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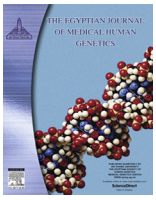

Original article

XRCC1 Arg194Trp polymorphism is no risk factor for skin cancer development in Kashmiri population

Rouf Maqbool [a,*], Shajrul Amin [a], Sabhiya Majeed [b], Aaliya Bhat [a], Shayaq ul Abeer Rasool [c], Mudasar Nabi [a]

[a] Department of Biochemistry, University of Kashmir, Srinagar 190006, India
[b] Department of Biochemistry, Government Medical College, Srinagar, India
[c] Department of Biotechnology, University of Kashmir, Srinagar 190006, India

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ABSTRACT

Background: Recently, three coding polymorphisms in X-ray cross complementing gene 1 (XRCC1) have been identified; with probable effect on DNA repair capacity and thus modulation of cancer susceptibility. Moreover, association of these polymorphisms with the cancer risk are reported to be population dependent. Therefore, in this case control study we aimed to investigate the polymorphism at codon 194 (Arg to Trp) in XRCC1 gene and the possible association of its polymorphic genotypes with skin cancer in the ethnically different population of Kashmir.

Aim: To study if there is any possible association of Arg194Trp XRCC1 polymorphism with risk of developing skin cancer in ethnically different Kashmir population.

Subjects and methods: For this study 68 skin cancer patients and 60 healthy controls, matched for age and gender were recruited. PCR-RFLP followed by statistical analysis was employed to check for the C194T polymorphism and its possible association with the skin cancer risk in the population.

Result: An insignificant association among skin cancer patients with respect to the wild (Arg/Arg) versus variant (Trp/Trp) genotypes (OR = 0.34, 95% CI = 0.10–1.05, $p = 0.06$) was observed. However, individually homozygous and heterozygous variant alleles were observed to be associated with risk of developing skin cancer. As far as, individual allelic ratio among cases and controls is concerned Trp allele of codon194 showed a remarkably high frequency in cases (67.7% vs. 32.3%) in comparison with controls (OR = 1.94, 95% CI = 1.22–3.0, $p = 0.004$).

Discussion: These findings suggest that the combined homozygous and heterozygous variants of each codon and the 194Trp allele are associated with the disease, however when genotypes were compared individually, the association turned out to be insignificant.

1. Introduction

Skin cancer, like any other cancer, involves unaccountable growth of skin cells, having ability to invade or spread to other parts of body. It occurs when unrepaired DNA damage to skin cells (most often caused by ultraviolet radiation from sunshine) triggers mutations, or genetic defects, that lead the skin cells to multiply rapidly and form malignant tumors [1]. Skin cancers are now representing a major public health concern with nearly 15,000 deaths, 3.5 million new cases, and more than 3 billion dollars a year in medical costs in the United States alone [2]. In Kashmir, skin cancers ranks sixth among all cancers in males, corresponding to 3.46% of all cancers for the year 2000–2012 [3]. The major external cause of melanoma, as with all skin cancers, is sun exposure, but this is heavily modified by other personal risk factors such as the number and type of benign melanocytic naevi or moles (lesions of pigment forming skin cells), the character and intensity of skin pigmentation, and skin sensitivity to sunlight [4]. Extensive epidemiological and experimental data suggests that it is Ultraviolet (UV) radiation which is an important environmental carcinogen involved in the initiation and progression of skin cancer [5]. Currently, it is estimated that UV exposure is associated with 65% of melanoma cases and 90% of non-melanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma [6]. Direct absorption of UVA radiations at short wavelengths (280–320 nm) cause DNA damage in the form of cyclobutane pyrimidine dimmers and generates pyrimidine photoproducts [7], while as UVB at short wavelengths (320–400 nm) causes single-stranded breaks, DNA-protein cross

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* Corresponding author.
E-mail address: roufthakur714@gmail.com (R. Maqbool).

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linking, and also generates free radicals that cause oxidative damage to DNA [8]. Cells respond to this damage through the activation of various DNA repair pathways, including the base excision repair (BER) pathway.

DNA repair gene X-ray repair cross-complementing group-1 (*XRCC1*), the member of the base excision repair pathway, corrects defective DNA strand-break repair and sister chromatid exchange following treatment with ionizing radiation and alkylating agents [9]. Polymorphisms in several DNA repair genes have been described affecting DNA repair capability and modulate cancer susceptibility by means of gene-environment interactions [10] and studies have been reported that link it with the risk of various types of cancer including lung cancer [11], squamous cell carcinoma (SCC) of head and neck [12], pancreatic adenocarcinoma [13], bladder cancer [14], and breast cancer [15]. At least three genetic variants have been recognized in the multi-protein interacting regions of DNA repair gene *XRCC1* gene that result in amino acid changes from Arginine (Arg) to Tryptophan (Trp) at codon 194 (Arg/Trp), from Arginine (Arg) to Histidine (His) at codon 280 (Arg/His) and from Arginine (Arg) to Glutamine (Gln) 399 (Arg/Gln), respectively, thereby weakening the DNA repair capacity [16].

While *XRCC1* has been seen to be important in DNA repair and a number of studies have been carried out regarding the role of polymorphic forms of *XRCC1* in susceptibility to cancer, the effect of genetic polymorphisms on the risk of disease may vary from one population to the others due to the differences of the frequencies and types of polymorphisms as well as the exposed carcinogens in a studied population [17–19]. Kashmir valley is distinct from rest of India as far as its geography, climate, social and dietary habits are concerned. Till date no data exists, to our knowledge, on the association of *XRCC1* polymorphism in susceptibility to skin cancer among Kashmiri population. This study is therefore the first investigative effort in describing the association between *XRCC1* polymorphism and skin cancer susceptibility.

2. Subjects and methods

2.1. Sample selection and collection

After obtaining the necessary ethical clearance from the institutional ethics committee, 68 histopathologically confirmed skin cancer patients were recruited for the study at the Department of Dermatology, Shri Maharaja Hari Singh Hospital, Srinagar, Kashmir. The recruited subjects had no earlier history of any malignancy and had not received any type of pre-operative chemo or radiotherapy. Of the 68 recruited cases, 40 were male and rest females. For control group, 60 healthy individuals were recruited, of which 37 were males and 23 females. The subjects selected as controls had no family history of any malignancy. About 3 ml of peripheral blood was collected from each subject in sterilized vials coated with EDTA (0.5 M; pH-8.0) and stored at −80 °C for further analysis. All the necessary information for the study was collected from the cases and the control subjects and properly documented. The cases and control subjects were age and gender matched.

2.2. Whole genomic DNA isolation

Whole genomic DNA was isolated from the blood cells by phenol-chloroform method. The quality of the isolated genomic DNA was examined by gel electrophoresis using 1% agarose gel. Gel was visualized by a Gel doc system (Endura) under UV light. The ratio of A_{260}/A_{280} was also calculated and the DNA sample for which the ratio was 1.7–1.9 was considered for the future use. The DNA was stored at 4 °C for a short time but the vials were kept at −20 °C for longer duration storage.

2.3. PCR amplification

The isolated whole genomic DNA was subjected to Polymerase Chain Reaction (PCR) amplification in automated thermal cycler (eppendorf) to amplify the desired target i.e. exon 6, codon 194 of *XRCC1* gene, using the pair of primers (Forward primer: 5′-GCC CCGTCCCAGGTA-3′ and Reverse primer: 5′-AGCCCCAAGACCCTTT CACT-3′). PCR was performed in total volume of 25 μl volume under the following set of conditions (Table 1):

2.4. Restriction digestion

The PCR product of 491 bp was digested with specific restriction enzymes for detecting the codon 194 polymorphism of the *XRCC1* gene. The standard protocol for restriction digestion was used. Ten microliters of the PCR products were digested separately with 5 units (0.5 μl) of MspI (Fermantas, USA). The reaction mixture included 2 μl of 10x buffer and 18 μl of Milli Q water. The mixture was incubated at 37 °C for 24 h. The products were then resolved on 3% agarose gels. DNA molecular weight marker of 100 bp was used to assess the size of the PCR–RFLP (Restriction fragment length polymorphism) products.

2.5. Statistical analysis

Results were statistically analyzed and data was expressed as mean ± SD. Allele and genotype frequencies were compared between groups using the χ^2-test. The association between XRCC1 genotype and the risk of Skin cancer was estimated by calculating odds ratio (OR) and their 95% confidence intervals (95% CI). A P value of <0.05 was used as a criterion for statistical significance. For the analysis, statistical software Graph Pad Prism version 5.0 was used.

3. Results

3.1. General characteristics of study population

Present case-control study included 68 histopathologically confirmed skin cancer cases and 60 healthy controls, matched with respect to age and gender. General characteristics of the skin cancer patients and controls are given in Table 2. Out of 68 cases, 40 were males with mean age (51.12 ± 7.8) and 28 were females with mean age (50.85 ± 6.79) years. As far as age is concerned, 41 (60.3%) were found above 50 years of age and 27 (39.7%) were found below 50 years of age. Similarly, in 60 healthy controls, it was found that 37 were males with mean age (50.08 ± 8.01) and 23 were females with mean age (51.08 ± 8.23) years. Out of these controls, 35 (58.3%) were found above 50 years of age while as 25 (41.7%) were found below 50 years of age. Of all the regions of the Kashmir division, 35 (51.5%) cases turned out from the urban area and 33 (48.5%) were from rural areas, while as in case of controls 31 (51.6%) turned out from urban areas and 29 (48.4%) were from rural areas.

Table 1
PCR cycling parameters.

Steps	Temperature °C	Time	Number of cycles
Initial Denaturation	95	5 min	1
Denaturation	95	30 s	30
Annealing	58	40 s	
Extension	72	30 s	
Final extension	72	5 min	1

Table 2
General characteristics of study population.

Demographic features	Cases (n = 68)	Controls (n = 60)
Age	(mean ± SD)	(mean ± SD)
Males	51.12 ± 7.8	50.08 ± 8.01
Females	50.85 ± 6.79	51.08 ± 8.23
Gender		
Male	40 (58–8%)	37 (61.5%)
Female	28 (41.2%)	23 (38.5%)
Residence		
Urban	35 (51.5%)	31 (51.6%)
Rural	33 (48.5%)	29 (48.4%)
Family history of cancer		
Yes	17 (25%)	9 (15%)
No	51 (75%)	51 (85%)
X-ray radiation exposure		
Yes	49 (72%)	38 (63.3%)
Never	19 (28%)	22 (36.7%)

n = no of subjects, SD = standard deviation.

3.2. XRCC1 genotyping

Whole genomic DNA from 128 subjects was subjected to PCR amplification as per the protocol given in methods section. The PCR amplification of the desired target gene generated 491 bp product (Fig. 1) which was then subjected to restriction digestion, using Msp1 restriction enzyme. The product was then resolved on 3% agarose gel. The wild type C (Arg) allele for codon 194 was determined by the presence of a band at 292 bp, while the mutant T (Trp) allele was determined by the presence of a band at 313 bp (indicative of the absence of the MspI cutting site). In addition to these bands, a 174 bp band, resulting from an additional invariant cutting site for MspI in the 491 bp amplified fragment (codon 194) is always present and serves as internal control for complete MspI digestion. For homozygous wild type C/C (Arg/Arg), two bands 292 bp and 174 bp were identified, while as for heterozygous variant allele C/T (Arg/Trp), three bands 313 bp, 292 bp and 174 bp were identified. Similarly for homozygous mutant T/T (Trp/Trp), two bands 313 bp and 174 bp were identified. The digestion result of this SNP is shown in Fig. 2. The three genotypes, C/C, C/T and T/T are represented by the frequency of 52.99%, 29.4% and 17.6% in cases where as in controls these are represented by the frequency of 73.33%, 18.3% and 8.4%, respectively (Table 3). When the allelic frequencies were compared, wild type Arginine (C allele) was present in 67.7% of cases where as the mutant Tryptophan (T) allele was present in 32.3% of cases as compared to the 82.5% of Arginine and 17.5% of Tryptophan in controls (Table 3). The tryptophan allele was significantly associated with the risk of skin cancer in cases as compared to controls.

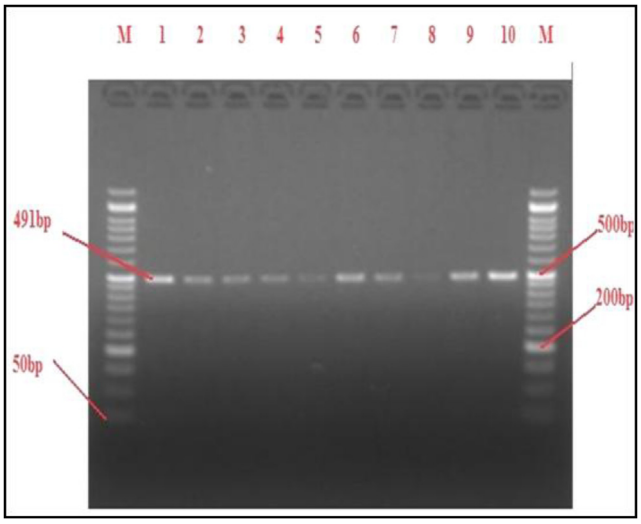

Fig. 1. Representative gel picture showing XRCC1 exon 6 Amplicon on 2% agarose gel. Lane M contains 50 bp DNA ladder. Lane 1–10 represent 491 bp amplicon of exon 6.

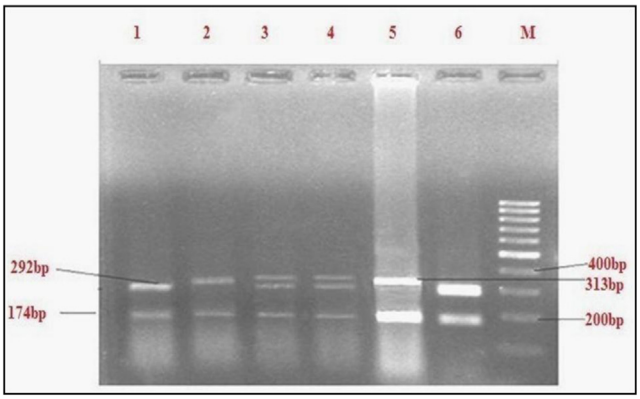

Fig. 2. Representative gel picture showing RFLP analysis of PCR product on 3% agarose gel. Lane M is the 100 bp DNA molecular weight marker. Lane no. 1 and 6 shows C/C wild genotype (292 bp and 174 bp). Lane no. 2 and 5 denotes T/T homozygous mutants (313 bp and 174 bp). Lane no. 3 and 4 represents C/T heterozygous variant respectively (313 bp, 292 bp and 174 bp).

3.3. Comparison of XRCC1 genotypic frequency with respect to age and gender of the study subjects

When XRCC1 genotypic frequency was stratified for age, below and greater than 50 years (Tables 4 and 5), no significant association was found when compared between cases and controls. Similarly, when comparing the genotypic frequency among the males and females, again no significant association was found with the risk of developing skin cancer among cases as compared to controls (Tables 6 and 7).

4. 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 major role in an individual's genetic susceptibility to cancer [20]. 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 [21]. The BER pathway has a primary role in the repair of oxidative base lesions such as 8-hydroxyguanine, formamidopyrimidines, and 5-hydroxyuracil [22] produced by methylation, oxidation or reduction by ionizing radiation or oxidative damage [23]. BER pathway serves as an important gladiator against DNA damage, which could lead to cancer, resulting from many factors, including altered metabolism, reactive oxygen species, and methylating and deaminating agents [24]. One such candidate gene involved in the base excision repair pathway is the X-ray repair cross-complementing group1 gene or *XRCC1* gene. 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 [16]. 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 codon 194 (Arg/Trp), 280

Table 3
Genotypic and allelic frequencies of *XRCC1* gene codon 194 among cases and controls and their association with risk of skin cancer.

Gene	Variants	Cases n = 68	Controls n = 60	χ^2	OR (95% CI)	*p* value
XRCC1 (codon 194) C to T	C/C (Arg/Arg)	36 (52.94%)	44 (73.3%)		1	Referent
	C/T (Arg/Trp)	20 (29.4%)	11 (18.3%)	3.4	0.45 (0.19–1.0)	0.09
	T/T (Trp/Trp)	12 (17.6%)	5 (8.4%)	3.67	0.34 (0.10–1.05)	0.06
	C	92 (67.7%)	99 (82.5%)		1	Referent
	T	44 (32.3%)	21(17.5%)	8.18	1.94 (1.22–3.0)	**0.004**
	C/T + T/T	32 (47%)	16 (26.7%)	5.66	0.4 (0.19–0.86)	**0.02**

n = no. of subjects. OR (odds ratio) calculated at 95% Confidence Interval (CI). *p*-value (two –sided) Pearson χ^2 chi square test. $p < 0.05$ is considered to be significant.

Table 4
Genotypic frequencies of *XRCC1* gene codon 194 among cases and controls stratified for below 50 years age.

Gene	Variants	Cases (n = 27)	Controls (n = 25)	χ^2	OR (95% CI)	*p* value
XRCC1 (codon 194) C to T	C/C	13 (48.2%)	16 (64%)		1	Referent
	C/T	9 (33.3%)	7 (28%)	0.54	0.63 (0.18–2.16)	0.54
	T/T	5 (18.5%)	2 (8%)		0.32 (0.05–1.95)	0.40

n = no. of subjects. OR (odds ratio) calculated at 95% Confidence Interval (CI). *p*-value (two-sided) Pearson χ^2 chi square test. $p < 0.05$ is considered to be significant.

Table 5
Genotypic frequencies of *XRCC1* gene codon 194 among cases and controls stratified for above 50 years age.

Gene	Variants	Cases (n = 41)	Controls (n = 35)	χ^2	OR (95% CI)	*p* value
XRCC1 (codon 194) C to T	C/C	23 (56.1%)	28 (80%)		1	Referent
	C/T	11 (26.8%)	4 (11.4%)	3.7	0.29 (0.08–1.06)	0.07
	T/T	7 (17.1%)	3 (8.6%)		0.35 (0.08–1.51)	0.18

n = no. of subjects. OR (odds ratio) calculated at 95% Confidence Interval (CI). *p*-value (two-sided) Pearson χ^2 chi square test. $p < 0.05$ is considered to be significant.

Table 6
Genotypic and allelic frequencies of XRCC1 gene among cases and controls stratified for males.

Gene	Variants	Cases (n = 40)	Controls (n = 37)	χ^2	OR (95% CI)	*p* value
XRCC1 (codon 194) C to T	C/C	22 (55%)	28 (75.7%)		1	Referent
	C/T	11 (27.5%)	6 (16.2%)	2.18	0.42 (0.13–1.34)	0.16
	T/T	7 (17.5%)	3 (8.1%)		0.33 (0.07–1.45)	0.17

n = no. of subjects. OR (odds ratio) calculated at 95% Confidence Interval (CI). *p*-value (two-sided) Pearsons χ^2 chi square test. $p < 0.05$ is considered to be significant.

Table 7
Genotypic and allelic frequencies of XRCC1 gene among cases and controls stratified for females.

Gene	Variants	Cases (n = 28)	Controls (n = 23)	χ^2	OR (95% CI)	P value
XRCC1 (codon 194) C to T	C/C	14 (50%)	16 (69.6%)		1	Referent
	C/T	9 (32.2%)	5 (21.7%)	1.19	0.48 (0.13–1.79)	0.34
	T/T	5 (17.8%)	2 (8.7%)		0.35 (0.07–2.09)	0.40

n = no. of subjects. OR (odds ratio) calculated at 95% Confidence Interval (CI). *p*-value (two-sided) Pearsons χ^2 chi square test. $p < 0.05$ is considered to be significant.

(Arg/His) and 399 (Arg/Gln) [16,25]. These non-conservative amino acid changes may alter *XRCC1* function and may have an impact on individual susceptibility to the development of cancers [26] .There are previous reviews and *meta*-analyses that have been discussed the association between *XRCC1* polymorphisms and the risk of developing cancer [27,28], but not skin cancer specifically. Even though, several epidemiological studies have explored the relationship between *XRCC1* polymorphisms and the development of melanoma, basal cell carcinoma, and squamous cell carcinoma, these studies have reached inconsistent conclusions on whether any *XRCC1* genetic variant could serve as a biomarker for skin cancer, with some studies showing an association [29,30] and some studies failing to show any association [31,32]. There is another study which reports that the Arg194Trp (C to T base change) variant increases the risk of basal cell carcinoma at sun-exposed sites in a Japanese population [33].

In our case-control study, the overall association between the *XRCC1* Arg194Trp polymorphism and the skin cancer was found to be insignificant (OR = 0.34, 95% CI = 0.10–1.05, $p = 0.06$) (Table 5). On combining the homozygous and heterozygous variants of each codon, the variants seemed to be at a relatively higher risk of developing skin cancer, and it was found statistically significant (OR = 0.4, 95% CI = 0.19–0.86, $p = 0.02$). We also assessed the individual allelic frequencies among cases and controls, the T (Trp) allele of codon194 showed a remarkably high frequency in cases (67.7% vs. 32.3%) in comparison with controls (OR = 1.94, 95% CI = 1.22–3.0, $p = 0.004$), this also showed a statistically significant result. In this population-based case control study, we also observed that most of the cases belong to the age group of over 50 years. Similarly while comparing gender we observed that males are more affected than females. However, while assessing the relationship between the genders across the genotypes of *XRCC1* Arg194Trp polymorphism, no statistically significant association was observed. Moreover we also observed insignificant association of Arg194Trp polymorphic variants across various age groups of the study subjects. 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 [17,18,34]. 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. In addition, the potential gene-gene and gene-environment interactions may also play vital roles in the pathogenesis.

5. Conclusion

In conclusion, this case-control study in Kashmiri subjects shows that a C to T variation (Arg to Trp) of DNA repair gene *XRCC1* is not associated with the risk of developing skin cancer, suggesting that the variant genotype of *XRCC1* at codon 194 may not play a major role in the etiology of skin cancer. However, statistical analysis of the combined homozygous and heterozygous variants of each codon showed a relatively higher risk of developing skin cancer and the individual 194Trp allele also showed a borderline significance. This discrepancy can be attributed to relatively small sample size analyzed in the study. To the best of our knowledge, this is the first report on this *XRCC1* Arg194Trp polymorphism in a Kashmiri population. This association warrants further study in larger population.

Conflict of interest

Authors declare no conflict of interest.

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