

RESEARCH ARTICLE

Polymorphism of the DNA Repair Gene XRCC1 (Arg194Trp) and its role in Colorectal Cancer in Kashmiri Population: a Case Control Study

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Abstract

Background: Genetic polymorphisms in DNA repair genes may influence individual variation in DNA repair capacity, which may be associated with risk of developing cancer. For colorectal cancer the importance of mutations in mismatch repair genes has been extensively documented. **Materials and Methods:** In this study we focused on the Arg194Trp polymorphism of the DNA repair gene XRCC1, involved in base excision repair (BER) and its role in colorectal cancer in Kashmiri population. A case-control study was conducted including 100 cases of colorectal cancer, and 100 hospital-based age- and sex-matched healthy controls to examine the role of XRCC1 genetic polymorphisms in the context of colorectal cancer risk for the Kashmiri population. **Results:** Genotype analysis of XRCC1 Arg194Trp was conducted with a restriction fragment length polymorphism (RFLP) method. The overall association between the XRCC1 polymorphism and the CRC cases was found to be significant ($p < 0.05$) with both the heterozygous genotype (Arg/Trp) as well as homozygous variant genotype (Trp/Trp) being moderately associated with the elevated risk for CRC [OR=2.01 (95% CI=1.03-3.94) and OR=5.2(95% CI=1.42-19.5)] respectively. **Conclusions:** Our results suggest an increased risk for CRC in individuals with XRCC1 Arg194Trp polymorphism suggesting BER repair pathway modulates the risk of developing colorectal cancer in the Kashmiri population.

Keywords: Colorectal cancer - Kashmir - polymorphism - DNA repair - RFLP - XRCC1 - BER

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death in many parts of the Western world (Gellad and Provenzale, 2010). CRC is a commonly diagnosed cancer in both men and women, and ranks third most common cancer in men and second most in women worldwide (Jemal et al., 2011). The incidence of this malignancy shows considerable variation among racially or ethnically defined populations in multiracial/ethnic countries. Kashmir has been reported as a high-incidence area of gastrointestinal cancers (GIT) (Mir et al., 2005; Jemal et al., 2011; Rasool et al., 2012; Sameer, 2013a). In Kashmir valley CRC represents the third most common GIT cancer (Sameer et al., 2012; Sameer, 2013a; 2013b) after esophageal and gastric cancer; and among males CRC ranks as fourth common cancer and third among females (Rasool et al., 2012; Sameer, 2013).

Genetic polymorphisms in DNA repair genes which

lead to amino acid substitution may lead to differential capacity to repair DNA damage. This effect has been found to be associated with increased genetic instability and carcinogenesis (de Boer, 2002). In mammalian cells four different DNA repair mechanisms have been identified: base excision repair (BER), nucleotide excision repair (NER), double-strand break repair and mismatch repair (Yu et al., 1999, Christmann et al., 2003). All these DNA repair pathways are finely regulated for the maintenance of genomic integrity and modulation of repair capacity in response to DNA damage and thus susceptibility to CRC (Naccarti et al., 2007).

The BER pathway has a primary role in the repair of oxidative base lesions such as 8-hydroxyguanine, formamidopyrimidines, and 5-hydroxyuracil (Mynard et al., 2009) produced by methylation, oxidation or reduction by ionizing radiation or oxidative damage (Duarte et al., 2005). BER pathway serves as an important gladiator against DNA damage that could lead to cancer resulted from many factors, including altered metabolism, reactive

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oxygen species, and methylating and deaminating agents (Lindahl and Wood, 1999; Hoeijmakers, 2001; Wood et al., 2001; Friedberg, 2003).

XRCC1 (X-ray repair cross-complementing group1) gene is located on chromosome 19q13.2-13.3 which codes for a 633 amino acid residue Xrcc1 protein (Nissar et al., 2013). Xrcc1 protein functions as scaffolding protein with many DNA interacting proteins important of which are DNA polymerase beta, apurinic/apyrimidinic endonuclease 1 (APE1), human 8-oxoguanine glycosylase 1 (hOGG1), poly-(ADP-ribose) polymerase (PARP) and DNA ligase III to facilitate BER and single-strand break-repair (SSBR) processes (Thompson and West, 2000; Vidal et al., 2001; Marsin et al., 2003; Brem and Hall, 2005)

About sixty validated single nucleotide polymorphisms (SNPs) in the XRCC1 gene have been identified till date among which three affect the coding region of the gene namely codons 194 (Arg>Trp), 280 (Arg>His) and 399 (Arg>Gln) (Shen et al., 1998; Skjelbred et al., 2006). These non- conservative amino acid changes may alter Xrcc1 function and may have an impact on individual susceptibility to the development of cancers (Marsin et al., 2003; Liu et al., 2013). XRCC1 gene polymorphisms have been reported to be associated with the risk of different kinds of cancers, including bladder cancer, thyroid cancer, lung cancer, breast cancer, gastric cancer, non-melanoma skin cancer, oral cancer as well as colorectal cancer (Abdel-Rahman et al., 2000; Duell et al., 2001; Lee et al., 2002; Mort et al., 2003; Yeh et al., 2005; Wang et al., 2010; Custodio et al., 2011; Chiyomaru et al., 2012; Chen et al., 2012; Du et al., 2013; Nissar et al., 2013; Zhang et al., 2013; Feng et al., 2014).

In the present paper, we conducted a case- control study to examine the role of genetic polymorphism Arg194Trp of DNA repair gene XRCC1 in context of colorectal cancer risk for the Kashmiri Population. Further we also investigated whether there is a link between the clinic- pathological variables with the XRCC1 Arg194Trp genotype and hence its role in modulating the risk of colorectal cancer.

Materials and Methods

Subjects

This study included 100 consecutive primary colorectal cancer patients. All CRC patients were recruited from Department of Surgery, Sher-I-Kashmir Institute of Medical Science. 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. Blood samples of 100 age and sex matched individuals with no signs of any malignancy were collected for controls. The mean age of both patient and control groups was 55 years.

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, 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.

DNA extraction & genotype analysis:

DNA extraction was performed using Ammonium Acetate Method. One μL of DNA was used as the template for each PCR cycle. Genotype analysis of XRCC1 gene was carried out by PCR-RFLP using primers (F: 5'-GTG AAG GAG GAG GAT GAG AGC-3'; R: 5'-CCC CAG CCC CCT CTA CCC T-3') generating a fragment of 160 bp as previously described (Figure1) (Custodio et al., 2011). Briefly 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 94°C for 7 min, followed by 35 denaturation cycles of 1min at 94°C, 1min of annealing at 60°C, and 1min of extension at 72°C, followed by a final elongation cycle at 72°C for 10 min.

PCR product of 160 bp was digested by 10 U MspI at 37°C. For codon 194, two bands of 110 and 60 bp were identified as homozygous wild type Arg/Arg, while three bands of 160, 110 and 60 bp was identified as heterozygous variant allele Arg/Trp and the homozygous mutant type

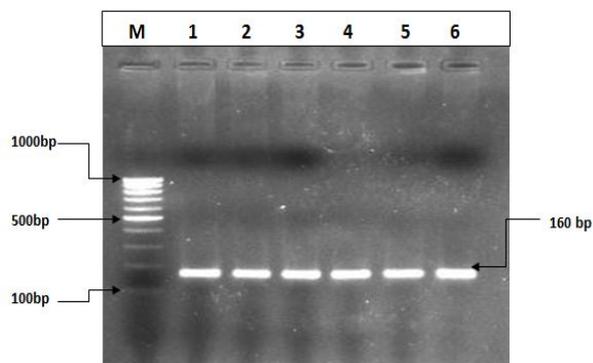


Figure 1. Representative gel picture showing XRCC1 exon 6 Amplicon. Lane M Contains 100 bp DNA Molecular Weight Marker. Lane 1-6 Represent 160 bp Amplicon of Exon6

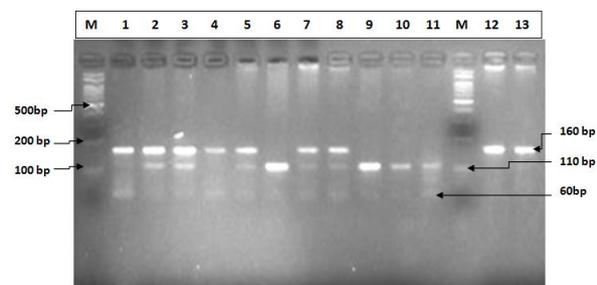


Figure 2. Representative gel picture showing RFLP analysis of XRCC1 Codon194 against 100 bp Marker. Lane no. 6, 9, 10 and 11 Shows Arg/Arg Wild Genotype; Lane no. 4, 12 and 13 Denotes Trp/Trp Homozygous Mutants and Lane no. 1, 2, 3, 5, 7 and 8 Represent Arg/Trp Heterozygous Variant Respectively

Trp/Trp displayed only one band of 160 bp (Figure 2).

Statistical analysis

The observed frequencies of the above genotypes in patients with CRC were compared with the controls using chi-square or Fisher exact tests when the expected frequencies were small. The chi-square test was used to verify whether the genotype distributions were in Hardy-Weinberg equilibrium (for allele and genotype frequencies in our population). Statistical significance was set at $p < 0.05$. Statistical analyses were performed using PASW version 18 software.

Results

A total of 100 cases and 100 control subjects were included in this study with prior consent. All of cases presented constipation and bleeding per rectum as their chief complaint. Furthermore, out of 100 confirmed cases of CRC, 55 males and 45 cases were females (M/F ratio=1.22), 61 were rural and 39 were urban, 44 cases had carcinoma in colon and 56 in rectum and 60 were smokers and 40 non-smokers (Table 1). The mean age of patients having confirmed CRC was 55 years. Among control subjects, 54 consisted of males and 46 females (M/F ratio = 1.17). No significant gender- or age-related differences were observed between the groups ($p > 0.05$). Among the CRC cases, we found the frequency of the XRCC1 genotype to be 59.0 per cent (59/100) for Arg/Arg, 29.0 per cent (29/100) for Arg/Trp and 12.0 per cent (12/100) for Trp/Trp, while the frequency in the general control population was 78.0 per cent (78/100) for Arg/Arg, 19.0 per cent (19/100) for Arg/Trp and 3.0 per cent (3/100) for Trp/Trp. The overall association

Table 1. Frequency Distribution Analysis of selected Demographic and Risk Factors in Colorectal Cancer Cases and Control

Variable	Cases n = 100	Controls n = 100	P-Value
Age			
> 50	54	52	0.88
≤ 50	46	48	
Sex			
Males	55	54	1
Females	45	46	
Smoking Status			
Ever	60	55	0.56
Never	40	45	
Dwelling			
Rural	61	58	0.77
Urban	39	42	

Table 2. Genotype Frequencies of XRCC 1 Gene Polymorphism in CRC Cases & Controls

XRCC1 Genotype	CRC Cases (n= 100)	Controls (n=100)	OR (95% CI) [†] ; [‡] P , [§] P	χ^2 , P Value (Overall)
Arg/Arg – (Wild)	59 (59.0%)	78 (78.0%)	1	
Arg/Trp – (Heterozygous)	29 (29.0%)	19 (19.0%)	2.01 (1.03-3.94); 0.03; 0.04	10.12,
Trp/Trp – (Variant)	12 (12.0%)	03 (3.0%)	5.2 (1.42-19.5); 0.006; 0.01	0.006

[†] Pearson's P Value; [‡] Fisher Exact P Value; Significant P values are shown in bold

between the XRCC1 polymorphism and the CRC cases was found to be significant ($p < 0.05$) (Table 2). Overall both the heterozygous genotype (Arg/Trp) as well as homozygous variant genotype (Trp/Trp) were associated with the elevated risk for CRC (OR=2.01 (95%CI=1.03-3.94) and OR=5.2(95%CI=1.42-19.5)). Also, independent analysis for the Arg/Trp and Trp/Trp genotypes revealed a significant association with the risk of CRC ($p < 0.05$). The overall hazard ratio of the XRCC1 Trp allele in CRC was 5.2 (95%CI=1.42-19.5).

The correlation of XRCC1 polymorphic status with the clinico-pathological characteristics was also carefully analyzed. However, we did not find any significant association (p value > 0.05) with any of the characteristic (Table 3).

Discussion

There is increasing evidence that genetic variation leads to different DNA repair capacities in the human population, hence such common polymorphisms can play a role in an individual's genetic susceptibility to cancer (Berwick and Vineis, 2000). Mutations in XRCC1 gene may lead to decrease or loss of its DNA repair capacity and confer the variation in susceptibility to diverse malignant tumors among individuals. More than 300 SNPs in XRCC1 gene have been demonstrated in previous studies, among which the XRCC1 Arg194Trp and XRCC1

Table 3. Association between XRCC1 Gene Polymorphism and Clinico-pathologic Characteristics

Variables	Cases (n = 100)				χ^2 , p value
	n = 100	Arg/Arg 59(59.0%)	Arg/Trp 29(29.0%)	Trp/Trp 12 (12.0%)	
Age group					
≤50	54 (54.0%)	33	15	6	0.23, 0.89
>50	46 (46.0%)	26	14	6	
Gender					
Female	45 (45.0%)	24	16	5	1.71, 0.42
Male	55 (55.0%)	35	13	7	
Dwelling					
Rural	61 (61.0%)	37	16	8	0.65, 0.72
Urban	39 (39.0%)	22	13	4	
Smoking status					
Ever	60 (60.0%)	36	17	7	0.06, 0.97
Never	40 (40.0%)	23	12	5	
Tumor location					
Colon	44 (44.0%)	21	17	6	4.38, 0.11
Rectum	56 (56.0%)	38	12	6	
Nodal status					
Involved	57 (57.0%)	38	12	7	4.22, 0.12
Not Involved	43 (43.0%)	21	17	5	
Tumor grade					
WD	63 (63.0%)	37	18	8	0.08, 0.96
MD+PD	37 (37.0%)	22	11	4	

Arg399Gln polymorphisms are the most extensively studied SNPs (Lamerdin et al., 1995).

In this hospital-based case-control study, we investigated the relationship of DNA repair gene XRCC1 Arg194Trp polymorphism with colorectal carcinogenesis and its concomitant role in the modulation of risk of colorectal cancer in our population taking into view that our previous study on XRCC1 Arg399Gln polymorphism, had demonstrated that although there was no direct significant association between XRCC1 genotypes and CRC, but that Arg/Gln heterozygous genotype was associated with the elevated risk of CRC (OR>1.47) and Gln/Gln variant genotype was associated with an increased risk of CRC in various clinic-pathological parameters (Wang et al., 2010).

In this study we found that among the CRC cases, the frequency of the XRCC1 and Arg/Arg genotype to be 59.0 per cent (59/100), Arg/Trp to be 29.0 per cent (29/100) and Trp/Trp to be 12.0 per cent (12/100), while the frequency of XRCC1 and Arg/Arg genotype in controls was 78.0 per cent (78/100), 19.0 per cent (19/100) for Arg/Trp and 3.0 per cent (3/100) for Trp/Trp. The overall association between the XRCC1 Arg194Trp polymorphism and the CRC was found to be significant ($p=0.006$) (Table 4.2). We also found that variant allele (Trp) in both conditions - heterozygous (Arg/Trp) genotype and homozygous (Trp/Trp) genotype was associated with the elevated risk for CRC (OR=2.01 (95%CI=1.03-3.94)) and (OR=5.2(95%CI=1.42-19.5)) respectively.

These results are in agreement with the study of Abdel Rehman et al., (2000) on Egyptian population, who first reported the significant relationship between XRCC1 polymorphism and CRC, providing the first evidence that individuals inheriting the 194Trp variant allele of XRCC1 gene were more likely to develop CRC.

A large case control study in the United States reported that 194Trp allele, was associated with a modest increase in the risk of colon cancer with alcohol consumption (Curtin et al., 2009). Likewise Yin et al., 2012 reported individuals with the 194Arg allele showed a moderately increased risk of colorectal cancer with high alcohol consumption.

Similarly, Gao et al., (2013) reported that XRCC1 194Trp allele in interaction with the high alcohol intake played a significant role in elevating the risk of CRC ($P < 0.01$) concluding the fact that CRC susceptibility may be altered by gene-environment interactions. Furthermore the meta-analysis by Mao et al., (2013) suggests that the XRCC1 Arg194Trp polymorphism may modify the risk for CRC, particularly in patients with colon cancer. Also XRCC1 and Arg194Trp SNP has been indicated as modifier of the effect of tobacco smoking and alcohol consumption on CRC risk, suggesting the role of gene-environment interaction in colorectal carcinogenesis.

However, our results were not consistent with many other studies like Hong et al., (2005) and Importa et al., (2008) which suggested that XRCC1 polymorphism might have multiple and subtle influences on the carcinogenesis. They have also suggested that the effects are modulated by several genetic factors and/or environmental exposures.

However, few studies reported a reduced risk of

cancer associated with the XRCC1 194Trp variant form (Lamerdin et al., 1995; Duell et al., 2001; Mort et al., 2003) while as other study by Sjelkbred et al., (2006) and Muñiz-Mendoza et al., (2012) reported no association of codon 194 polymorphism with the risk of CRC, in a similar way as reported by Li et al., (2014) for hepatocellular carcinoma.

The divergence in results from different studies on XRCC1 polymorphism may be related to variation in carcinogenic exposure and ethnic origin of the studied population (Hong et al., 2005; Stern et al., 2005; Moreno et al., 2006; Berndt et al., 2007; Sliwinski et al., 2008). Since carcinogenesis is a complex process and inter related pathways of biological response to DNA damage exist involving multiple genetic mechanisms, therefore such inconsistency in results among different populations can be attributed to the fact that polymorphism might have multiple effects on cancer formation, which depend on other genetic factors or environmental exposures. The small sample size plus other confounding factors like age, gender, diet and lifestyle may attribute to such differences.

The contradictory findings among different case-control studies might be attributed to different sample size, source of controls, genotyping method and matching criteria of subjects, and so on. In addition, the potential gene-gene and gene-environment interactions may also play vital roles in the pathogenesis.

In conclusion, our results suggest an increased risk for CRC in individuals with XRCC1 Arg194Trp polymorphism suggesting BER repair pathway modulates the risk of developing colorectal cancer in Kashmiri population.

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