Contribution of DNA Repair Xeroderma Pigmentosum Group D Genotypes to Colorectal Cancer Risk in Taiwan

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Abstract. *Background/Aim: It has been previously proposed that genetic variations on DNA repair genes confer susceptibility to cancer and the DNA repair gene Xeroderma Pigmentosum Group D (XPD) is thought to play the role of a helicase during excision repair and transcription. We investigated three genotypes of XPD, at promoter -114 (rs3810366), Asp312Asn (rs1799793) and Lys751Gln (rs13181), regarding their association with colorectal cancer susceptibility in a Taiwanese population. Materials and Methods: In total, 362 patients with colorectal cancer and 362 gender- and age-matched healthy controls were genotyped by polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP), and their XPD genotypes' association with colorectal cancer risk was investigated. Results: The genotypes of XPD Asp312Asn (p=0.2493), Lys751Gln (p=0.7547) and promoter -114 (p=0.8702), were not associated with susceptibility for colorectal cancer. The Chi-square test revealed that the variant alleles of XPD Asp312Asn, Lys751Gln and promoter -114 was not associated with susceptibility for colorectal cancer either [p=0.1330, 0.3888 and 0.8740; odds ratio (OR)=1.20, 0.83 and 0.98; 95% confidence interval (95%CI)=0.95-1.52, 0.54-1.27 and 0.80-1.21, respectively]. The risk of A/G and A/A genotypes have no association with cancer risk among non-alcohol drinkers (OR=1.24, 95%, CI=0.90-1.72, p=0.2103) or alcohol drinkers (OR=1.51, 95% CI=0.64-3.55, p=0.4648). There exists no obvious contribution of XPD genotypes to tumor size (p=0.3531), location (p=0.3006) and lymph node metastasis (p=0.1061). Conclusion: Asp312Asn, Lys751Gln and promoter -114 of the XPD gene were not found to be adequate predictive markers for colorectal cancer risk in Taiwan.*

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and there exist nearly one million cases of CRC cases diagnosed each year worldwide (1, 2). The prevalent incidence and age-adjusted mortality of CRC keeps increasing in recent years and the incidence and mortality of CRC has occupied the first and third places among common cancers in Taiwan. The increase in incidence and mortality has been proposed to closely associate with dietary changes to Western food style, including a decreased consumption of dietary fiber or grain-made foods. Etiological studies have attributed more than 85% of CRC to several environmental factors (1, 2), and in particular meat consumption, cigarette smoking, exposure to carcinogenic aromatic amines, such as arylamines and heterocyclic amines (3, 4). Approximately 15-20% of CRC cases have a strong familial history of cancer, suggesting that additional inherited susceptibility factors are not yet revealed (5-7).

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The DNA repair system protects the genome from exogenous and endogenous DNA insults through removing all types of DNA adducts induced by endogenous and exogenous damage during our daily life (8). Inherited functional polymorphisms or sporadic mutations on DNA repair genes may influence the overall repair capacity to remove the damaged DNA and thus explain the etiology of cancer (9). The *XPD* gene, which is important in nucleotide excision repair (NER) sub-pathway in DNA repair system, is believed to be responsible for removing the helix-distorting base lesions produced by platinum agents, ultraviolet light (UV) and other carcinogenic agents (10). It is also known as the excision repair cross-complementing group 2 (ERCC2), encoding a helicase to participate in DNA unwinding during both NER and transcription (11-13). In the literature, it has been reported that mutations on the *XPD* gene diminish its helicase activity, resulting in a defective NER capacity, in transcription activity and in an abnormal response to apoptosis (14).

The most widely investigated nucleotide polymorphisms of *XPD* are the non-synonymous A to C substitution in exon 23 causing a lysine (Lys) to glutamine (Gln) substitution in codon 751 (Lys751Gln, rs13181, and merged from rs1052559), and a non-synonymous G to A substitution in exon 10 leading to an aspartic acid (Asp) to asparagine (Asn) substitution in codon 312 (Asp312Asn, rs1799793) (15-18). The two variant genotypes are both associated with deficiency in DNA repair capacity (15, 16, 19, 20). The two polymorphisms are reported to be significantly associated with the risk of many types of cancers, including lung cancer (21), melanoma (22), head and neck (23), bladder (24-26), esophageal cancer (27), breast cancer (28-31) and gastric cancer (32-39). As for CRC, few studies have examined the contribution of *XPD* genotypes to the risk of this prevalent cancer type (40, 41), and its associations with progression-free survival and overall survival of CRC patients undergoing oxaliplatin-based chemotherapy from a meta-analysis viewpoint (42-45). However, none of them were investigating the Taiwanese population, which is of high prevalence, high death rate, and conserved in genetic background and very different from Caucasian populations.

In the current study we explored whether the genotypes of *XPD* are associated with CRC risk in Taiwan. For this purpose, we revealed the genotypic frequencies of three polymorphisms of the *XPD* gene at Asp312Asn, Lys751Gln, and promoter region -114 (rs3810366) among a central Taiwanese hospital-based population, and analyzed the contribution of *XPD* genotypes to CRC susceptibility and their interactions with alcohol drinking and clinical indexes (age, gender, tumor size, location and lymph node metastasis).

Materials and Methods

Collection of investigated population and their clinical information. The investigated population consisted of 362 CRC patients and 362 cancer-free control volunteers. Patients diagnosed with CRC were recruited at the outpatient clinics of general surgery during 2002-2008 at the China Medical University Hospital in Taiwan. The clinical characteristics of patients, including histological details, were all graded and defined by expert surgeons (46-49). All patients voluntarily participated, completed a self-administered questionnaire and provided peripheral blood samples. An equal number of non-cancer healthy volunteers was selected as control by matching for age, gender and some indulgences, after initial random sampling from the Health Examination Cohort of the hospital. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin, and any familial or genetic diseases. This study was approved by the Institutional Review Board of the China Medical University Hospital and written-informed consent was obtained from all participants. The details of the characteristics of the patients and controls were summarized in Table I.

XPD genotyping assays. Genomic DNA from the subjects was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan), aliquoted, stored and further processed as our previous articles (50-53). The primers for *XPD* genotyping were designed as in our previous articles (39, 54, 55). Briefly, for *XPD* Asp312Asn, the primers 5'-TGGCCCCTGTCTG ACTTGTCCC-3' and 5'-GACGGGGAGGCGGGAAAGGGACT-3' were used, for XPD Lys751Gln, the primers 5'-ACTTCATAAG ACCTTCTAGC-3' and 5'-GATTATACGGACATC TCCAA-3' were used, and for *XPD* promoter -114, the primers 5'-ATGAATATTCA GCGAGAGGC-3' and 5'-CTGGGTTCGATCA ATACTCAAT-3' were used. The polymerase chain reaction (PCR) protocols included starting stage at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension step at 72˚C for 10 min. Then the PCR products were identified for their polymorphic genotypes after digestion with *Hpy99I, EarI,* and *Bme1580I* for *XPD* Asp312Asn (cut from 250 bp A type into 188+62 bp G type), 751 (cut from 326 bp C type into 127+199 bp A type) and promoter -114 (cut from 303 bp G type into 101+202 bp C type), respectively.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *XPD* SNP in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. To compare the distribution of the *XPD* genotypes between case and control groups, Pearson's chi-square test with Yate's correction was applied. CRC risk associated with the *XPD* genotypes was estimated as odds ratio (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. Analyzing result was recognized as significant when the statistical *p*-value was less than 0.05.

Results

The clinical characteristics of the CRC patient group in addition to the control group are summarized in Table I. There was no difference in the distribution of age (p=0.9324) and gender (p=0.7075) among the CRC patients and non-cancer controls. The percentages of patients with tumor size less than 5 cm and larger or equal to 5 cm were 53.9% and 46.1%, respectively. The percentages of patients with tumor at the colon and rectum were 71.0% and 29.0%, respectively.

Table I. *Distributions of selected characteristics of investigated colorectal cancer patients and non-cancer healthy controls.*

Characteristics	Controls (n=362)		Cases (n=362)		*p*-Value[a]
	n	%	n	%	
Age (years)					
≤60	93	25.7%	95	26.2%	
>60	269	74.3%	267	73.8%	0.9324
Gender					
Male	209	57.7%	203	56.1%	
Female	153	42.3%	159	43.9%	0.7075
Tumor size					
<5 cm			195	53.9%	
≥5 cm			167	46.1%	
Location					
Colon			257	71.0%	
Rectum			105	29.0%	
Lymph node metastasis					
Negative			210	58.0%	
Positive			152	42.0%	

[a]Statistical analysis based on Chi-square test.

Table II. *Association of XPD Asp312Asn, Lys751Gln, promoter -114 polymorphisms and colorectal cancer risk.*

Genotype	Cases (%)	Controls (%)	Odds Ratio (95% CI)[a]	*p*-Value[b]
XPD Asp312Asn				
G/G	214 (59.1)	235 (64.9)	1.00 (ref)	
G/A	97 (26.8)	80 (22.1)	1.33 (0.94-1.89)	0.1284
A/A	51 (14.1)	47 (13.0)	1.19 (0.77-1.85)	0.5001
with A	148 (40.9)	127 (35.1)	1.28 (0.95-1.73)	0.1257
P for trend				0.2493
XPD Lys751Gln				
A/A	329 (90.9)	323 (89.2)	1.00 (ref)	
A/C	24 (6.6)	28 (7.7)	0.84 (0.48-1.48)	0.6501
C/C	9 (2.5)	11 (3.1)	0.80 (0.33-1.96)	0.7995
with C	33 (9.1)	39 (10.8)	0.83 (0.51-1.35)	0.5346
P for trend				0.7547
XPD promoter -114				
C/C	107 (29.6)	102 (28.2)	1.00 (ref)	
C/G	187 (51.6)	194 (53.6)	0.92 (0.66-1.29)	0.6853
G/G	68 (18.8)	66 (18.2)	0.98 (0.64-1.52)	0.9352
with G	255 (70.4)	260 (71.8)	0.93 (0.68-1.29)	0.7429
P for trend				0.8702

[a]CI, confidence interval; [b]*p*-value based on Chi-square test with Yate's correction.

The percentages of patients with or without lymph node metastasis were 58.0% and 42.0%, respectively (Table I).

The distributions of genotypes for *XPD* Asp312Asn, Lys751Gln and promoter -114 polymorphisms among the CRC and control subjects are shown and analyzed in Table II. Compared to the G/G wild-type genotype of Asp312Asn, there was obvious increased risk in the G/A and A/A groups (OR=1.33, 95%CI=0.94-1.89, OR=1.19, 95% CI=0.77-1.85, respectively; p=0.2493). A combination of the homozygotes and heterozygotes of A (with A) at *XPD* Asp312Asn behaved a non-significant increased risk for CRC (OR=1.28, 95% CI=0.95-1.73). Neither hetero- nor homozygotes of variant C allele of *XPD* Lys751Gln, seemed to be risky genotypes for CRC (OR=0.84, 95%CI=0.48-1.48, OR=0.80, 95%CI=0.33-1.96, respectively; p=0.7547), as was also the case for the hetero- or homozygotes variant G allele at *XPD* promoter -114 polymorphic site (OR=0.92, 95%CI=0.66-1.29, OR=0.98, 95%CI=0.64-1.52, respectively; p=0.8702) (Table II).

The frequencies of the alleles for the *XPD* Asp312Asn, Lys751Gln and promoter -114 polymorphisms between CRC and control groups are presented and analyzed in Table III. The distributions of all three polymorphisms were in the Hardy-Weinberg equilibrium and similar between the CRC patients and controls (data not shown). The data showed that variant A allele at *XPD* Asp312Asn was associated with a border-line increased CRC risk (OR=1.20, 95%CI=0.95-1.52, p=0.1330). On the contrary, the variant C allele at *XPD* Lys751Gln, or the variant G allele at *XPD* promoter -114, were not differently distributed in the CRC patient and control groups (p=0.3888 and 0.8740, respectively) (Table III).

Table III. *Allele frequencies for XPD Asp312Asn, Lys751Gln and promoter-114 polymorphisms in the colorectal cancer and control groups.*

Allele	Cases (%) N=724	Controls (%) N=724	Odds Ratio (95% CI)[a]	*p*-Value[a]
XPD Asp312Asn				
Allele G (Asp)	525 (65.6)	550 (76.0)	1.00 (ref)	
Allele A (Asn)	199 (34.4)	174 (24.0)	1.20 (0.95-1.52)	0.1330
XPD Lys751Gln				
Allele A (Lys)	682 (94.2)	674 (93.1)	1.00 (ref)	
Allele C (Gln)	42 (5.8)	50 (6.9)	0.83 (0.54-1.27)	0.3888
XPD promoter-114				
Allele C	401 (55.4)	398 (55.0)	1.00 (ref)	
Allele G	323 (44.6)	326 (45.0)	0.98 (0.80-1.21)	0.8740

[a]*p*-value based on Chi-square test.

Since cigarette smoking and alcohol drinking status were the environmental risk factors for CRC, we were interested to examine the interaction of genotype of *XPD* and smoking and drinking status for CRC risk in Taiwan. First, the interactions of *XPD* Asp312Asn genotypes and alcohol consumption for the risk of CRC are presented and analyzed in Table IV. As shown in Table IV, the genotypic distributions of *XPD* Asp312Asn GG and AG+AA were neither significantly different among CRC non-alcohol drinkers and

Table IV. *Distribution of XPD Asp312Asn genotypes in colorectal cancer patients after stratification by personal alcohol drinking status.*

Genotypes	Non-drinkers		*p*-Value	OR (95% CI)a	Drinkers		*p*-Value	OR (95% CI)[a]
	Controls (%)	Cases (%)			Controls (%)	Cases (%)		
GG	199 (64.0)	187 (58.8)	0.2103	1.000 (Reference)	36 (70.6)	27 (61.4)	0.4648	1.000 (Reference)
AG+AA	112 (36.0)	131 (41.2)		1.24 (0.90-1.72)	15 (29.4)	17 (38.6)		1.51 (0.64-3.55)
Total	311 (100)	318 (100)			51 (100)	44 (100)		

[a]OR: Odds ratio, CI: confidence interval; ORs were estimated with multivariate logistic regression analysis. *Statistically identified as significant.

control non-alcohol drinkers (p=0.2103) nor among CRC alcohol drinkers and control alcohol drinkers (p=0.4648) (Table IV). Similarly, we also analyzed the interactions of *XPD* Lys751Gln and promoter-114 genotypes and alcohol consumption for the risk of CRC, and no interaction was found between alcohol drinking and *XPD* Lys751Gln and promoter-114 genotypes (data not shown). By the same strategy, we analyzed the interaction of *XPD* Asp312Asn, Lys751Gln and promoter -114 genotypes and smoking status, and no obvious interaction was found either (data not shown).

Finally, the correlations between genotypes of *XPD* Asp312Asn and clinicopathological features of the 362 investigated Taiwanese CRC patients were analyzed and presented in Table V. The data showed that no statistically significant correlation was observed between genotypic distributions and the clinicopathological features including the colorectal patients' age, gender, tumor size, tumor location, or lymph node metastasis (all p>0.05).

Table V. *Correlation between XPD Asp312Asn genotypes and clinicopathological properties of 362 colorectal cancer patients.*

Characteristics	Total cases	Genotypes			*p*-Value
		GG (%)	AG (%)	AA (%)	
Age (years)					
≤60	95	52 (54.7)	28 (29.5)	15 (15.8)	
>60	267	162 (60.7)	69 (25.8)	36 (13.5)	0.5984
Gender					
Male	203	123 (60.6)	48 (23.6)	32 (15.8)	
Female	159	91 (57.2)	49 (30.8)	19 (12.0)	0.2463
Tumor size					
<5 cm	195	122 (62.6)	48 (24.6)	25 (12.8)	
≥5 cm	167	92 (55.1)	49 (29.3)	26 (15.6)	0.3531
Location					
Colon	257	156 (60.7)	63 (24.5)	38 (14.8)	
Rectum	105	58 (55.2)	34 (32.4)	13 (12.4)	0.3006
Lymph node metastasis					
Negative	210	118 (56.2)	65 (31.0)	27 (12.8)	
Positive	152	96 (63.2)	32 (21.1)	24 (15.7)	0.1061

Discussion

Discovering appropriate biomarkers for early detection and prediction is helpful in controling CRC high incidence and mortality. In recent years, several potential early detective and predictive markers for CRC in Taiwan were proposed, including *caveolin-1* G14713A, *caveolin-1* T29107A, *Ku80*G-1401T and *XRCC4* G-1394T and *cyclin D* A870G (46-49). *XPD* is a DNA helicase to participate in the unwinding of DNA for further repair machinery of NER. In the current study, the associations of *XPD* Asp312Asn, Lys751Gln and promoter -114 genotypes with CRC risk were investigated in a Taiwanese population. The results of analyzing the *XPD* genotypic distribution of control and patient groups demonstrated that the heterozygotic G/A and homozygotic A/A genotypes of *XPD* Asp312Asn were not associated with risk of developing CRC in Taiwanese (Table II). In addition, not any of the variant genotype at *XPD* Lys751Gln or promoter -114 was associated with CRC risk in Taiwan (Table II). In the allelic frequency analysis, there was no association between any of the allele at *XPD* Asp312Asn, Lys751Gln or promoter -114 with CRC risk (Table III). Our results of *XPD* Asp312Asn association analysis is consistent with the findings of a meta-analysis performed by Zhang and his colleagues in 2014, analyzing eleven published papers comprising of 2,961 CRC patients and 4,539 controls for the possible association of *XPD* Lys751Gln polymorphism with susceptibility to CRC (41). In that study, four pooled databases were from Asians (56-59) and seven were from Caucasians (60-66). In the sub-group analysis stratified by ethnicity, there was still no significant association detected in the homozygous, heterozygous, or dominant model (41). We provided extended cancer genomic evidence showing that in addition to *XPD* Lys751Gln, the genotypes of *XPD* Asp312Asn and promoter -114 are not associated with altered CRC susceptibility in Taiwan.

It is now widely known that the pathogenesis of CRC is closely related to multifactorial interactions among environmental insults and genomic susceptibility. We are interested in investigating the synergistic effects of *XPD* genotypes and risky behaviors, such as smoking and alcohol drinking, on CRC susceptibility. The results showed that the genotypes of *XPD* Asp312Asn (Table IV), Lys751Gln or promoter -114 (data not shown), had no influence on altering the risk of CRC for alcohol consumers or non-alcohol consumers. With respect to interaction of smoking habit and XPD genotypes, the genotypes of *XPD* Asp312Asn, Lys751Gln or promoter -114 had no influence on altering the risk of CRC for smokers or non-smokers either (data not shown). There is no obvious contribution of *XPD* genotypes to tumor size, location and lymph node metastasis (Table V). In the future, further analysis of the possible biological reasons behind the non-existence of a casual relationship such as the interaction of personal diet and excretion habits with XPD Asp312Asn, Lys751Gln and promoter -114 in determining the CRC susceptibility for Taiwanese is required.

With regard to molecular mechanics, the variant genotypes of *XPD* Asp312Asn, *XPD* Lys751Gln are reported to be associated with lower capacity of DNA repair causing a higher susceptibility to tumorigenesis (15, 16, 19, 20). In a genotype-phenotype correlation study, it is reported that the variant genotypes of *XPD* Asp312Asn and Lys751Gln led to the decrease of their mRNA levels in the lymphocytes of healthy subjects (67). More interesting, the decrease at mRNA levels was even more significant among elder people and smokers, which was further exacerbated by the recorded smoking duration and intensity (67). Thus, it is reasonable that the *XPD* Asp312Asn and Lys751Gln genotypes were associated with smoking-related cancers, for instance, lung cancer (21).

In summary, analysis of allelic and genotypic frequencies revealed no causal relationship between *XPD* Asp312Asn, Lys751Gln and promoter -114 and CRC risk in Taiwan. There is no interaction of *XPD* genotypes with alcohol drinking or smoking on CRC risk. The single nucleotide polymorphisms at Asp312Asn, Lys751Gln and promoter -114 of the *XPD* gene were not feasible predictive markers for CRC risk in Taiwan.

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