Original Article

Association of Xeroderma Pigmentosum Group D (XPD) gene Polymorphism with Colorectal Cancer Risk

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Abstract

Background: The xeroderma pigmentosum group D (*XPD*) gene plays a key role in nucleotide excision repair pathway of the damaged DNA. Genetic polymorphisms in coding region of *XPD* gene may alter DNA repair capacity of the protein and hence can modulate the risk of colorectal cancer (CRC) risk. The aim of the study was to determine the genetic association of *XPD Lys751Gln* polymorphism with the risk of CRC development. **Materials and Methods:** One hundred and twenty CRC patients and 160 normal controls were assessed for genotype frequencies of *XPD Lys751Gln* polymorphism. We used polymerase chain reaction–restriction fragment length polymorphism technique to assess the *XPD Lys751Gln* polymorphism. **Results:** We observed a significant association ($P < 0.05$) between the *XPD Lys751Gln* polymorphism and the risk of developing CRC ($P < 0.05$). In addition, *Gln/Gln* genotype of *XPD* gene doubled the risk for the development of CRC ($P < 0.05$; odds ratio = 2.25, 95% confidence interval [1.07–4.7]). **Conclusions:** Our results suggest that there is a significant association between the *XPD* Lys751Gln polymorphism and the risk of CRC.

Keywords: *Colorectal cancer, DNA repair, nucleotide excision repair, polymorphism, restriction fragment length polymorphism, xeroderma pigmentosum group D*

Introduction

Colorectal cancer (CRC) is one of the top most cancers that affect humans, characterized by malignancy of colon or rectal lumen cells.[1] The incidence rate of CRC varies widely across the globe, but it is reported lately that it has been rising on a yearly basis since the last decade.[2] In 2018, CRC became the third common cancer and second most deadly cancer in the world, affecting both genders equally.[3] There is a lot of disparity in CRC incidence geographically; Western countries tend to have the highest incidences of CRC in comparison to the Asian and Middle East countries.[4-7]

Nucleotide excision repair (NER) is one of the important pathways of genome maintenance that is primarily responsible for repairing DNA adducts and other types of damage that cause distortions in the helical structure of DNA.[8,9] NER pathway requires the involvement of numerous enzymes including xeroderma pigmentosum complementary groups A, C, D, and F (*XPA, XPC, XPD, and XPF*, respectively), replication protein A, and excision repair cross-complementing 1.[10]

The *XPD* gene (MIM: 126340; rs13181), also known as excision repair cross -complementation group 2 (ERCC2), is mapped at chromosome 19q13.3 and encodes a helicase that is an essential component of the transcription factor BTF2/TFIIH complex.[11] XPD protein is unique in having an DNA-dependent ATPase activity and 5'-3' DNA helicase activity, because of which it serves as an essential member of the NER pathway.[11,12]

NER recognizes and repairs a wide range of structurally unrelated lesions such as bulky adducts, thymidine dimers (ultraviolet [UV] induced) as well as damage by chemotherapy in DNA molecule.[13-15] XPD protein has ATP-DNA-dependent helicase activity and also acts as a subunit of the basal transcription factor TF2/TFIIH complex.[11] Mutations in the *XPD* gene have been demonstrated to cause diminished activity of the TFIIH complexes, therefore, increasing the likelihood of repair defects, transcription defects, and abnormal responses to apoptosis.[16] The *XPD* Lys751Gln

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single-nucleotide polymorphism (SNP) is attributed to a (A→C) transversion at exon 23 of the gene.[17] It has also been demonstrated that *XPD* 751*Gln/Gln* individuals had suboptimal DNA repair capacity in regard to its ability to remove UV photoproducts as compared to the *XPD* 751 Lys/Lys and Lys/Gln individuals.[18]

Several epidemiological studies have investigated the association between *XPD* gene polymorphism and CRC, whereas some studies found a significant association between the two;[19-24] others failed to link them.[25-29]

In the present study, we conducted a case–control study to find the potential role of *XPD Lys751Gln* polymorphism on the risk of CRC in Kashmiri population. Furthermore, we also investigated an association between the clinic-pathological variables and the *XPD Lys751Gln* genotypes to ascertain any association.

Materials and Methods

Subjects

This study included 120 consecutive primary CRC patients from 2012 to date. All CRC patients were recruited from the Department of Surgery of Sher I Kashmir Institute of Medical Sciences (SKIMS). Tumor types and stages were determined by two experienced pathologists. The cases who had not received any chemo- or radiotherapy were chosen for this study. The study protocol was approved by the Institutional Ethical Committee.

Blood samples of 160 age-matched and sex-matched controls, with no signs of any malignancy, were collected from the outpatient department of the same hospital to serve as controls for the genotypic analysis. Controls represented the patients who visited the outpatient department for the treatment of common ailments such as cold, fever, and urinary tract infection. The mean age of both the patients and the control group was 54 years, and 64 of the patients and 104 of the controls were >50 years of age or older.

Data on all CRC patients were obtained from personal interviews with patients and/or guardians (for those who were illiterate), medical records, and pathology reports. The data collected included sex, age, dwelling, tumor location, Dukes stage, and lymph node status. All patients and/or guardians were informed about the study, and their will to participate in this study was taken on predesigned questionnaire (available on request). The collection and use of tumor and blood samples for this study were previously approved by the appropriate Institutional Ethics Committee in line with the Helsinki declarations.

DNA extraction and polymerase chain reaction–restriction fragment length polymorphism

DNA extraction was performed using an ammonium acetate method. One microliter of DNA was used as the template for each polymerase chain reaction (PCR) cycle.

Analysis of *XPD* Lys751Gln polymorphism was performed using a PCR-restriction fragment length polymorphism method. Primers for *XPD* Lys751Gln were forward (F5' GCCCGCTCTGGATTATACG) and reverse (R5' CTATCATCTCCTGGCCCCC), and Pst-I enzyme was used to carry out restriction digestion. PCR was carried out in a final volume of 25 μL containing 50 ng genomic DNA template, 1X PCR buffer with 2 mM $MgCl_2$, 0.5 μM of each primer, 50 μM dNTPs, and 0.5 U DNA polymerase. For PCR amplification, the standard program was used as follows: one initial denaturation step at 95°C for 7 min, followed by 35 denaturation cycles of 30 s at 95°C, 30 s of annealing at 57°C, and 30 s of extension at 72°C, followed by a final elongation cycle at 72°C for 7 min.

PCR product of 436 bp for *XPD Lys751Gln* was digested at 37°C. *XPD* wild genotype (Lys/Lys) got digested into two bands of 290 bp and 146 bp, *XPD* (Lys/Gln) heterozygous genotype was identified by four digestion products of 290 bp, 227 bp, 146 bp, and 63 bp, whereas *XPD* variant (*Gln/Gln*) produced three digestion bands of 227 bp, 146 bp, and 63 bp.

Statistical analysis

The observed frequencies of the above genotypes in patients with CRC were compared with the controls using the Chi-square or Fisher's exact test when the expected frequencies were small. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS software (IBM, USA; Version 24).

The effective sample size and the statistical power were computed using the "Genetic Power Calculator" developed by Purcell *et al*. (http://pngu.mgh.harvard.edu/~Purcell/gpc/). The statistical power of 80% is widely used in genetic association studies to avoid Type II errors and to determine a cost-effective sample size under the assumption of 10% to 25% variant allele frequency, 1:1 case-to-control ratio, and 5% Type I error rate (α). We obtained a healthy power score of about 85% for the SNP under the study in our case–control study design with 160 cases and 200 controls.

Results

A total of 120 cases and 160 controls were included in this study with prior consent. Of 120 confirmed cases of CRC, 64 were >50 years old and 56 were ≤50 years of age, 72 were male and 48 were female, 57 were rural and 63 were urban, 53 cases had carcinoma in the colon and 67 in the rectum, and 59 were smokers and 61 nonsmokers. The mean age of patients having confirmed CRC was 54 years. Among controls, 88 consisted of males and 72 females. No significant gender- or age-related differences were observed between the groups ($P > 0.05$) [Table 1].

Among 120 CRC cases, we found that the frequency of *XPD* genotype was 51.60% (62/120) for Lys/Lys, 30.0% (36/120)

for Lys/Gln, and 14.1% (22/120) for *Gln/Gln*, whereas the frequency in the general control population was 55.60% (89/160) for Lys/Lys, 35.6% (57/160) for Lys/Gln, and 8.7% (14/160) for *Gln/Gln*. The overall association between the *XPD Lys751Gln* polymorphism and the CRC cases was found to be significant ($P < 0.05$) [Table 2]. In addition, *Gln/Gln* genotype showed a significant doubling of the risk for the development of CRC (odds ratio = 2.25, 95% confidence interval [1.07–4.7]). Furthermore, we found the *XPD* Gln allele frequency to be about 26% among controls and almost 33% among CRC patients; however, the distribution was not found to be significantly different ($P = 0.05$) [Table 2].

We also analyzed the correlation of *XPD Lys751Gln* polymorphism with the clinicopathological characteristics and found the *Gln/Gln* genotype to be significantly associated with the age of the CRC patients ($P = 0.01$) and involvement of nodes ($P = 0.006$) [Table 3].

Discussion

CRC is one of the most frequent common types of malignancy as well as leading cause of death around the world. Incidence rates vary widely according to region. CRC shows considerable variation among racially or ethnically defined populations in multiracial/ethnic countries.[5,30] Kashmir has a high-incidence area of gastrointestinal tract (GIT) cancers;[31,32] wherein CRC represents the third most common GIT cancer.[1,32]

The XPD protein plays a pivotal role in NER pathway. It participates in the unwinding of the DNA double-stranded helix around the damaged site with its intrinsic helicase activity so as to allow the removal of DNA lesions.[33,34] XPD helicase is also required for p53-dependent apoptosis and cell cycle regulation.[35]

A number of SNPs have been found in the *XPD* gene affecting both exonic and intronic regions of the gene. Among all of the SNPs, four result in amino acid changes: (i) isoleucine to methionine in codon 199, (ii) histidine to tyrosine in codon 201, (iii) aspartic acid to asparagine in codon 312, and (iv) lysine to glutamine in codon 751.[17] Of these four, only two SNPs are the most commonly occurring ones – codon 312 and 751.[33] *XPD Lys751Gln* is one of the most common SNP located in exon 23 of the gene which affects the important domain (C-terminal) of XPD helicase that is known to interact with p44 protein of TFIIH complex. This cross talk stimulates XPD by activating its helicase activity.[16] Therefore, this SNP may affect different protein interactions and hence diminish the activity of TFIIH complexes.[17] In addition, *XPD Lys751Gln* SNP is also known to reduce the ERCC2 protein expression by decreasing the ERCC2 mRNA stability.[36] Furthermore, it has been also reported that the *XPD Lys751* allele is associated with a high level of UVC-induced formation of DNA strand breaks.[37]

In addition, Lunn *et al*.[38] suggested that XPD Lys752 may alter XPD protein product resulting in the suboptimal repair of X-ray-induced DNA damage. This is the reason why Lys751Gln SNP is the most widely studied polymorphism with regard to its modulation of cancer risk. Lunn *et al*.[38] studied the functional significance of *XPD* polymorphisms with respect to chromosome aberrations and reported that individuals with the *XPD 751 Lys/Lys* genotype had a higher number of chromatid aberrations than those having a 751Gln allele. Possessing a *Lys/Lys751* genotype increased the risk of suboptimal DNA repair by almost 7-folds,

Table 1: Frequency distribution analysis of selected demographic and risk factors in colorectal cancer cases and controls

Variable	Cases (*n*=120)	Controls (*n*=160)	*P*
Age			
>50	64	104	0.04
≤50	56	56	
Sex			
Males	72	88	0.4
Females	48	72	
Smoking status			
Ever	59	70	0.36
Never	61	90	
Dwelling			
Rural	57	94	0.06
Urban	63	66	
Tumor location			
Colon	53		
Rectum	67		

Table 2: Genotype frequencies of xeroderma pigmentosum group D gene polymorphism in colorectal cancer cases and controls

XPD genotype	CRC cases (*n*=120), *n* (%)	Controls (*n*=160), *n* (%)	OR (95% CI); $P^{¥}$; $F^{ψ}$	χ^2; *P* (overall)
Lys/Lys (Wild)	62 (51.60)	89 (55.6)	1	**5.75; 0.05**
Lys/Gln (Heterozygous)	36 (30.0)	57 (35.6)	0.9 (0.53-1.53); 0.71; 0.78	
Gln/Gln (Variant)	22 (18.30)	14 (8.7)	**2.25 (1.07-4.7); 0.02; 0.03**	
Allele				
Lys	160 (66.7)	235 (73.4)		
Gln	80 (33.3)	85 (26.6)	1.38 (0.95-1.99); 0.08; 0.09	

¥Pearson's *P* value, ψFisher's exact *P* value. Significant *P* values are shown in bold. OR: Odds ratio, CI: Confidence interval, XPD: Xeroderma pigmentosum group D, CRC: Colorectal cancer

Table 3: Association between xeroderma pigmentosum group D gene polymorphism and clinicopathologic characteristics

Variables	Cases (*n*=120)				
	***n*=120**	**Lys/Lys (*n*=62; 51.6%)**	**Lys/Gln (*n*=36; 30.0%)**	***Gln/Gln* (*n*=22; 18.30%)**	**χ^2; *P***
Age group					
>50	64	38	12	14	**8.3; 0.01**
≤50	56	24	24	8	
Gender					
Female	48	26	13	9	0.33; 0.84
Male	72	36	23	13	
Dwelling					
Rural	57	25	20	12	2.66; 0.26
Urban	63	37	16	10	
Smoking status					
Ever	59	25	19	15	5.31; 0.07
Never	61	37	17	7	
Tumor location					
Colon	53	28	15	10	0.13; 0.93
Rectum	67	34	21	12	
Nodal status					
Involved	63	38	11	14	**9.97; 0.006**
Not involved	57	24	25	8	
Tumor grade					
WD	91	45	27	19	1.7; 0.42
MD + PD	29	17	9	3	

Significant *P* values are shown in bold. WD: Well differentiated, MD: Moderately differentiated, PD: Poorly differentiated

suggesting that the Lys751 (common) allele may alter the XPD protein product resulting in suboptimal repair of X-ray-induced DNA damage.

A number of studies have investigated the role of DNA repair gene polymorphisms in the patients suffering from CRC in Kashmir province, India.[39-42] In this hospital-based case–control study of CRC-suffering patients, we found polymorphisms in the pivotal DNA repair gene *XPD* to be associated with an elevated risk of CRC.

Our results indicate that the *XPD Lys751Gln* polymorphism may predispose our population to the development of CRC ($P < 0.05$), which is in concordance with many studies reported from different populations worldwide.[19-24] However, some of the researchers have reported no significant association between the *XPD Lys751Gln* polymorphism and CRC.[24,29,43,44] Furthermore, in our study, we found the *XPD* Gln allele frequency to be about 26% among controls and almost 33% among CRC patients, and this frequency is in accordance with the study of Moghtit *et al*.[27] However, this frequency is lower than that reported by other studies[22,24,37,45-48] but higher than that reported by other Asian/Caucasian populations.[29,49,50]

Two important early meta-analyses – one by Zhang *et al*.[25] on 11 case–control studies (including a total of 32,961 cases and 4539 controls) and another by Zhang *et al*.[28] on 15 case–control studies (including a total of 3042 cases and 4627 controls) – did not find any evidence of a link between the *XPD* Lys751Gln polymorphism and risk of CRC. A recent study by Moghtit *et al*.[27] on Western Algerian CRC patients (consisting of 129 cases and 148 controls) reported no association of the *XPD Lys751Gln* with CRC risk. However, the study by Rezaei *et al*.[22] on Iranian CRC patients (consisting of 88 cases and 88 controls) suggested that the individuals with heterozygous *XPD* genotype (Lys/Gln) may have an increased susceptibility to CRC compared to other genotypes, and the study of Wang *et al*. on Indian CRC patients found that *XPD 751Gln* allele demonstrated the 3.5 times increased risk of rectal cancer.[45]

However, a meta-analysis by Mandal *et al*.[51] of 13 case–control studies (including 3087 cases and 3599 controls) reported the likely association of the *XPD Lys751Gln* polymorphism with the risk of development of cancer in Indian population. Their meta-analysis concluded that *XPD Lys/Gln* and *XPD Gln/Gln* genotypes had had 1.3- and 1.6-fold increased risk of developing cancer as compared with the wild *XPD* Lys/Lys genotype, respectively. Similarly, another meta-analysis of 37 case–control studies (including 9027 cases and 16072 controls) by Du *et al*.[26] suggested that the *XPD 751Gln/Gln* genotype was a low-penetrate risk factor for developing digestive tract cancers, especially in Asian populations.

Acknowledging the relatively limited sample size in the subgroups for the low allelic frequencies, further studies incorporating a larger sample size and/or another ethnic population are needed to confirm the genetic role of DNA repair mechanisms as regards CRC susceptibility.

Conclusions

This study displays a significantly elevated risk for CRC in individuals with *XPD Gln/Gln* genotypes, thereby suggesting that the key enzymes of DNA repair pathway are modulating the risk of developing CRC in Kashmiri population with almost two and half times than *Lys*/*Lys* genotype.

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Conflicts of interest

There are no conflicts of interest.

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