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ORIGINAL RESEARCH

Lack of association between the *XPD* Lys751Gln polymorphism and colorectal cancer risk: a meta-analysis

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Background: The *xeroderma pigmentosum complementary group D* (*XPD*) gene has been linked to the development of colorectal cancer (CRC) through disruption of DNA repair. Several studies have suggested that the *XPD* polymorphism Lys751Gln is associated with an increased risk of developing CRC. However, previous results remain inconclusive. Herein, we performed a meta-analysis to evaluate the potential for this relationship.

Methods: Relevant studies were retrieved from the PubMed database. Strict selection and exclusion criteria were determined, and the odds ratio with a 95% confidence interval was used to assess the strength of associations. The fixed or random effects model was selected on the basis of heterogeneity tests among studies. Publication bias was estimated using funnel plots and Egger's regression test.

Results: The meta-analysis included 2,961 cases and 4,539 controls from eleven studies. The results indicated that the *XPD* Lys751Gln polymorphism had no association with CRC risk for all genetic models (Gln-Gln versus Lys-Lys, *P*=0.477; Lys-Gln versus Lys-Lys, *P*=0.283; Lys-Gln + Gln-Gln versus Lys-Lys, *P*=0.562), even when compared within subgroups based on ethnicity and source of controls.

Conclusion: Based on the results of our meta-analysis, there is no evidence of a link between the *XPD* Lys751Gln polymorphism and risk of CRC.

Keywords: *XPD* Lys751Gln polymorphism, colorectal cancer risk, meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors and is currently listed third under incidence and second under mortality worldwide.[1] The National Center for Health Statistics in the USA estimates that, in 2014, 71,830 men and 65,000 women will be diagnosed with CRC and 26,270 men and 24,040 women will die of the disease.[2] Worldwide, the prevention and treatment of CRC faces enormous challenges. Development of CRC is closely linked to many environmental and genetic factors, including lack of dietary fiber, overweight and obesity, physical inactivity, a short appendix vermiformis, a high-fat diet, smoking, and excessive alcohol consumption.[3] Genetic factors play an important role, as susceptibility to CRC may result from inherited mutations in genes involved in carcinogen metabolism and DNA repair.[4] It is now widely thought that the pathogenesis of CRC is related to environmental triggers and genetic susceptibility to multifactorial interactions.

Nucleotide excision repair is an important element of genome maintenance that is mainly responsible for repairing DNA adducts and other types of damage that cause helical distortions.[5] A number of enzymes are involved in the nucleotide excision

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repair pathway, including *xeroderma pigmentosum complementary groups A, C, D,* and *F* (*XPA*, *XPC*, *XPD*, and *XPF*, respectively), *replication protein A* (*RPA*), and *excision repair cross-complementing 1* (*ERCC1*).[6] *XPD* consists of about 20 kb on chromosome 19q13.3 and contains 23 exons. An A→C polymorphism in *XPD* codon 751 of exon 23 leads to a Lys→Gln amino acid substitution (Lys751Gln) that is associated with a DNA damage repair phenotype.[7] A difference in DNA repair capacity has been proposed to be a contributor to CRC susceptibility. Many studies have focused on the gene loci of *XPD* Lys751Gln.

To date, many studies focus on the genetic polymorphism of *XPD* and its contribution to CRC susceptibility; however, due to the interethnic heterogeneity of the disease, the limitations of statistical power in individual studies, small sample sizes, and other factors, the results are inconsistent. To reduce the research bias and improve the effectiveness of statistical correlation analysis, we conducted a comprehensive quantitative meta-analysis of previous results to evaluate the relationship between the *XPD* Lys751Gln polymorphism and the risk of CRC.

Materials and methods

Publication search

This meta-analysis adhered to the relevant criteria of the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement.[8] The PubMed database was searched through February 2014 for English material published between 1984 and 2014. Articles were sought with the following medical subject heading (MeSH) terms: *XPD* [All Fields] OR Lys751Gln [All Fields] AND ("colorectal neoplasms" [MeSH terms] OR ("colorectal" [All Fields] AND "neoplasms" [All Fields]) OR "colorectal neoplasms" [All Fields] OR ("colorectal" [All Fields] AND "cancer" [All Fields]) OR "colorectal cancer" [All Fields]). All references cited in the original studies or review articles concerning the relevant topic were retrieved to broaden the search for relevant publications.

Inclusion and exclusion criteria

In this meta-analysis, publications were included using the following criteria: case-control studies investigating the relationship between the *XPD* Lys751Gln polymorphism and CRC risk; patients with histologically confirmed CRC; sufficient genotype distribution information in cases and controls; and genotype distribution compliant with the Hardy-Weinberg equilibrium (HWE). The following exclusion criteria were used: abstracts and reviews; study designs other than case-control method; detailed genotype frequency not reported; and repeat or overlapping publications.

Data extraction

Data were independently extracted by two different investigators from all included studies: name of first author, publication year, country or area, characteristics of controls, sources of controls (population-based or hospital-based), genotyping method, fitness of HWE in controls, and genotype distribution. Any discrepancy was resolved through discussion or by a third person.

Statistical analysis

The crude odds ratio (OR) and 95% confidence interval (95% CI) were used to assess the strength of the association between the *XPD* Lys751Gln polymorphism and CRC risk. The pooled ORs were performed in homozygous (Gln-Gln versus Lys-Lys), heterozygous (Lys-Gln versus Lys-Lys),

Table 1 Study characteristics

Study	Ethnicity	Control source	Genotyping method	Case	Control	HWE
Yeh et al[10]	Asian	HB	PCR-RFLP	727	736	Y
Skjelbred et al[11]	Caucasian	HB	TaqMan-assay	157	399	Y
Hansen et al[12]	Caucasian	PB	TaqMan-assay	396	798	Y
Stern et al[13]	Asian	PB	TaqMan-assay	303	1,163	Y
Sliwinski et al[14]	Caucasian	HB	PCR-RFLP	100	100	Y
Joshi et al[15]	Caucasian	PB	TaqMan-assay	380	381	Y
Engin et al[16]	Caucasian	HB	PCR-RFLP	110	116	Y
Jelonek et al[17]	Caucasian	PB	PCR-RFLP	123	153	Y
Wang et al[18]	Asian	HB	PCR-RFLP	302	291	Y
Procopciuc and Osian[19]	Caucasian	HB	PCR-RFLP	150	162	Y
Ni et al[20]	Asian	HB	TaqMan-assay	213	240	Y

Abbreviations: HB, hospital-based; PB, population-based; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; Y, yes.

and dominant (Lys-Gln + Gln-Gln versus Lys-Lys) models. A chi square-based *Q*-test was used to test the assumption of heterogeneity. $P>0.1$ for the *Q*-test suggested a lack of heterogeneity among studies and required the fixed effects model (the Mantel-Haenszel method) to estimate the pooled OR of each study.[9] Otherwise, the random effect model was used. Egger's test and Begg's funnel plot was plotted to examine the underlying publication bias among the included studies. An asymmetric plot suggested possible publication bias, while $P>0.05$ suggested no bias. Statistical analyses were performed using Stata statistical software (version 10.0, Stata Corporation, College Station, TX, USA). $P<0.05$ was considered to be statistically significant, and all *P*-values were two-sided.

Results

Characteristics of studies

In this meta-analysis, eleven case-control studies were included to evaluate the relationship between the *XPD* Lys751Gln polymorphism and CRC risk, which provided a total of 2,961 cases

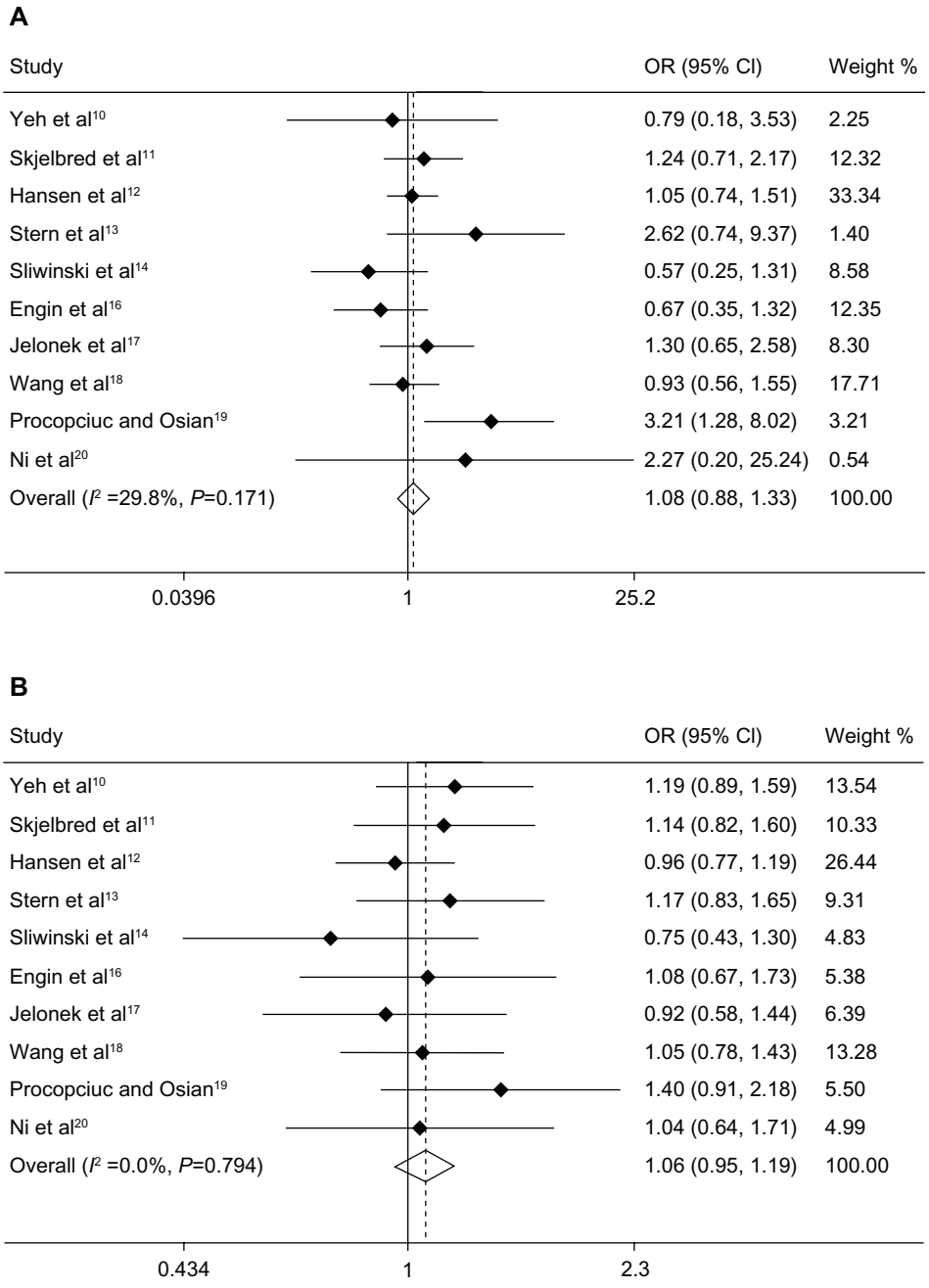

Figure 1 (*Continued*)

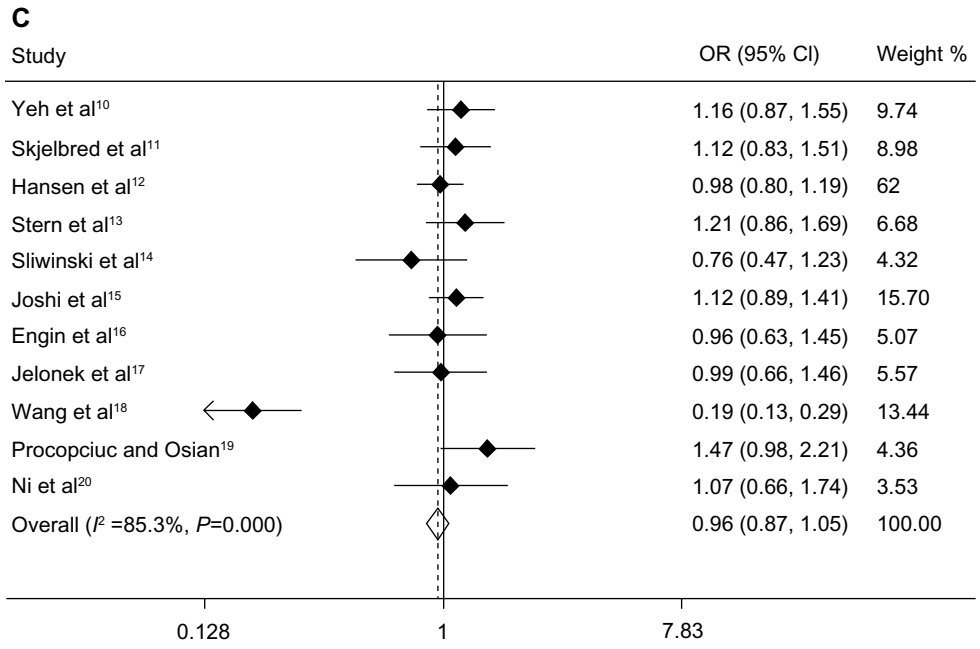

Figure 1 Association between the *XPD* Lys751Gln polymorphism and colorectal cancer risk. Forest plots of (**A**) homozygous model (Gln-Gln versus Lys-Lys), (**B**) heterozygous model (Lys-Gln versus Lys-Lys), and (**C**) dominant model (Lys-Gln + Gln-Gln versus Lys-Lys).
Abbreviations: CI, confidence interval; OR, odds ratio; *XPD, xeroderma pigmentosum complementary group D*.

and 4,539 controls for the present meta-analysis.[10–20] All cases were histologically confirmed as colon or rectal cancer. There were four studies from Asian populations[10,13,18,20] and seven from Caucasian populations.[11,12,14–17,19] Among the eleven studies, seven were hospital-based[10,11,14,16,18–20] and four were population-based.[12,13,15,17] Controls were mainly healthy populations and were matched for age and gender. Genotyping methods included polymerase chain reaction and restriction fragment length polymorphism and TaqMan in accordance with HWE (see Table 1).

Quantitative synthesis

Overall, there was no significant association between the *XPD* Lys751Gln polymorphism and risk of CRC. The specific results were as follows: homozygous model (Gln-Gln versus Lys-Lys, OR 1.08, P=0.477, 95% CI 0.88–1.33), heterozygous model (Lys-Gln versus Lys-Lys, OR 1.06, P=0.283, 95% CI 0.95–1.19), and dominant model (Lys-Gln + Gln-Gln versus Lys-Lys, OR 0.96, P=0.562, 95% CI 0.87–1.05, Figure 1). We performed subgroup analysis, and the results suggested no significant association in any of the genetic models with ethnicity or source of controls (see Table 2).

Tests of heterogeneity and publication bias

Due to heterogeneity in the meta-analysis of association between the dominant model and CRC risk (Lys-Gln + Gln-Gln versus Lys-Lys, I^2=85.3%, P=0.000), a random effects model was adopted for this analysis. Subgroup analysis indicated that ethnicity and source of controls were not significant sources of heterogeneity. The fixed effects model was used for the homozygous and heterozygous models because of the absence of heterogeneity (Gln-Gln versus Lys-Lys, I^2=29.8%, P=0.171; Lys-Gln versus Lys-Lys, I^2=0.0%, P=0.794).

Begg's funnel plot and Egger's test were used to assess the publication bias of the included articles. The shape of the funnel plot was not obviously asymmetric (see Figure 2). In addition, Egger's test revealed no evidence of publication bias (P>0.05).

Discussion

The pathogenesis of CRC has not been elucidated, but the following factors are thought to be contributory: diet and carcinogens; chronic colorectal inflammations such as ulcers, polyps, and schistosomiasis; tumor suppressor gene mutations or genetic instability; and colorectal adenomas and other precancerous lesions.[21–24] Currently, it is generally thought that the occurrence of CRC is a gradual process involving multiple oncogene activations and tumor suppressor gene inactivation.[25,26] DNA repair systems are the body's main defense barrier for internal and external environmental factors that are sources of genome instability. Defects in these systems or low DNA repair capacity increase

Table 2 Subgroup analysis of correlation between polymorphism of *XPD* 751 and CRC risk

Comparisons	Number of studies	Odds ratio		Test of heterogeneity		
		OR (95% CI)	*P*-value	*Z*-value	I^2 (%)	*P*-value
Asians						
Gln-Gln versus Lys-Lys	4	1.05 (0.72–1.53)	0.807	0.24	0.0	0.426
Lys-Gln versus Lys-Lys	4	1.12 (0.95–1.33)	0.181	1.34	0.8	0.930
Lys-Gln + Gln-Gln versus Lys-Lys	4	0.74 (0.33–1.67)	0.467	0.73	94.9	<0.001
Caucasians						
Gln-Gln versus Lys-Lys	6	1.07 (0.89–1.28)	0.497	0.68	49.8	0.076
Lys-Gln versus Lys-Lys	6	1.02 (0.88–1.18)	0.788	0.27	0.0	0.509
Lys-Gln + Gln-Gln versus Lys-Lys	7	1.05 (0.94–1.17)	0.424	0.80	85.3	<0.001
PB						
Gln-Gln versus Lys-Lys	3	1.12 (0.87–1.43)	0.369	0.90	3.5	0.355
Lys-Gln versus Lys-Lys	3	1.00 (0.84–1.18)	0.969	0.04	0.0	0.794
Lys-Gln + Gln-Gln versus Lys-Lys	4	1.05 (0.93–1.20)	0.423	0.80	0.0	0.657
HB						
Gln-Gln versus Lys-Lys	7	1.02 (0.81–1.28)	0.876	0.16	41.4	0.115
Lys-Gln versus Lys-Lys	7	1.11 (0.96–1.28)	0.154	1.43	0.0	0.745
Lys-Gln + Gln-Gln versus Lys-Lys	7	0.84 (0.52–1.35)	0.475	0.71	90.6	<0.001

Abbreviations: CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; HB, hospital-based; PB, population-based; *XPD, xeroderma pigmentosum complementary group D*.

the risk of genetic mutations and cell carcinogenesis. Thus, individuals with compromised DNA repair capacity are susceptible to tumors.

XPD is an important DNA repair gene involved in base and nucleotide excision repair of DNA. Single nucleotide polymorphisms present in multiple sites of this gene have been linked to enhanced susceptibility to various cancers, including lung cancer, gastric cancer, and breast cancer.[7,27,28] *XPD* participates in unwinding the DNA helix to allow excision of damaged DNA fragments.[29] A study of the *XPD* gene found that a mutation at the codon 751 allele is most common.[25] Many epidemiological studies have thereafter been indicating the role of Lys751Gln polymorphism on CRC susceptibility, but the result remains controversial.

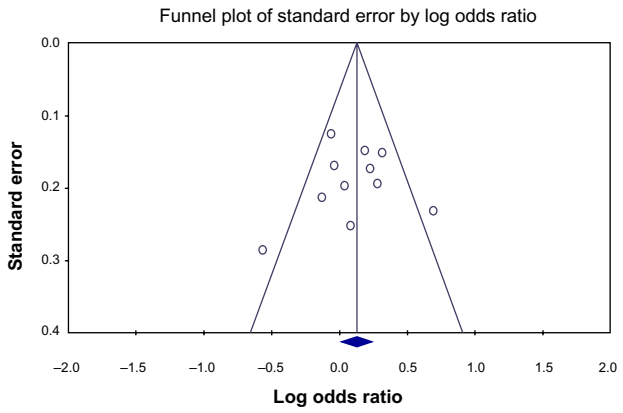

Figure 2 Funnel plot of standard error observed in each study by the log odds ratio.

Thus, our meta-analysis, comprising 2,961 CRC patients and 4,539 controls from eleven studies, was performed to assess precisely the possible association of *XPD* Lys751Gln polymorphism with susceptibility to CRC. Our meta-analysis suggests that *XPD* Lys751Gln polymorphism was not associated with CRC risk. In the subgroup analysis, where studies were divided by ethnicity or source of controls, there was still no significant association detected in the homozygous, heterozygous, or dominant model.

Meta-analysis is reliant on available published data, and publication bias is common. Through the qualitative funnel plot and quantitative Egger's linear regression, we have shown that there is no significant publication bias in the current study. However, there are some limitations to this meta-analysis. First, the studies included involve only Asian and Caucasian populations, without representation of other racial or ethnic groups, including the African population. Additionally, we could only carry out a subgroup analysis for a large geographical area despite the presence of different national characteristics within a region due to the lack of raw data for each study. Moreover, we could not carry out individual subgroup analysis for patients with colon and colorectal cancer due to the lack of availability of raw data. Finally, the potential effect of gene-gene or gene-environment interactions on the statistical results was not considered.

In summary, our meta-analysis pooled all available data related to potential links between *XPD* Lys751Gln and CRC, and found no evidence that the polymorphism is associated with CRC risk.

Disclosure

The authors report no conflicts of interest in this work.

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