heterogeneity, whereas the fixed-effects model (the Mantel-Haenszel method) would be performed [23-25]. The funnel plot and the Egger's linear regression test were used to assess publication bias. In addition, sensitivity analysis was also applied to assess the strength of the study. The meta-analysis was conducted using STATA version 11.0 (Stata Corporation, College Station, TX, USA).

Results

Population characteristics

The demographic characteristics of 1019 CRC patients and 1036 cancer-free controls were shown in **Table 1**. No significant difference was observed in the distributions of age (*P* = 0.508) and gender (*P* = 0.230) between the cases and controls. The percentage of ever smokers (28.75%) were significantly lower in cases than in controls (45.46%). Significant difference was also detected in pack-years between cases and controls. Moreover, cases were less likely to be drinkers than controls. As to the location of tumor, 46.81% of lesions (477 cases) occurred in colon, while 53.19% of lesions (542 cases) in rectum. In term of tumor stage, 46 (4.51%), 314 (30.81%), 380 (37.29%), and 279 cases (27.38%) were diagnosed with Duke's stage A, B, C, and D diseases, respectively.

XPG gene rs17655 G > C polymorphism and colorectal cancer risk

The genotype distribution of the *XPG* gene rs17655 G > C and the association results were summarized in **Table 2**. The frequency distribution of rs17655 G > C was consistent with HWE in the control subjects (*P* = 0.854). We observed no significant association between rs17655 G > C and CRC risk.

Stratification analysis

The stratified study was performed to explore the association between rs17655 G > C polymorphism and CRC risk by age, gender, BMI, smoking status, pack-year, drinking status, tumor location, and Duke stage. However, we

Table 3. Stratification analysis for the association between *XPG* rs17655 G > C polymorphism and colorectal cancer risk

Variables	GG	CG/CC	OR (95% CI)	*P*	AOR (95% CI)[a]	*P*[a]
	Cases/controls					
Age, median						
≤ 58	124/125	422/415	1.03 (0.77-1.36)	0.864	1.01 (0.75-1.35)	0.964
> 58	124/140	349/356	1.11 (0.83-1.47)	0.483	1.04 (0.77-1.42)	0.789
Gender						
Females	92/90	297/279	1.04 (0.75-1.45)	0.812	1.06 (0.74-1.51)	0.764
Males	156/175	474/492	1.08 (0.84-1.39)	0.543	1.02 (0.78-1.32)	0.910
BMI						
< 18.0	19/6	71/3	7.47 (1.71-32.68)	0.008	13.58 (2.33-79.11)	0.004
18-24.9	171/150	546/456	1.05 (0.82-1.35)	0.702	1.04 (0.80-1.34)	0.788
25.0-29.9	53/93	140/269	0.91 (0.62-1.36)	0.652	0.87 (0.58-1.32)	0.512
> 30.0	5/16	14/43	1.04 (0.32-3.36)	0.946	1.09 (0.33-3.66)	0.887
Smoking status						
Never	174/134	552/431	0.99 (0.76-1.28)	0.917	0.93 (0.71-1.22)	0.579
Ever	74/131	219/340	1.14 (0.82-1.59)	0.438	1.15 (0.81-1.64)	0.425
Pack-year						
0	174/134	552/431	0.99 (0.76-1.28)	0.917	0.94 (0.72-1.24)	0.676
≤ 30	34/82	117/212	1.33 (0.84-2.11)	0.222	1.26 (0.77-2.05)	0.361
> 30	40/49	102/128	0.98 (0.60-1.60)	0.923	0.75 (0.43-1.33)	0.324
Drinking status						
Never	205/180	642/583	0.97 (0.77-1.22)	0.774	0.95 (0.75-1.21)	0.677
Ever	43/85	129/188	1.36 (0.88-2.09)	0.165	1.29 (0.82-2.02)	0.271
Tumor locations						
Colon	117/265	360/771	1.06 (0.82-1.36)	0.664	1.00 (0.76-1.30)	0.969
Rectal	131/265	411/771	1.08 (0.85-1.37)	0.540	1.07 (0.83-1.38)	0.607
Duke stages						
A + B	90/265	270/771	1.03 (0.78-1.36)	0.829	1.04 (0.78-1.39)	0.783
C + D	158/265	501/771	1.09 (0.87-1.37)	0.457	1.02 (0.80-1.30)	0.859

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; BMI, body mass index. [a]Adjusted for age, gender, BMI, smoking and drinking status.

Table 4. Main characteristics of included studies for the final meta-analysis

Name	Year	Region	Ethnicity	Design	Genotype	Case				Control				MAF	HWE
					Method	GG	CG	CC	All	GG	CG	CC	All		
Bigler	2005	USA	Caucasian	PB	Taqman	440	237	36	713	353	226	37	616	0.24	0.917
Huang	2006	USA	Caucasian	PB	Sequencing	407	243	29	679	403	265	29	697	0.23	0.073
Pardini	2008	Czech	Caucasian	HB	PCR-RFLP	334	177	21	532	356	153	23	532	0.19	0.211
Joshi	2009	USA	Caucasian	FB	Taqman	183	114	11	308	213	137	11	361	0.22	0.046
Canbay	2011	Turkey	Caucasian	PB	PCR-RFLP	43	34	2	79	148	83	16	247	0.23	0.352
Gil	2012	Poland	Caucasian	PB	PCR-RFLP	86	35	11	132	64	31	5	100	0.21	0.625
Liu	2012	China	Asian	HB	PCR-RFLP	233	603	192	1028	329	537	219	1085	0.45	0.996
Du	2014	China	Asian	HB	TaqMan	286	459	133	878	355	405	124	884	0.37	0.623
Steck	2014	USA	Caucasian	PB	MassARRAY	183	100	15	298	335	170	27	532	0.21	0.372
Steck	2014	USA	African	PB	MassARRAY	65	120	39	224	100	151	66	317	0.45	0.519
Paszkowska-Szczur	2015	Poland	Caucasian	HB	Taqman	429	272	32	733	869	404	85	1358	0.21	0.0001
Sun	2015	China	Asian	HB	PCR-RFLP	216	476	198	890	227	497	186	910	0.48	0.004
Kabzinski	2015	Poland	Caucasian	HB	QPCR	36	171	27	234	43	175	20	238	0.45	< 0.001
Su	Current	China	Asian	HB	Taqman	248	510	261	1019	265	515	256	1036	0.50	0.854

MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; PB, population based; HB, hospital based; FB, family based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table 5. Meta-analysis of the association between *XPG* rs17655 G > C polymorphism and colorectal cancer risk

Variables	No. of studies	Cases/controls	Homozygous		Heterozygous		Recessive		Dominant		Allele comparing	
			CC vs. GG		CG vs. GG		CC vs. CG/GG		CC/CG vs. GG		C vs. G	
			OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}	OR (95% CI)	P^{het}
All	14	7747/8913	1.09 (0.98-1.22)	0.584	1.14 (1.01-1.28)	0.002	0.99 (0.90-1.09)	0.593	1.12 (1.01-1.24)	0.013	1.06 (1.01-1.11)	0.477
Ethnicity												
Caucasian	9	3708/4681	0.93 (0.76-1.15)	0.651	1.07 (0.93-1.23)	0.046	0.91 (0.75-1.12)	0.503	1.05 (0.94-1.18)	0.163	1.02 (0.95-1.10)	0.557
Asian	4	3815/3915	1.18 (1.04-1.35)	0.716	1.25 (1.00-1.54)	0.006	1.03 (0.92-1.15)	0.572	1.23 (1.03-1.47)	0.025	1.10 (1.03-1.17)	0.394
African	1	224/317	0.91 (0.55-1.51)	/	1.22 (0.83-1.81)	/	0.80 (0.52-1.24)	/	1.13 (0.78-1.64)	/	0.98 (0.77-1.25)	/
Source of control												
PB	6	2125/2509	0.91 (0.71-1.17)	0.757	0.97 (0.85-1.12)	0.330	0.89 (0.70-1.13)	0.639	0.95 (0.84-1.07)	0.544	0.95 (0.86-1.05)	0.806
HB	7	5314/6043	1.14 (1.01-1.29)	0.395	1.26 (1.11-1.44)	0.041	1.01 (0.91-1.12)	0.336	1.24 (1.11-1.37)	0.148	1.11 (1.05-1.17)	0.804
FB	1	308/361	1.16 (0.49-2.75)	/	0.97 (0.71-1.33)	/	1.18 (0.50-2.76)	/	0.98 (0.72-1.34)	/	1.00 (0.77-1.30)	/
HWE												
> 0.05	10	5582/6046	1.11 (0.98-1.26)	0.100	1.14 (0.98-1.33)	0.090	0.98 (0.88-1.09)	0.709	1.20 (0.98-1.28)	0.105	1.05 (0.98-1.13)	0.141
≤ 0.05	4	2165/2867	1.05 (0.81-1.37)	0.722	1.13 (0.94-1.36)	0.196	1.02 (0.75-1.38)	0.895	1.13 (1.00-1.28)	0.047	1.07 (0.98-1.17)	0.116

OR, odds ratio; CI, confidence interval; PB, population based; HB, hospital based; FB, family based; HWE, Hardy-Weinberg equilibrium.

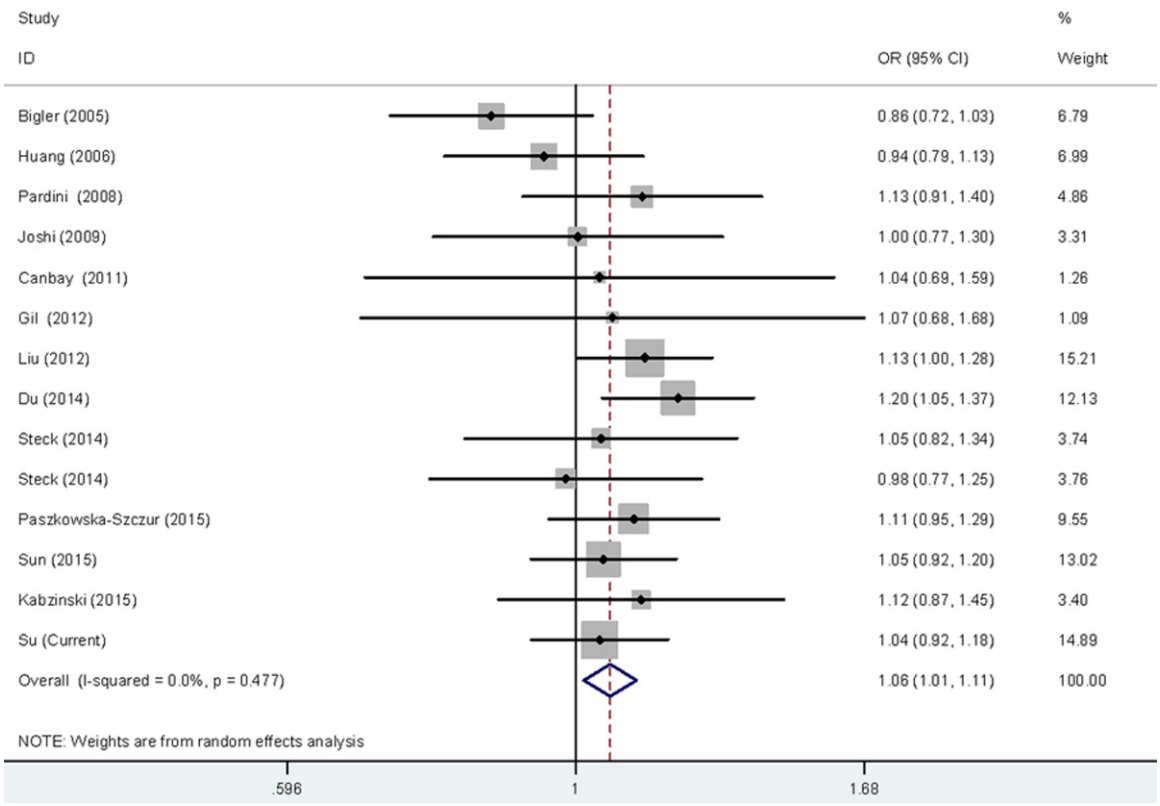

Figure 1. Forest plot for the CRC susceptibility associated with the rs17655 G > C polymorphism under allele comparison model. The horizontal lines represent the study-specific ORs and 95% CIs, respectively. The diamond represents the pooled results of OR and 95% CI.

did not find any significant association (**Table 3**).

Meta-analysis results

Meta-analysis was also carried out to further explore the association of rs17655 G > C polymorphism with CRC risk by combining qualified publications and our data. Overall, 14 eligible case-control studies were pooled together to evaluate such association [26-37] (**Table 4**). As shown in **Table 5** and **Figure 1**, pooled results indicated that rs17655 G > C polymorphism was associated with an increased CRC susceptibility (CG vs. GG: OR = 1.14, 95% CI = 1.01-1.28; CC/CG vs. GG: OR = 1.12, 95% CI = 1.01-1.24; C vs. G: OR = 1.06, 95% CI = 1.01-1.11). Stratified analysis by ethnicity revealed significant association between rs17655 G > C genotype and CRC risk among Asian (CC vs. GG: OR = 1.18, 95% CI = 1.04-1.35; CG vs. GG: OR = 1.25, 95% CI = 1.00-1.54; CC/CG vs. GG: OR = 1.23, 95% CI = 1.03-1.47; C vs. G: OR = 1.10, 95% CI = 1.03-1.17), but not among Caucasians or Africans (**Figure 2**). Regarding source of controls (**Figure 3**), significant association was detected between rs17655 G > C and an increased CRC risk in hospital-based studies (CC vs. GG: OR = 1.14, 95% CI = 1.01-1.29; CG vs. GG: OR = 1.26, 95% CI = 1.11-1.44; CC/CG vs. GG: OR = 1.24, 95% CI = 1.11-1.37; C vs. G: OR = 1.11, 95% CI = 1.05-1.17). Regarding HWE (**Figure 4**), significant association was only detected between rs17655 G > C and an increased CRC risk in HWE ≤ 0.05 studies (CC/CG vs. GG: OR = 1.13, 95% CI = 1.00-1.28). Leave-one-out sensitivity analysis result demonstrated that no removal of any single study could lead to substantial change in pooled results. Moreover, no evidence of obvious asymmetry in Begg's funnel plots was found.

Discussion

In the present study, we further explored the predisposing role of *XPG* rs17655 G > C polymorphism in CRC. The results of our case-control study failed to provide supportive evidence

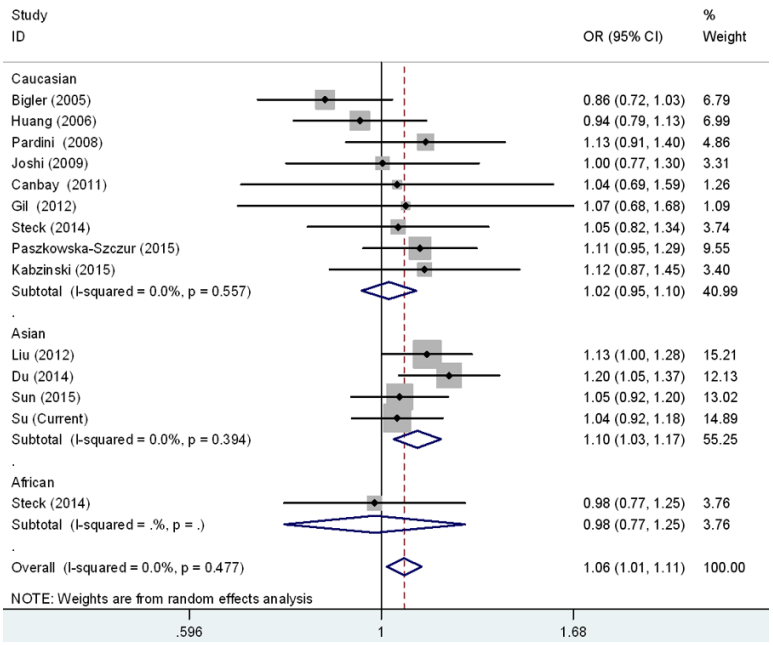

Figure 2. Forest plot for the CRC susceptibility associated with the rs17655 G > C polymorphism stratified by ethnicities under allele comparison model. The horizontal lines represent the study-specific ORs and 95% CIs, respectively. The diamond represents the pooled results of OR and 95% CI.

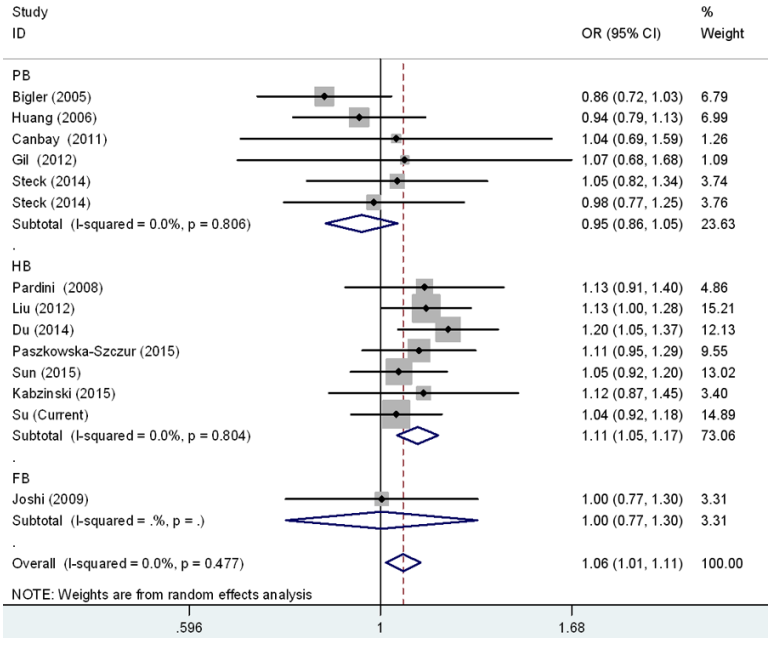

Figure 3. Forest plot for the CRC susceptibility associated with the rs17655 G > C polymorphism stratified by design under allele comparison model. The horizontal lines represent the study-specific ORs and 95% CIs, respectively. The diamond represents the pooled results of OR and 95% CI.

of the association between the *XPG* gene rs17655 G > C polymorphism and CRC risk. However, the following meta-analysis demonstrated that the *XPG* rs17655 G > C polymorphism confers increased CRC risk.

XPG is an endonuclease responsible for a dual incision in NER pathway. XPG cut the DNA strand at the 3' end of the lesion, and maintain the DNA repair complex in the damaged site with ERCC1/XPF complex by generating 5' incision [38-41]. Genetic variations of *XPG* may impair the DNA repair capacity and genome integrity, consequently leading to the initiation of carcinogenesis. The association of *XPG* rs17655 G > C (Asp1104His) polymorphism with colorectal cancer risk has been widely investigated, and results are controversial. Paszkowska-Szczur et al. [35] failed to detect significant associations between *XPG* rs17655 G > C and CRC risk. Such null associations were also presented in a study conducted by Canbay et al. [31] in Turkish population with 79 CRC cases and 247 healthy controls. Opposite results regarding the association were also reported. In a Czech hospital-based case-control study including 532 cases and 532 controls, the *XPG* rs17655 G > C was shown to increase the risk of CRC [29]. Liu et al. [33] observed that heterozygotes and homozygotes of this variant were more likely to have CRC than wild controls, in a Chinese population study including 1028 CRC cases and 1085 controls. More recently, Du et al. [26] also verified the risk effect of *XPG* rs17655 G > C polymorphism on CRC in a Chinese population.

Replication study is a golden standard to validate a association. We performed this case-control study to further elucidate the contribution of *XPG* rs17655 G > C polymorphism to

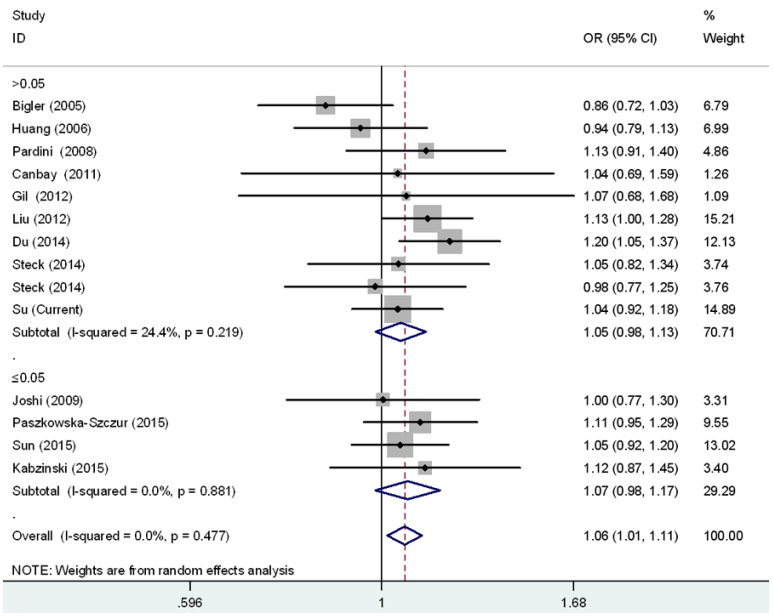

Figure 4. Forest plot for the CRC susceptibility associated with the rs17655 G > C polymorphism stratified by HWE under allele comparison model. The horizontal lines represent the study-specific ORs and 95% CIs, respectively. The diamond represents the pooled results of OR and 95% CI.

CRC susceptibility. We found that the *XPG* rs17655 G > C polymorphism was not significantly associated with CRC risk, either in the overall analysis or stratification analysis. The null association may be attributed to the relatively small sample size or the low-penetrance of this SNP. Therefore, we next conducted a meta-analysis to comprehensively evaluate this association. Our meta-analysis indicated that individuals with CG and CC/CG genotype were more likely to be susceptible to CRC. Stratified analysis by ethnicity showed that significant association was observed among Asians, but not Caucasians. A variety of reasons may help to explain the discrepant results, such as differences in linkage disequilibrium structure, allele frequency, and lifestyles as well as diversities of geography and living environments [42]. Moreover, different results from the current study and meta-analysis regarding the association between rs17655 G > C and CRC risk might be due to different sample size, ethnicity, allele frequency and histological type of tumor.

The sample size of this study is moderate with 1019 cases and 1036 controls. Moreover, this meta-analysis is by far the largest pooled study to investigate the association of interest. Therefore, the conclusion obtained is convincing. However, several limitations still exist. First, we only analyzed one SNP in this study, more potentially functional SNPs in the *XPG* gene should be explored in the future. Second, the environmental variables were not included, which might also affect the risk of CRC. Third, selection bias and information bias could not be ruled out since all the participants were enrolled from the same hospital. Fourth, the moderate sample size of this study might have no sufficient power to detect the weak impact of SNP. Fifth, our study was a case-control study with subjects from north China. The current findings may not well represent other nationality and ethnicities. Finally, functional studies should be performed to elucidate the mechanism underlying this association.

In conclusion, we found that *XPG* rs17655 G > C polymorphism was associated with CRC susceptibility in Asian populations. More case-control studies with larger sample size are warranted to confirm our findings.

Acknowledgements

This study was funded by the Institutional Fund of the First Affiliated Hospital of Zhengzhou University.

Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statis-

tics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.
[3] Fahy B and Bold RJ. Epidemiology and molecular genetics of colorectal cancer. Surg Oncol 1998; 7: 115-123.
[4] Ishikawa T, Zhang SS, Qin X, Takahashi Y, Oda H, Nakatsuru Y and Ide F. DNA repair and cancer: lessons from mutant mouse models. Cancer Sci 2004; 95: 112-117.
[5] Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001; 411: 366-374.
[6] Wood RD, Mitchell M, Sgouros J and Lindahl T. Human DNA repair genes. Science 2001; 291: 1284-1289.
[7] Leibeling D, Laspe P and Emmert S. Nucleotide excision repair and cancer. J Mol Histol 2006; 37: 225-238.
[8] Constantinou A, Gunz D, Evans E, Lalle P, Bates PA, Wood RD and Clarkson SG. Conserved residues of human XPG protein important for nuclease activity and function in nucleotide excision repair. J Biol Chem 1999; 274: 5637-5648.
[9] De Weerd-Kastelein EA, Keijzer W and Bootsma D. Genetic heterogeneity of xeroderma pigmentosum demonstrated by somatic cell hybridization. Nat New Biol 1972; 238: 80-83.
[10] Emmert S, Schneider TD, Khan SG and Kraemer KH. The human XPG gene: gene architecture, alternative splicing and single nucleotide polymorphisms. Nucleic Acids Res 2001; 29: 1443-1452.
[11] Gillet LC and Scharer OD. Molecular mechanisms of mammalian global genome nucleotide excision repair. Chem Rev 2006; 106: 253-276.
[12] Lin J, Swan GE, Shields PG, Benowitz NL, Gu J, Amos CI, de Andrade M, Spitz MR and Wu X. Mutagen sensitivity and genetic variants in nucleotide excision repair pathway: genotype-phenotype correlation. Cancer Epidemiol Biomarkers Prev 2007; 16: 2065-2071.
[13] Scherly D, Nouspikel T, Corlet J, Ucla C, Bairoch A and Clarkson SG. Complementation of the DNA repair defect in xeroderma pigmentosum group G cells by a human cDNA related to yeast RAD2. Nature 1993; 363: 182-185.
[14] Lee SK, Yu SL, Prakash L and Prakash S. Requirement of yeast RAD2, a homolog of human XPG gene, for efficient RNA polymerase II transcription. implications for Cockayne syndrome. Cell 2002; 109: 823-834.
[15] Barreto G, Schafer A, Marhold J, Stach D, Swaminathan SK, Handa V, Doderlein G, Maltry N, Wu W, Lyko F and Niehrs C. Gadd45a promotes epigenetic gene activation by repair-mediated DNA demethylation. Nature 2007; 445: 671-675.
[16] Zhou RM, Niu CX, Wang N, Liu L, Huang X, Chen ZF, Huo XR, Hao YL and Li Y. XPG gene polymorphisms and the risk of gastric cardia adenocarcinoma. Genet Test Mol Biomarkers 2016; 20: 432-437.
[17] He J, Qiu LX, Wang MY, Hua RX, Zhang RX, Yu HP, Wang YN, Sun MH, Zhou XY, Yang YJ, Wang JC, Jin L, Wei QY and Li J. Polymorphisms in the XPG gene and risk of gastric cancer in Chinese populations. Hum Genet 2012; 131: 1235-1244.
[18] Hua RX, Zhuo ZJ, Zhu J, Jiang DH, Xue WQ, Zhang SD, Zhang JB, Li XZ, Zhang PF, Jia WH, Shen GP and He J. Association between genetic variants in the XPG gene and gastric cancer risk in a southern Chinese population. Aging (Albany NY) 2016; 8: 3311-3320.
[19] Mirecka A, Paszkowska-Szczur K, Scott RJ, Gorski B, van de Wetering T, Wokolorczyk D, Gromowski T, Serrano-Fernandez P, Cybulski C, Kashyap A, Gupta S, Golab A, Slojewski M, Sikorski A, Lubinski J and Debniak T. Common variants of xeroderma pigmentosum genes and prostate cancer risk. Gene 2014; 546: 156-161.
[20] Ma SH, Ling FH, Sun YX, Chen SF and Li Z. Investigation on the role of XPG gene polymorphisms in breast cancer risk in a Chinese population. Genet Mol Res 2016; 15.
[21] Hua RX, Zhuo ZJ, Zhu J, Zhang SD, Xue WQ, Zhang JB, Xu HM, Li XZ, Zhang PF, He J and Jia WH. XPG gene polymorphisms contribute to colorectal cancer susceptibility: a two-stage case-control study. J Cancer 2016; 7: 1731-1739.
[22] Zhu ML, Wang M, Cao ZG, He J, Shi TY, Xia KQ, Qiu LX and Wei QY. Association between the ERCC5 Asp1104His polymorphism and cancer risk: a meta-analysis. PLoS One 2012; 7: e36293.
[23] Zhao J, Chen S, Zhou H, Zhang T, Liu Y, He J, Zhu J and Ruan J. XPG rs17655 G > C polymorphism associated with cancer risk: evidence from 60 studies. Aging (Albany NY) 2018; 10: 1073-1088.
[24] He J, Liao XY, Zhu JH, Xue WQ, Shen GP, Huang SY, Chen W and Jia WH. Association of MTHFR C677T and A1298C polymorphisms with non-Hodgkin lymphoma susceptibility: evidence from a meta-analysis. Sci Rep 2014; 4: 6159.
[25] He J, Wang F, Zhu JH, Chen W, Cui Z and Jia WH. No association between MTR rs1805087 A > G polymorphism and non-Hodgkin lymphoma susceptibility: evidence from 11 486 subjects. Leuk Lymphoma 2015; 56: 763-767.
[26] Du H, Zhang X, Du M, Guo N, Chen Z, Shu Y, Zhang Z, Wang M and Zhu L. Association study between XPG Asp1104His polymorphism and colorectal cancer risk in a Chinese population. Sci Rep 2014; 4: 6700.
[27] Bigler J, Ulrich CM, Kawashima T, Whitton J and Potter JD. DNA repair polymorphisms and risk of colorectal adenomatous or hyperplastic

polyps. Cancer Epidemiol Biomarkers Prev 2005; 14: 2501-2508.
[28] Huang WY, Berndt SI, Kang D, Chatterjee N, Chanock SJ, Yeager M, Welch R, Bresalier RS, Weissfeld JL and Hayes RB. Nucleotide excision repair gene polymorphisms and risk of advanced colorectal adenoma: XPC polymorphisms modify smoking-related risk. Cancer Epidemiol Biomarkers Prev 2006; 15: 306-311.
[29] Pardini B, Naccarati A, Novotny J, Smerhovsky Z, Vodickova L, Polakova V, Hanova M, Slyskova J, Tulupova E, Kumar R, Bortlik M, Barale R, Hemminki K and Vodicka P. DNA repair genetic polymorphisms and risk of colorectal cancer in the Czech republic. Mutat Res 2008; 638: 146-153.
[30] Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martinez ME, Ahnen DJ, Sandler RS, Lance P and Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. Carcinogenesis 2009; 30: 472-479.
[31] Canbay E, Cakmakoglu B, Zeybek U, Sozen S, Cacina C, Gulluoglu M, Balik E, Bulut T, Yamaner S and Bugra D. Association of APE1 and hOGG1 polymorphisms with colorectal cancer risk in a Turkish population. Curr Med Res Opin 2011; 27: 1295-1302.
[32] Gil J, Ramsey D, Stembalska A, Karpinski P, Pesz KA, Laczmanska I, Leszczynski P, Grzebieniak Z and Sasiadek MM. The C/A polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer. Mol Biol Rep 2012; 39: 527-534.
[33] Liu D, Wu HZ, Zhang YN, Kang H, Sun MJ, Wang EH, Yang XL, Lian MQ, Yu ZJ, Zhao L, Olopade OI and Wei MJ. DNA repair genes XPC, XPG polymorphisms: relation to the risk of colorectal carcinoma and therapeutic outcome with Oxaliplatin-based adjuvant chemotherapy. Mol Carcinog 2012; 51 Suppl 1: E83-93.
[34] Steck SE, Butler LM, Keku T, Antwi S, Galanko J, Sandler RS and Hu JJ. Nucleotide excision repair gene polymorphisms, meat intake and colon cancer risk. Mutat Res 2014; 762: 24-31.
[35] Paszkowska-Szczur K, Scott RJ, Gorski B, Cybulski C, Kurzawski G, Dymerska D, Gupta S, van de Wetering T, Masojc B, Kashyap A, Gapska P, Gromowski T, Kladny J, Lubinski J and Debniak T. Polymorphisms in nucleotide excision repair genes and susceptibility to colorectal cancer in the Polish population. Mol Biol Rep 2015; 42: 755-764.
[36] Sun K, Gong A and Liang P. Predictive impact of genetic polymorphisms in DNA repair genes on susceptibility and therapeutic outcomes to colorectal cancer patients. Tumour Biol 2015; 36: 1549-1559.
[37] Kabzinski J, Przybylowska K, Dziki L, Dziki A and Majsterek I. An association of selected ERCC2 and ERCC5 genes polymorphisms, the level of oxidative DNA damage and its repair efficiency with a risk of colorectal cancer in Polish population. Cancer Biomark 2015; 15: 413-423.
[38] Friedberg EC, Bond JP, Burns DK, Cheo DL, Greenblatt MS, Meira LB, Nahari D and Reis AM. Defective nucleotide excision repair in xpc mutant mice and its association with cancer predisposition. Mutat Res 2000; 459: 99-108.
[39] Friedberg EC. DNA damage and repair. Nature 2003; 421: 436-440.
[40] O'Donovan A, Davies AA, Moggs JG, West SC and Wood RD. XPG endonuclease makes the 3' incision in human DNA nucleotide excision repair. Nature 1994; 371: 432-435.
[41] Wakasugi M, Reardon JT and Sancar A. The non-catalytic function of XPG protein during dual incision in human nucleotide excision repair. J Biol Chem 1997; 272: 16030-16034.
[42] Sawyer SL, Mukherjee N, Pakstis AJ, Feuk L, Kidd JR, Brookes AJ and Kidd KK. Linkage disequilibrium patterns vary substantially among populations. Eur J Hum Genet 2005; 13: 677-686.