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L.Z. (zhulingjun@njmu.
edu.cn)* These three authors
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Association study between *XPG* Asp1104His polymorphism and colorectal cancer risk in a Chinese population

Haina Du^{1*}, Xizhi Zhang^{2*}, Mulong Du^{3,4*}, Nannan Guo¹, Zhipeng Chen⁵, Yongqian Shu¹, Zhengdong Zhang^{3,4}, Meilin Wang^{3,4} & Lingjun Zhu¹

¹Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, ²Department of Medical Oncology, Subei People's Hospital, Clinical Medical College of Yangzhou University, Yangzhou, China, ³Department of Environmental Genomics, Jiangsu Key Laboratory of Cancer Biomarkers, Prevention and Treatment, Cancer Center, Nanjing Medical University, Nanjing, China, ⁴Department of Genetic Toxicology, the Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing, China, ⁵Department of Oncology, The first people's Hospital of Zhangjiagang City, Suzhou, China.

Previous studies have reported that the Asp1104His polymorphism in *Xeroderma Pigmentosum complementation group G (XPG)* was associated with the susceptibility to colorectal cancer (CRC), although the results were inconsistent. This study was aim to investigate whether there existed an association between *XPG* Asp1104His polymorphism and CRC risk in the Chinese population, and a further meta-analysis was performed to consolidate the results. We found that *XPG* Asp1104His polymorphism was associated with a significantly increased CRC risk (dominant model: His/His + Asp/His vs. Asp/Asp, adjusted OR = 1.39, 95% CI = 1.14–1.69). Stratification analysis by clinical characteristics indicated that the His/His + Asp/His genotypes were associated with increased CRC susceptibility in patients with moderately differentiated grade, but not in poorly and well differentiated grade. Furthermore, a total of 5 eligible studies, including 2,649 CRC cases and 2,848 controls, were recruited for the meta-analysis. We identified that the meta-analysis reported a similar result in dominant model (OR = 1.35; 95% CI = 1.20–1.51). Especially, when stratified by ethnicity, an evidently increased risk was identified in the Asian population. In conclusion, our findings suggest that *XPG* Asp1104His polymorphism may increase the susceptibility of CRC, especially in Asian populations.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cases and 608,700 deaths estimated in every year¹. The development of CRC has been demonstrated as a complex process caused by many factors, such as environmental and genetic mutation². Many studies indicated that DNA damage was significantly associated with cancer development, which caused errors during DNA synthesis. Besides, it has reported that the DNA repair capacity was related to the inherited factors. Therefore, individuals with inherited impairment in DNA repair capacity are often associated with increased risk of cancers³.

Emerging evidence have demonstrated that the DNA damage repair can be activated by various pathways, including nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), double-strand break repair (DSBR), and direct repair (DR). Among these, the NER is mainly responsible for repairing bulky DNA damage, such as DNA adducts caused by UV radiation, mutagenic chemicals and chemotherapeutic drugs⁴. Besides, many key NER genes, such as *ERCC1*, *XPA*, *XPB/ERCC3*, *XPC*, *XPD/ERCC2*, *XPE/DBP1*, *XPB/ERCC4*, and *XPG/ERCC5*, have been identified, which play vital roles in DNA damage repairing and maintaining genome integrity.

Xeroderma Pigmentosum complementation group G (XPG), also named *ERCC5*, is located on chromosome 13q22–q33, consisting of 15 exons and 14 introns⁵. *XPG* is a member of the flap structure-specific endonuclease 1 (FEN1) family and encodes a protein of 1186 amino acids. It has reported that a defective *XPG* plays a pivotal role in the initiation of carcinogenesis and leads to DNA repair defects, genomic instability, and failure of gene



Table 1 | Distribution of selected variables between colorectal cancer cases and controls

variables	Cases (n=878)		Controls (n=884)		Chi-square P -value
	n	%	n	%	
Age (mean±SD)	60.0 ± 12.9		60.3 ± 13.7		0.632
Sex					0.125
Male	541	61.6	513	58.0	
Female	337	38.4	371	42.0	
Smoking status					0.187
Never	580	66.1	610	69.0	
Ever	298	33.9	274	31.0	
Drinking status					0.222
Never	636	72.4	663	75.0	
Ever	242	27.6	221	25.0	
Family history of cancer					<0.001
No	672	76.5	797	90.2	
Yes	206	23.5	87	9.8	
Tumor site					
Colon	459	52.3			
Rectum	419	47.7			
Tumor grade					
Low	62	7.1			
Intermediate	677	77.1			
High	139	15.8			
Dukes stage					
A	61	7.0			
B	392	44.6			
C	321	36.6			
D	104	11.8			

SD: standard deviation.

transcription modulation⁶⁻⁸. To date, at least six single-nucleotide polymorphisms (SNPs) in *XPG* gene have been identified, and the common Asp1104His polymorphism (rs17655 G/C, minor allele frequency ≥ 0.444 , CHB in HapMap), regarded as a tagSNP, was widely investigated for its relationship to the risk of different cancers⁹. Recently, some studies have reported that Asp1104His polymorphisms in *XPG* were associated with risk of CRC; but, the results remained inconsistent. Thus, we genotyped the *XPG* Asp1104His polymorphism and evaluated its association with CRC susceptibility in an independent Chinese population.

Results

Study Characteristics. A total of 878 CRC cases and 884 healthy controls were recruited in our analysis, and the characteristics are summarized in Table 1. Except that more individuals with family history of cancer were in cases than that in controls (23.5% in CRC cases; 9.8% in controls, $P < 0.001$), there were no significant difference in distributions of age, sex, smoking status and drinking status ($P = 0.632, 0.125, 0.187$ and 0.222 , respectively). Among the CRCs, 52.3% of patients suffered from colon cancer, and 47.7% from rectum cancer. Moreover, 7.1%, 77.1%, and 15.8% of cases were classified as poor, moderate and well differentiation grade, respectively. The Dukes A, B, C, and D stages were 7.0%, 44.6%, 36.6%, and 11.8%, respectively. The genotype distributions of the

XPG polymorphism between the cases and controls are listed in Table 2. The genotype frequencies of *XPG* Asp1104His polymorphism were 32.6% (Asp/Asp), 52.3% (Asp/His) and 15.1% (His/His) in the cases, which were significantly different from those in the controls (40.2%, 45.8%, 14.0%). Besides, the *XPG* C (His) allele frequency was 52.6% among the cases, while 47.4% among the controls, indicating a significantly statistically difference ($P = 0.008$). The observed genotype frequencies among the controls were in agreement with the HWE ($P = 0.622$). Furthermore, the MAF of *XPG* Asp1104His is 0.369 in the controls, which was about the same as that in HapMap-CHB database (<http://www.ncbi.nlm.nih.gov>).

Effects in association between *XPG* Asp1104His and CRC risk. We adjusted age, sex, smoking status, and drinking status for multivariate logistic regression analysis, revealing that the individuals with the His/His or Asp/His had a significantly increased risk of CRC (His/His vs Asp/Asp, adjusted OR = 1.03, 95% CI = 1.06–1.11; Asp/His vs Asp/Asp, adjusted OR = 1.41, 95% CI = 1.15–1.74), compared with the Asp/Asp genotype; besides, the His/His + Asp/His genotypes were related to higher CRC susceptibility (adjusted OR = 1.40, 95% CI = 1.15–1.70). In the stratification analyses on the dominant model, as shown in Table 3, the His/His + Asp/His genotypes were associated with an

Table 2 | Distribution of genotypes of *XPG* Asp1104His and their associations with risk of colorectal cancer

Genotypes	Cases(n=878) n/%		controls(n=884) n/%		Crude OR(95%CI)	Adjusted OR(95%CI)*	P
Asp/Asp	286	32.6	355	40.2	1.00(reference)	1.00(reference)	
Asp/His	459	52.3	405	45.8	1.41(1.15–1.73)	1.41(1.15–1.74)	0.001
His/His	133	15.1	124	14.0	1.33(1.00–1.78)	1.34(1.00–1.79)	0.048
His/His + Asp/His	592	67.4	529	59.8	1.39(1.14–1.69)	1.40(1.15–1.70)	<0.001
His allele	725	52.6	653	47.4	1.20(1.05–1.37)		0.008

*Adjusted for age, sex, and smoking and drinking status in logistic regression model.



increased risk of CRC in every subgroup except for the female. Moreover, the relationships of *XPG* Asp1104His polymorphism to the clinicopathological characteristics were also evaluated (Table 4). The risk effect of His/His + Asp/His genotypes was found in each group of tumor site and Dukes stage (all $P < 0.05$); however, only in the subgroup of moderately differentiated grade, we identified a significant increased risk (adjusted OR = 1.44, 95% CI = 1.17–1.78), but not in the subgroup of poorly and well differentiated grade (OR = 1.20, CI = 0.70–2.06; OR = 1.27, 95% CI = 0.87–1.85).

The results of meta-analysis. A total of five eligible studies^{2,10–12}, including 2649 cases and 2848 controls were recruited for meta-analysis (Table S1). We observed a significant association between *XPG* Asp1104His polymorphism and CRC risk under homozygote comparison (His/His vs. Asp/Asp: OR = 1.24; 95% CI: 1.03–1.47; $P = 0.02$; Figure 1a), and dominant model (His/His + Asp/His vs. Asp/Asp: OR = 1.35; 95% CI: 1.20–1.51; $P < 0.001$; Figure 1b). When stratified by ethnicity, an evidently increased risk was identified in the Asian populations: His/His vs. Asp/Asp: OR = 1.28; 95% CI: 1.05–1.55; $P = 0.012$ (Figure S1a); Asp/His vs. Asp/Asp: OR = 1.49; 95% CI: 1.29–1.73; $P < 0.001$ (Figure S1b); His/His + Asp/His vs. Asp/Asp: OR = 1.44; 95% CI: 1.25–1.65; $P < 0.001$ (Figure S1c). No heterogeneities were observed in our meta-analysis (all $P > 0.1$; Table 5). We used the Begg's rank correlation method and Egger's weighted regression method to assess publication bias. Fortunately, there was no obvious publication bias in this meta-analysis (His/His vs. Asp/Asp: Begg's test $P = 0.327$, Egger's test $P = 0.326$, $t = -1.17$, 95% CI = -3.020 – -1.394 ; His/His + Asp/His vs. Asp/Asp: Begg's test $P = 0.142$, Egger's test $P = 0.139$, $t = -2.01$, 95% CI = -4.394 – -0.997) (Figure 2).

Discussion

In the NER pathway, *XPG* cleaves the damaged DNA 3' to the damaged site, nonenzymatically participates in the 5' incision and stabilizes the DNA repair complex to the damaged DNA¹³. The SNPs in the coding region of the *EECC5/XPG* gene may result in a subtle alteration of the ERCC5/*XPG* activity and modulation of cancer susceptibility¹⁴. Berhane N et al. indicated that an amino acid changing from an acidic aspartic acid residue to a basic histidine residue could affect the protein structure of *XPG*, and thus influence the protein–protein interactions and the stability of the preincision com-

plex *XPG* C-terminus¹⁵. To date, it has been proven that *XPG* SNPs were associated with some cancers, such as lung cancer¹⁶ and breast cancer¹⁷. These implied a certain link between the *XPG* polymorphisms and the development of certain cancers.

The association between CRC and *XPG* Asp1104His polymorphism has been widely studied^{2,10,18}. Liu et al. have suggested that the *XPG* Asp1104His polymorphism contributed to the increased risk for CRC and also was associated with shorter PFS for the CRC patients receiving oxaliplatin-based chemotherapy¹⁰. However, Mort R et al. reported that *XPG* Asp1104His were not associated with CRC risk¹⁹. In addition, no previous studies examined the association between the *XPG* Asp1104His SNP and the risk of CRC with demographic characteristics and clinic pathological parameters. Thus, we conducted a hospital-based case-control study and meta-analysis to comprehensively evaluate the association of the Asp1104His polymorphisms with CRC.

In this study, we investigated the association between the *XPG* Asp1104His and CRC susceptibility. Our findings showed a significant increased frequency of the variant allele in cases (C-allele 0.526) compared to controls (C-allele 0.474). We found that the *XPG* Asp1104His was related to an increased the risk of CRC in codominant and dominant model, as Liu et al.⁹ reported. In subgroup analysis, the male in the dominant model of *XPG* Asp1104His seemed to be more susceptible to CRC, but not the female (Table 3). The reason might be that women have relatively healthy living habits and particular physiological mechanisms, which protect them from CRC. Furthermore, in the subgroup of clinicopathology characteristics, we observed that the Asp/His+His/His genotype were associated with a significantly increased risk of intermediate grade CRC, but not the low and high grade CRC. This phenomenon may be due to the relatively small number of patients with low and high grade CRC; and in the subgroups of tumor location and tumor stage, the associations remained still. These results suggested that *XPG* Asp1104His polymorphism could help to diagnose CRC. As the cancer stage was correlated to prognosis, we inferred that the *XPG* Asp1104His polymorphism did not predict the progression of CRC based on our results.

Furthermore, our meta-analysis revealed that individuals with His/His and His/His + Asp/His genotype were more likely to susceptible to CRC, which was similar to the result of our study. In the subgroup of ethnicity, we found that the *XPG* His/His and Asp/

Table 3 | Association between *XPG* Asp1104His Genotypes and demographic characteristics

Variables	Genotypes				<i>P</i>	Adjusted* OR(95% CI)	<i>P</i> for interaction
	Asp/Asp		His/His + Asp/His				
	n(cases/controls)	%	n(cases/controls)	%			
Total	286/355	32.6/40.2	592/529	67.4/59.8	<0.001	1.40 (1.15–1.70)	
Age							
≤60	142/172	32.3/42.9	298/229	67.7/57.1	0.002	1.57 (1.18–2.09)	
>60	144/183	32.9/37.9	294/300	67.1/62.1	0.05	1.31 (1.00–1.74)	
Sex							
Male	178/218	32.9/42.5	363/295	67.1/57.5	0.001	1.52 (1.18–1.96)	
Female	108/137	32.1/37.0	229/234	67.9/63.0	0.111	1.30 (0.94–1.79)	
Smoking status							
Never	194/237	33.5/38.9	386/378	66.5/61.1	0.041	1.28 (1.01–1.63)	0.172
Ever	92/118	30.9/43.1	206/156	69.1/56.9	0.002	1.72 (1.21–2.43)	
Drinking status							
Never	209/260	32.9/39.2	427/403	67.1/60.8	0.014	1.33 (1.06–1.68)	0.367
Ever	77/95	31.8/43.0	165/126	68.2/57.0	0.016	1.62 (1.10–2.40)	
family history of cancer							
No	222/316	33.0/39.7	450/481	67.0/60.3	0.007	1.35 (1.09–1.67)	0.330
Yes	39/64	31.1/44.8	142/48	68.9/55.2	0.028	1.81 (1.07–3.07)	

CI confidence interval, OR odds ratio.

*Adjusted for age, sex, smoking, and drinking status in logistic regression model.



Table 4 | Association between XPG Asp1104His Genotypes and Clinical Characteristics of Colorectal Cancer

Variables	Asp/Asp	His/His+Asp/His	Crude OR(95%CI)	Adjusted *OR(95% CI)	P
	n/%	n/%			
Controls(n=884)	355/40.2	529/59.8	1.00 (reference)	1.00 (reference)	
Cases(n=878)	286/32.6	592/67.4	1.39 (1.14–1.69)	1.40 (1.15–1.70)	<0.001
Tumor site					
Colon	144/31.4	315/68.6	1.47 (1.16–1.86)	1.48 (1.16–1.87)	0.001
Rectum	142/33.9	277/66.1	1.31 (1.03–1.67)	1.32 (1.03–1.69)	0.026
Tumor grade					
Low	22/35.5	40/64.5	1.22 (0.71–2.09)	1.20 (0.70–2.06)	0.507
Intermediate	216/31.9	461/68.1	1.43 (1.16–1.77)	1.44 (1.17–1.78)	<0.001
High	48/34.5	91/65.5	1.27 (0.88–1.85)	1.27 (0.87–1.85)	0.216
Dukes stage					
A+B	144/31.8	309/68.2	1.44 (1.13–1.83)	1.15 (1.14–1.84)	0.002
C+D	142/33.4	283/66.6	1.34 (1.05–1.70)	1.35 (1.06–1.72)	0.017

*Adjusted for age, sex, smoking, and drinking status in logistic regression model.

His genotypes seemed to be more susceptible to CRC in Asians, but not in European. This might be account for ethnic differences and diverse live environment. In addition, it was also likely that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect²⁰.

Some limitations should be noted when interpreting our findings. Firstly, many exposure variables were not taken into account, such as diet in general, history of other cancer and chronic diseases, which may affect the reliability of the results. Thus, more comprehensive studies are needed to validate these findings. Secondly, the sample sizes in our case-control study and meta-analysis study both are relatively small and might not provide sufficient power to assess the association between XPG Asp1104His polymorphism and CRC risk. Thirdly, our study population only included the Chinese; studies with ethnically diverse populations are warranted.

In conclusion, our study showed that the XPG Asp1104His polymorphism appeared to confer susceptibility to CRC. Further well-designed studies with larger sample sizes will be needed to confirm the impact of XPG Asp1104His polymorphism on CRC susceptibility.

Methods

Ethics statement. The study was approved by the institutional review board of the First Affiliated Hospital of Nanjing Medical University. The informed written consent was obtained from all subjects. In addition, the methods were carried out in

accordance with the approved guidelines. And, all experimental protocol was approved by the institutional review board of the First Affiliated Hospital of Nanjing Medical University.

Study population. We recruited CRC (CRC) cases and healthy controls from September 2010 to October 2013. Patients without restriction on age and sex were consecutively recruited at The First Affiliated Hospital of Nanjing Medical University, Nanjing, China. All of the cases were pathologically or histologically confirmed. The pathological stage of CRC at the time of diagnosis was classified into Dukes A, B, C, and D. Tumor grade was classified into well differentiated, moderately differentiated and poorly differentiated. Controls were randomly selected from a healthy screening campaign in the same region. The selection criteria for controls included cancer-free individuals and frequency matched to cases for sex and age. All of the participants were interviewed with a self-administered questionnaire after obtaining a written informed consent. After interview, about 5 ml of venous blood sample was collected from each subject.

Genotyping. Genomic DNA isolated from 5 ml whole blood was used to genotype XPG Asp1104His by using the TaqMan assay (Applied Biosystems). The sequences of primer and probe for each SNP are available on request. Genomic DNA of 50 ng and 0.56 mix (TaKaRa Bio, JPN) was used for each reaction and amplification was performed under the following conditions: 50°C for 2 min, 95°C for 10 min followed by 45 cycles of 95°C for 15 sec, and 60°C for 1 min. We assessed genotype data quality by typing 10% blinded replicate samples and the concordance rate was 100.0%.

Statistical analysis. For the case-control study, the Hardy–Weinberg equilibrium (HWE) for genotype distribution in controls was tested by a goodness-of-fit χ^2 test. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate association between the genotypes and risk of CRC according to the significant genetic models by univariate and multivariate unconditional logistic regression models, respectively. $P < 0.05$ was considered as statistically significant,

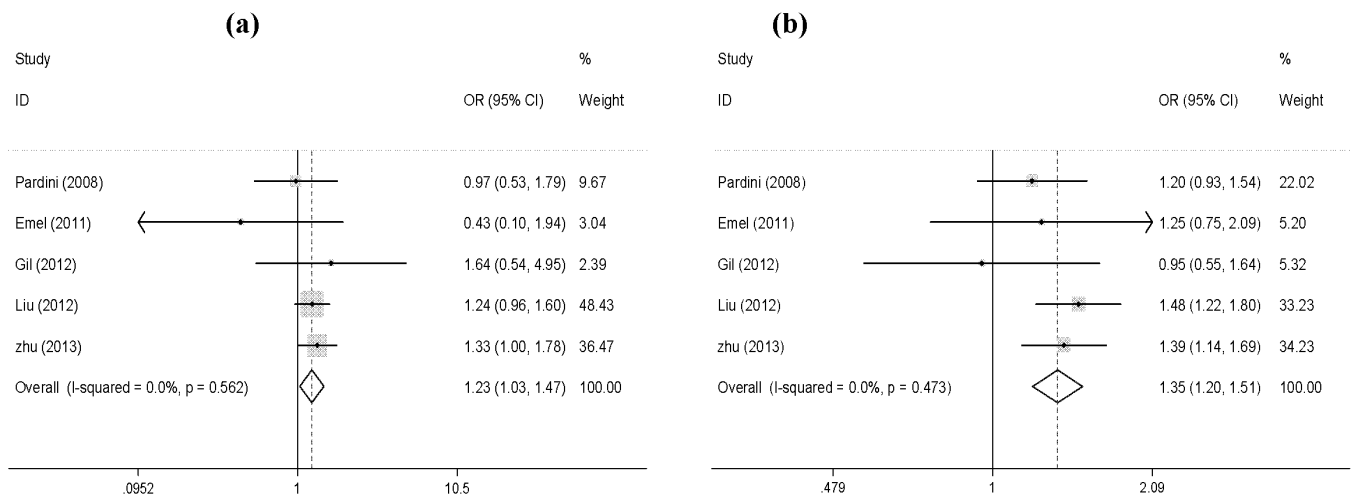


Figure 1 | The association between XPG Asp1104His polymorphism and colorectal cancer under: (a) homozygote comparison (His/His vs. Asp/Asp); (b) dominant model (His/His + Asp/His vs. Asp/Asp).



Table 5 | Meta-analysis of the association between the XPG Asp1104His polymorphism and colorectal cancer risk

Stratification	No. case/control	His/His vs. Asp/Asp		Asp/His vs. Asp/Asp		His/His + Asp/His vs. Asp/Asp		His/His vs. Asp/His + Asp/Asp	
		OR (95%CI)	P/P _{he}	OR (95%CI)	P/P _{he}	OR (95%CI)	P/P _{he}	OR (95%CI)	P/P _{he}
Total	2649/2848	1.24(1.03–1.47)	0.020/0.562	0.85(0.69–1.05)	0.127/0.303	1.35(1.20–1.5)	0/0.473	0.97(0.83–1.14)	0.750/0.430
Ethnicity									
Asian	1906/1969	1.28(1.05,1.55)	0.012/0.473	1.49(1.29,1.73)	0/0.418	1.44(1.25,1.65)	0/0.636	0.98(0.83,1.16)	0.285/0.797
Caucasian	743/879	0.97(0.59,1.58)	0.900/0.372	1.19(0.96,1.48)	0.109/0.397	1.16(0.94,1.44)	0.147/0.718	0.92(0.57,1.48)	0.720/0.262

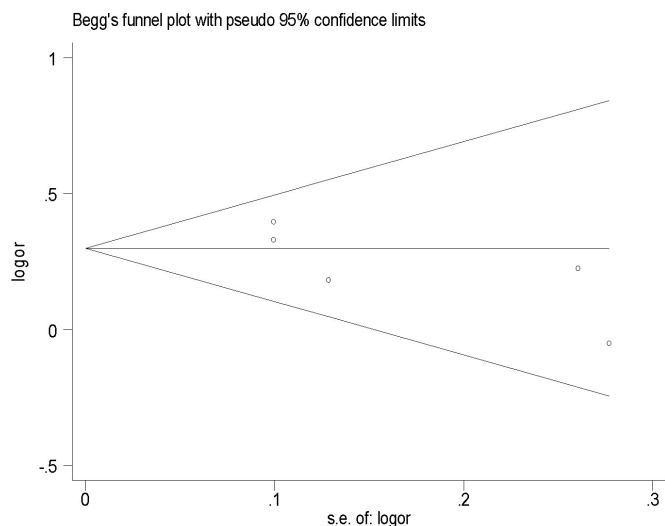


Figure 2 | Funnel plot of publication bias for XPG Asp1104His polymorphisms with CRC risk (based on a dominant model).

and all statistical tests were two sided. Statistical analyses were done using SAS 9.1.3 (SAS Institute, Cary, NC).

Meta-analysis. Eligibility of relevant studies. To further confirm the relationship between XPG Asp1104His polymorphism and CRC, we carried out a meta-analysis. The PubMed database was searched with terms “XPG”, “ERCC5”, “viceversa Xeroderma Pigmentosum group G”, “excision repair cross-complementing group 5”, “polymorphism”, “colorectal cancer”, as well as their combinations for all genetic studies on the relationship between XPG polymorphism and CRC risk up to March 2014. We also searched references in published articles and reviews on this topic in PubMed. Eligible studies had to meet the following criteria: (a) only case-control design; (b) studies exploring the correlation between CRC and XPG Asp1104His polymorphism. A total of 5 potential relevant studies (including our study) were retrieved through PubMed^{2,10–12}.

Data extraction. Two investigators find the publications on the topic and then a selection of the detected studies independently according to the inclusion criteria listed above. Then, the following information was collected from each study: first author’s name, year of publication, study design, ethnicity and numbers of cases and controls with the XPG Asp1104His genotypes, respectively (Table S1).

Statistical analysis. The chi-square based Q-test was used to evaluate the heterogeneity. The pooled OR was assessed in the fixed-effects model by Mantel-Haenszel method when $P > 0.05$. Otherwise, the random-effects model by DerSimonian and Laird method was used²¹. The modified Egger’s linear regression test was used to detect the potential publication bias. Crude ORs and 95% CIs were used to assess the intensity of the correlation between XPG Asp1104His polymorphism and CRC risk. The pooled ORs were evaluated on co-dominant model (His/Asp vs. Asp/Asp, His/His vs. Asp/Asp), dominant model (His/His + Asp/His vs. Asp/Asp, recessive model (His/His vs. Asp/His + Asp/Asp) and allele (His vs. Asp), respectively. Statistical analyses were used by STATA version 11.0 (Stata Corporation, College Station, TX, USA).

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Author contributions

Conceived and designed the experiments: H.D., X.Z. and M.D. Performed the experiments: N.G. and M.D. Analyzed the data: H.D., Z.C. and M.W. Contributed analysis tools: Y.S., Z.Z., L.Z. and M.W. Wrote the main manuscript: H.D., X.Z. and M.D. Reference collection and data management: H.D., X.Z., M.D. and N.G. Statistical analyses: H.D. and X.Z.

Additional information

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