

## ORIGINAL ARTICLE

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# Frequency of XRCC1 Exon 9 G>A gene polymorphism in Saudi Arabian population: A comparative study with worldwide ethnic groups

Shafiu Haque

Research and Scientific Studies Unit, College of Nursing & Applied Health Sciences, Jazan University, Jazan-45142, Saudi Arabia

### Summary

**Purpose:** The human genome encompasses around three billion base genes. They are continuously being exposed and vulnerable to different endogenous and environmental mutagens that affect its integrity. However, the identification of the genetic polymorphisms responsible for the compromised DNA repair capacity (DRC) can help in cancer prevention. The main aim of the current study was to evaluate the frequency distribution of single nucleotide polymorphism (SNP) Arg280His Exon 9 (C>G) (rs25489) of XRCC1 gene in Saudi Arabian population and its comparison with the worldwide ethnic groups.

**Methods:** PUBMED (Medline) online web-database was searched for the required epidemiological studies of different ethnic groups.

**Results:** The allelic frequency distribution in wild type of

XRCC1 Exon 9 (G>A) was found to be 26.5% (A). Significant frequency distributions were observed in Norway ( $p < 0.001$ ), Taiwan ( $p < 0.001$ ), USA ( $p < 0.001$ ), China ( $p < 0.009$ ), Iran ( $p < 0.001$ ), North Africa ( $p < 0.001$ ), Spain ( $p < 0.001$ ) and North India ( $p < 0.001$ ) as compared to the Saudi Arabian population.

**Conclusions:** This study concludes that the frequency of the mentioned DNA repair gene demonstrates a unique pattern in Saudi Arabia population, which could be attributed to ethnicity variation. The current finding can help in screening of high risk and vulnerable individuals exposed to environmental carcinogens and cancer predisposition in different ethnicities.

**Key words:** cancer, DNA repair genes, ethnicity, genetic variations, single nucleotide polymorphism, XRCC1

### Introduction

Genetic variation in human genome is a reliable and promising source for exploring the underlying cause of cancer, which is a complex disease caused by genetic as well as environmental factors. The interaction of the genes with the environment can be seen in numerous ways like the risk effects based on an individual's genotype or as differential gene risk effects based on exposure [1]. Human genome constantly gets damaged by exogenous stresses like ionizing radiation (IR), ul-

traviolet (UV) light and chemical compounds, or from endogenous agents such as reactive oxygen species (ROS) etc [2]. This unrepaired damage if left in the DNA often results in transcription or replication defects, mutations, genomic instability and ultimately lead to uncontrolled cell growth and cancer. The unbelievable and sophisticated DNA repair mechanisms evolved in mammalian cells remove these errors and help in maintaining the genomic integrity.

Single-nucleotide polymorphisms (SNPs) are the DNA base variants present in the human population with a frequency of at least 1% [3]. The nonsynonymous coding SNPs (nsSNPs) and SNPs in regulatory regions have the highest impact on phenotype. These high frequency variants are ultimately increasing the cancer incidence. Though they play small role in reducing the function of genes and they enhance their susceptibility to cancer causing-agents. Different molecular epidemiology studies have suggested that individuals with "adverse" genotypes with reduced DNA repair capacity (DRC) are at a higher risk of developing cancer than the general population [4]. The studies done on inter individual variations in different ethnic groups hopefully can provide an opportunity to discover candidate susceptibility alleles.

The genetic association studies on cancer risk these days are mainly focusing on identifying the effects of SNPs in candidate genes with more emphasis on DNA repair genes as they play critical role in maintaining genome integrity. The DNA base excision repair (BER) pathway repairs the DNA base damage caused by oxidative reagents and alkylation and hence safeguards the cells against the toxic effects of endogenous and exogenous agents. XRCC1 gene located on chromosome 9q13.2 presents at least 32 SNPs with >5% frequency (<http://snp500cancer.nci.nih.gov/home.cfm>). It acts as scaffolding intermediate and interacts with a complex of DNA repair proteins, including poly (ADP-ribose) polymerase, DNA ligase 3, and DNA polymerase  $\beta$ , and coordinates the gap-sealing process in the short-patch BER [5]. Shen et al. [6] described three polymorphisms of XRCC1 gene, which resulted in amino acid changes at evolutionary conserved regions: C>T substitution in codon 194 of exon 6 (Arg>Trp); G>A substitution in codon 280 of exon 9 (Arg>His) and G>A substitution in codon 399 of exon 10 (Arg>Gln). Lunn et al. [7] reported that, all these SNPs could alter the XRCC1 function and impair the repair efficiency or accuracy. Healthy individuals differ in their intrinsic capacity in repairing DNA damage and this variation could be a result of variants in DNA repair genes that consequently can modify

the individual susceptibility to different kind of disease including cancer.

The present study is an attempt to investigate the frequency distribution of Exon 9, Arg280His, G27466A (rs25489) polymorphism of XRCC1 gene. The study identified the said polymorphism in normal healthy individuals from Saudi Arabia and compared it with a sufficient number of epidemiologic studies of other ethnic groups. This is the very first study on mutant allele frequency of the XRCC1 exon 9 G>A in the Saudi population in comparison with other ethnic groups.

## Methods

### Prevalence of gene variants

A systematic search was conducted on PubMed (MEDLINE) web-database using a search string "XRCC1" and "polymorphism" for the published articles. The search was restricted to human subjects with no language cap. For case-control studies, only genotype frequencies for the control population were considered. The studies reporting only allele frequencies and no genotype frequencies were not included in the current analysis. Also, the studies based on fewer than 70 persons were excluded. In case of more than one hits or article for the same study population, only the most recent publications were included.

### Statistics

Pearson's  $\chi^2$  test was performed to compare the genotype and allelic frequencies of the different populations by using SPSS (version 21) statistical software program. Court-Lab (web-based software program) was used to evaluate the Hardy-Weinberg equilibrium. P value of <0.05 was considered to be statistically significant.

## Results

The number of pertinent publications identified in PubMed were fourteen [8-21] that reported the prevalence of XRCC1 Exon 9 (C>G) polymorphism, and were used for the comparative study with the Saudi Arabian population. The distribution of XRCC1 exon 9 (G>A) genotype frequencies in the Saudi Arabian population is shown in Table 1. The genotype distributions were in agreement

**Table 1.** Observed and expected genotypic frequencies of XRCC1 Exon 9 gene polymorphism in the control group

Gene	Genotype	Observed n (%)	Expected n (%)	p value (HWE)
XRCC1 Exon 9	GG	129 (56.3)	124 (54.1)	0.25
G27466A	GA	79 (34.5)	89 (38.9)	
(rs25489)	AA	21 (9.2)	16 (7)	

HWE: Hardy-Weinberg equilibrium

**Table 2.** Genotypes and allele frequency distribution of XRCC1 Exon 9 gene polymorphism in various populations and p values in comparison to Saudi Arabian population

Gene	Country/ ethnicity	n	Age (years), mean±SD	Genotype			p value	A*	Reference [No.]
				GG	GA	AA			
XRCC1 Exon 9	Saudi Arabia	229	NM	129 (56.3)	79 (34.5)	21 (9.2)	Ref	26.5	Siraj et al. 2008 [8]
	France	312	54.5±6.7	283 (90.7)	29 (9.3)	0	0.998	4.7	Moullan et al. 2003 [9]
	Norway	377	NM	350 (92.8)	24 (6.4)	3 (0.8)	<0.001	4	Zienolddiny et al. 2006 [10]
	Taiwan	283	NM	215 (76.0)	66 (23.3)	2 (0.7)	<0.001	12.4	Cho et al. 2003 [11]
	USA	195	63.3±10.4	180 (92)	13 (7)	2 (1)	<0.001	4.4	Stern et al. 2001 [12]
	Pakistan	74	NM	44 (59.5)	27 (36.5)	3 (4)	0.175	22.3	Gulnaz et al. 2013 [13]
	China	249	48.9±4.1	153 (61.4)	58 (23.3)	38 (15.3)	0.009	27	Hu et al. 2011 [14]
	Belgium	110	61 ± 12.3	96 (87.3)	14 (12.7)	0 (0)	0.998	6.4	De Ruyck et al. 2007 [15]
	Korea	159	45-60	139 (82.7)	29 (17.3)	0 (0)	0.998	3.5	Tae et al. 2004 [16]
	Iran	193	NM	173 (89.6)	18 (9.3)	2 (1.1)	<0.001	5.7	Fard-Esfahani et al. 2011 [17]
	North Africa	506	NM	405 (80)	92 (18.2)	9 (1.8)	<0.001	10.9	Laantri et al. 2011 [18]
	Finland	302	55-63**	260 (86.1)	42 (13.9)	0 (0)	0.998	7	Misra et al. 2003 [19]
	Spain	473	45.99±17.26	426 (90.1)	44 (9.3)	3 (0.6)	<0.001	5.3	García et al. 2011 [20]
	North India	200	59.1±10.4	108 (54)	32 (16)	60 (30)	<0.001	38	Mandal et al. 2010 [21]

\*variant allele frequency, \*\*range, NM: not mentioned

with Hardy-Weinberg equilibrium (HWE). The frequency distribution of different genotypes and alleles of this SNP with different populations were compared using  $\chi^2$  test (Table 2). The variant allele frequency in the studied population was 26.5%. Significant frequency distributions were observed for Norway ( $p < 0.001$ ), Taiwan ( $p < 0.001$ ), USA ( $p < 0.001$ ), China ( $p < 0.009$ ), Iran ( $p < 0.001$ ), North Africa ( $p < 0.001$ ), Spain ( $p < 0.001$ ) and North India ( $p < 0.001$ ) as compared to the Saudi Arabian population.

## Discussion

Maintaining the integrity of the genome is the utmost parameter for the survival and propagation of human species. The continuous activity of different DNA repair pathways is essential for this maintenance. Contrary to high-penetrance alleles, the SNPs in genes involved in DNA damage repair predisposes the carriers to destabilization of the

genome and increased higher risk of developing different types of cancer. Due to profound variations in the distribution of DNA repair gene polymorphisms in different ethnic populations across the world, the data from 'normal healthy' populations are of special interest for finding out the relevance as well as the evaluation of the investigated genetic markers in susceptibility, disease manifestations, and prognosis or treatment of diseases. It is well known that ethnic background plays an important role in determining the susceptibility of different individuals to suffer from certain diseases [22].

However, it is essentially required to conduct extensive investigations about the distribution of these genetic polymorphisms in different ethnic groups. Therefore, variation in Saudi Arabian population, in contrast to other populations worldwide, signifies the impact of ethnicity. Saudi Arabian population is believed to be one of the most diverse among all ethnicities. The study of genetic variation can reveal critical determinants

in environmental exposure and cancer that could have good implications for preventive and early intervention strategies. It could lead to better survival and sustenance of different human ethnicities. The main reasons for differences in the allelic frequencies detected among these studies are considered to be ethnic variations, heterogeneity of study populations and different sample sizes.

The role of DNA repair genetic polymorphisms in cancer risk modulation has been well established. The literature on the functional significance of the majority of DNA repair genes are relatively scanty [23]. The hypothesis given by Zhang et al. [24] explained that SNPs in *XRCC1* are associated with risk of Chronic Benzene Poisoning (CBP), as benzene-induced DNA damage includes single- and double-strand breaks. They further indicated the possibility of the role of the contribution of polymorphisms at the exonic region of *XRCC1* to CBP in Chinese occupational population.

The important finding in the current study on Saudi Arabian population is about the frequency of mutant allele (A) *XRCC1* Exon 9. The frequency of the aforementioned mutant allele was found to be 26.5%. The percentage of the observed frequency 26.5% was significantly lower in Norway, Taiwan, USA, Iran, North Africa and Spain. It was found to be similar in China but higher in north India. The reported AA genotype was 0% in France, Belgium, Korea and Finland. However, earlier studies have reported the distinctive patterns of DNA repair genes as compared with other population [25,26], but not for *XRCC1* Exon 9 G>A.

The role of high penetrance cancer genes is more significant vis-à-vis increased/decreased risk associated with individual DNA repair SNPs. The public health implications of DNA repair SNPs are big. The epidemiological investigations of DNA repair gene polymorphisms are showing positively for screening different types of cancer incidence [27]. Large and combined analyses are basically preferred to minimize the likelihood of both false-positive and false-negative results. The confusing factors are required to be controlled with respect

to race and ethnicity. Because of the differences in the prevalence of DNA repair polymorphisms across different populations, it is important to keep in mind that a susceptibility factor in one population may not hold true for another population. This kind of studies may form the basis for the establishment of epidemiological and clinical databases in the years to come. The present analysis suggests that *XRCC1* exon 9 G>A gene polymorphism can be used as a biomarker for disease susceptibility as it works as a contributing factor in the development of cancer.

We acknowledge that a systematic well designed larger study with enough subjects should be carried out. The tissue-specific biochemical and biological characterization will further help evaluate potential gene-to-gene and gene-to-environment interactions on DNA repair polymorphisms and cancer risk. This type of studies may benefit from analysis of multiple genes or polymorphisms and from the consideration of relevant exposures that may influence the likelihood of cancer in the presence of reduced DRC. It is an important goal of biological and clinical research to detect genetic components like DNA repair gene polymorphisms as possible indicators of different type of diseases including carcinogenesis. The differences in the distribution of DNA repair genes between Saudi Arabian healthy population and other ethnic groups may help in building a profile that would help in assessing the disease predisposition and prevalence.

### Acknowledgements for Research Support

The author Shafiul Haque sincerely acknowledges the Deanship of Scientific Research, Jazan University, Jazan-45142, Saudi Arabia, for providing the infrastructural and software related support for this research study.

### Conflict of interests

The authors declare no conflict of interests.

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