Base Excision Repair Pathway Gene Polymorphisms in South Indian Population

Ramesh Mandarapu[1], Geethakumari Konathala[1]

ABSTRACT

Introduction: Damage of DNA takes place at a rate of 10,000 to 1,000,000 molecular lesions per cell per day due to environmental factors and normal metabolic processes. Thus, to maintain the integrity of the human genome, DNA repair systems play a crucial role. Deficiency in these repair systems may contribute to alterations in the DNA repair capacity leading to cancer. The interindividual inconstancy as well as ethnic differences in DNA repair polymorphisms, stress the attention to setup genotype profiles unique to a population. So far, no extensive study has been carried out on the overall distribution of BER SNPs in the Indian population, a conglomeration of multiple civilizational histories contributed by extensive migrations and admixtures over historical time resulting in a rich socio-cultural, linguistic and biological diversity.

Material and Methods: A total of 225 venous blood samples were collected from healthy and unrelated individuals living in Visakhapatnam city. The present work was carried out to actuate the distribution of XRCC1 194 C>T, 280 G>A and 399 G>A gene polymorphisms in North Indian population and compare with different populations globally. XRCC1 genotypes were determined using PCR-RFLP with Msp1 and Rsa1 enzymes respectively.

Results: Allelic frequencies in wild-type of XRCC1 194 C>T were 20% C(Arg), 280 G>A were 40% G(Arg) and 399 G>A were 36% G(Arg) respectively. No significant difference in the distribution of genotypes was seen based on gender. In addition, we also compared frequency distribution for these genes with other published studies in various ethnicities. Our results suggest that frequency in these DNA repair genes exhibit a distinctive pattern in South Indian population that could be attributed to ethnicity variation.

Conclusions: In conclusion, our preliminary findings showed that the XRCC1 genetic polymorphic forms are widely distributed in South Indian population. The noticed discrepancies among various studies could be because of population specific differences as well as the lesser sample size and multiple subgroup analysis. Correspondingly, the meager number of subjects observed here remains a restriction to be conclusive regarding the outcomes obtained.

Keywords: XRCC1, Polymorphism, PCR-RFLP, DNA damage, Base excision repair

INTRODUCTION

Humans are continuously exposed to mutagenic and carcinogenic amines via smoking, cooked food and other environmental sources. These chemicals can form DNA adducts in vivo and consequently prompt to DNA harm bringing about one million individual molecular lesions per cell per day.[1] To counteract the deleterious consequences of the DNA damaging agents, the integrity of the damaged DNA is typically reestablished as a repercussion of the action of certain DNA repair enzymes. The normal function of DNA repair enzymes is important for maintaining genome integrity and preventing cellular neoplastic transformation.[2] In humans, more than 150 genes are involved in DNA repair, which is crucial for maintaining genomic integrity.[3] DNA repair pathways play a crucial role in sustaining genetic integrity and it is becoming clear that errors in repair pathways are associated to various diseases. It is now considered that an individual's DNA repair capacity is genetically regulated and is the result of combinations of multiple genes that may display slight differences in their action.[4] Inactivating mutations in DNA repair genes are uncommon, bringing about embryonic lethality or serious genetic diseases, reflecting the significance of the gene products, nonetheless, polymorphisms have now been determined in a number of DNA repair genes (XRCC1, XRCC3, and XPD). A number of these polymorphisms result in amino acid substitutions and henceforth may modify the wild-type protein function and alter cellular ability to repair endogenous and exogenous DNA damage, subsidizing to disease susceptibility.

DNA repair enzyme involved in the base excision repair (BER) pathway, one of the main defense mechanisms, is generally considered to constitute the fundamental defense against small lesions such as single strand breaks (SSBs), non-bulky adducts, oxidative damage, alkylation, and methylation.

The known genetic polymorphisms of the DNA repair genes, x-ray cross-complementary group 1 (XRCC1) and group 3 (XRCC3) genes have been studied most commonly. XRCC1 is a major gene involved in DNA repair by BER. So far more than 20 BER genes identified. Human XRCC1was cloned and it is the first mammalian gene to be isolated.[5] The gene is mapped to chromosome #19q13.2-13.3. The size of the gene was identified to be 31.9kb and consists of 17 exons. It encodes a 2.2 kb transcript, which corresponds to a putative protein of 633 amino acids and hold a molecular weight of 70 KD. The XRCC1 gene encodes the XRCC1 protein has no catalytic activity of its own but it acts both as a scaffold and a modulator of the different activities involved in base excision repair. This protein provides a physical link between the incision and sealing steps of the BER process.

The XRCC1 complex has also been detailed as an alternative route of DNA double-strand break (DSB) non-homologous end rejoining, *i.e,* PARP1-dependent end-joining of DSBs.[6]

[1]Assistant Professor, Research Associate, Department of Human Genetics, Andhra University, Visakhapatnam, India

Corresponding author: Dr Ramesh Mandarapu, Department of Human Genetics, Andhra University, Visakhapatnam- 530003, Andhra Pradesh, India.

How to cite this article: Ramesh Mandarapu, Geethakumari Konathala. Base excision repair pathway gene polymorphisms in south indian population. International Journal of Contemporary Medical Research 2016;3(12):3558-3564.

The XRCC1 protein is essential for mammalian viability and XRCC1 deficient cells are genetically unstable and sensitive to DNA damaging agents. The XRCC1 gene exhibits more than 300 SNPs, among these, approximately 35 variants are located in the exons or the promoter region of the gene. A total of eight non-synonymous SNPs were reported in XRCC1, but the three most commonly identified SNPs lead to amino acid substitutions in XRCC1 at codons 194 (exon 6, C→T, Arg→Trp), 280 (exon 9, G→A, Arg→His) and 399 (exon 10, G→A, Arg→Gln).[7] This diversity occurring at the evolutionarily conserved amino acid residues are thought to bring about altered efficiency of the protein. These mutations could modify XRCC1 function, diminish repair kinetics and influence susceptibility to adverse health effects such as cancer risk, birth defects, and a reduced life span within the exposed population. Allelic variants of XRCC1 have been associated with increased risk of various cancers like head and neck, breast, lung, gastric, esophageal, glioma, skin, bladder, colorectal and colon cancers. Available literature on genotype distribution of XRCC1 and its association with different types of cancers suggest that the results vary among different populations and ethnic groups in various parts of the world.

The genetic diversity of the localized subpopulations of India is a primary prerequisite for understanding the genetic basis of several critical community-specific complex disorders. Therefore, the present endeavor was an effort to decipher the frequencies of mutant alleles related to our pathways of interest and complex diseases of maximum focus so as to prepare a repository of allele frequencies of vital genes for normal individuals from various subpopulations and subpopulation clusters of India. India, with its 40,000 endogamous populations is familiar for its unique population structure. The present study was carried out to gather the preliminary data on of XRCC1 (codon: 194, 280 and 399) genotype distributions in population of North Coastal Andhra Pradesh.

MATERIAL AND METHODS

Study Subjects

A total of 225 randomly selected unrelated healthy adult individuals from North Coastal Andhra Pradesh. Of the 225 individuals, 115 were males and 110 were females. The local [Andhra University] ethics committee has approved for collecting blood samples from the human subjects. The age of the individuals ranged from 20-60 years with mean age of 36 years. 5ml of intravenous blood samples were collected in the sterile blood collecting vials containing 15% EDTA solution as an anticoagulant. All successive voluntary subjects presenting no clinical signs to suggest any form of the disease were included in this study. Blood samples were collected from these individuals with informed written consent.

XRCC1 genotyping analysis

The genomic DNA was isolated from whole blood with slight modifications of Nasiri et al., 2005.[8] Extracted DNA was stored at -20°C until used for genotyping. The genotypes for XRCC1 codons 194, 280 and 399 were studied by PCR followed by restriction fragment length polymorphism (PCR-RFLP).[9] The polymorphisms are amplified by the following primers:

codon194:
F: 5'-GCCCCGTCCCAGGTA-3';
R: 5'-AGCCCCAAGACCCTTTCACT-3';
codon 280:
F: 5'-CCAGCTCCAACTCGTACC-3';
R: 5'-ATGAGGTGCGTGCTGTCC-3';
codon 399:
F: 5'-TTGTGCTTTCTCTGTGTCCA-3';
R: 5'-TCCTCCAGCCTTTTCTGATA-3'.

The PCR reaction mixture (10 µl) includes 1xPCR buffer (50 mM KCl; 2.5 mM MgCl2; 20 mM Tris-HCl, pH 8.4), each dNTP-200 µM, for codons 194 and 399, 0.6 µg/ml and for codon 280, 0.8 µg/ml of primers, genomic DNA-100ng and Taq polymerase-0.75U/ml (Sigma). Initial denaturation at 94ºC for 30 seconds, annealing at 64ºC, 61ºC and 64ºC for codons 194, 280 and 399 respectively for 30 seconds and synthesis at 72ºC for 30 seconds. Final elongation was performed at 72ºC for 10 min. Later, digestion of the amplified PCR products of the 3 codons was done with 5U of Msp1 (Sigma), for 12-16 h at 37ºC and resolved on 2% agarose gel. Codon 280 amplification product was treated with 5U of Rsa1 (Sigma) under similar conditions and electrophoresed on 2% agarose gel.

STATISTICAL ANALYSIS

Epi Info (v.5) software is used for data analysis. The genotype frequencies were tested for Hardy–Weinberg equilibrium using the chi-square ($\chi 2$) test by comparing the observed frequencies with the expected frequencies. $P<0.05$ was considered statistically significant.

RESULTS

The allele and genotype frequencies of XRCC1 Arg194Trp, Arg280Gln and Arg399Gln polymorphisms in the North Coastal Andhra Pradesh population are summarized in Table 1. The observed allele frequencies of SNP XRCC1 codon 194 and 399 were in Hardy–Weinberg equilibrium. Whereas, codon 280 is deviating from Hardy–Weinberg equilibrium. Gender-wise stratification of the genotype and allele frequencies of the three SNPs was done and is shown in. The allele frequencies when observed between males and females did not show any significant difference.

XRCC1 Arg194Trp C>A (rs1799782): The observed genotype and allele frequencies of XRCC1 Arg194Trp are shown in Table 1. The genotype frequencies were 20%, 47%, and 33%, for CC, CT, and TT respectively. A comparative table of polymorphisms of DNA repair gene XRCC1-194 has been summarized in (Table 2).[9,10-26] The frequency of a variant allele (T) varied from 3% among healthy individuals in Poland to 59% in North Indians. Pair wise Chi-square (χ^2) test revealed that the allele frequencies of the South Indian population studied differed significantly from all the populations compared except North Indian population.

XRCC1 Arg280His G>A (rs25489): The frequencies were 40% for GG, 38% for GA, and 22% for AA genotypes (Table 1). The G allele frequency was calculated to be 59%, and the A allele frequency was 41%. The chi-square test for homogeneity was found to be significant (p = 0.001) in South Indian population with respect to SNP XRCC1 codon 280. A comparative table of polymorphisms of DNA repair gene XRCC1-280 has been summarized in (Table 3).[10,13] The minor allele frequency varied from 32% in North Indian studies to 99% in LWK. The allele

XRCC1	Phenotype	Observed	Expected	Allele	Frequency	p - value
Codon 194	CC	45	42.58			
	CT	105	110.60	A	0.4350 ± 0.0234	
	TT	75	71.82	T	0.5650 ± 0.0234	0.4535
	Total	225	225.00			
Codon 280	GG	90	78.03			
	GA	85	108.94	G	0.5900 ± 0.0232	
	AA	50	38.03	A	0.4100 ± 0.0232	0.0010**
	Total	225	225.00			
Codon 399	GG	82	77.44			
	GA	100	109.12	G	0.5850 ± 0.0232	0.2099
	AA	43	38.44	A	0.4150 ± 0.0232	
	Total	225	225.00			

Table-1: Distribution of phenotype and allele frequencies of XRCC1 in the study population

Study Population	N	XRCC1 Genotypes of Codon 194			Allele Frequency		Pairwise χ^2 test	References
		CC (%)	CT (%)	TT (%)	Wild (C)	Variant (T)		
PS (SInd)	225	45 (20)	105 (47)	75(33)	0.43	0.57	Ref	-
NInd	150	28 (19)	68 (45)	54 (36)	0.41	0.59	0.08[a]	Kiran et al. (2010)[10]
NInd	209	174 (83)	33 (16)	02 (1)	0.91	0.09	52.10	Gangwar et al. (2008)[11]
NInd (Luknow)	250	207 (83)	41 (16)	02 (1)	0.91	0.09	52.10	Mittal et al. (2012)[12]
NInd (MP)	250	162 (65)	74 (30)	14 (6)	0.80	0.20	28.90	Nishank (2015)[13]
China	216	117 (54)	84 (39)	15 (7)	0.74	0.26	19.80	Gong et al. (2015)[14]
China	135	51 (38)	66 (49)	18 (13)	0.62	0.38	7.24	Zhang et al. (2005)[15]
Poland/Finland	298	282 (95)	16 (5)	00 (0)	0.97	0.03	69.40	Forsti et al. (2004)[16]
Spain	1022	906 (89)	115 (11)	01 (0)	0.94	0.06	60.30	Figueroa et al. (2007)[17]
France	312	270 (87)	41 (13)	01 (0)	0.93	0.07	55.60	Moullan et al. (2003)[18]
Europe	1094	951 (87)	141 (13)	02 (0)	0.93	0.07	55.60	Matullo et al. (2006)[19]
USA	182	153 (84)	27 (15)	02 (1)	0.91	0.09	52.10	Van Gils et al. (2002)[20]
Brazil	262	225 (86)	37 (14)	00 (0)	0.93	0.07	55.60	Duarte et al. (2005)[21]
Brazil	58	50 (86)	8 (14)	00 (0)	0.93	0.07	55.60	Rossit et al. (2002)[22]
North America	169	150 (89)	19 (11)	01 (0)	0.94	0.06	60.30	Lunn et al. (1999)[9]
North America	461	406 (88)	55 (12)	00 (0)	0.94	0.06	60.30	David et al. (2001)[23]
North America	300	264 (88)	36 (12)	01 (0)	0.92	0.08	54.70	Smith et al. (2003)[24]
Egypt	48	43 (90)	5 (10)	00 (0)	0.95	0.05	63.20	Abdel-Rahman et al. (2000)[25]
Taiwan	120	67 (56)	42 (35)	11 (9)	0.73	0.27	18.50	Lunn et al. (1999)[9]
China	166	70 (42)	76 (46)	18 (12)	0.65	0.35	9.70	Shen et al. (2000)[26]
CEU	120	102 (85)	14 (12)	04 (03)	0.91	0.09	52.10	HapMap
HCB	90	50 (56)	36 (40)	04 (04)	0.76	0.24	22.60	HapMap
JPT	90	46 (51)	38 (42)	06 (07)	0.72	0.28	17.21	HapMap
YRI	120	102 (85)	16 (13)	02 (02)	0.92	0.08	54.72	HapMap
CHD	88	50 (57)	34 (39)	04 (04)	0.76	0.24	49.94	HapMap

[a]Chi-square test at 5% significance level, indicating these studies are not significantly different from present study.
Abbreviations: N - number of subjects; SInd - South Indian; NInd - North Indian; MP – Madhya Pradesh; CEU - Utah residents with Northern and Western European ancestry; HCB - Han Chinese in Beijing, China; JPT - Japanese in Tokyo, Japan; YRI - Yoruba in Ibadan, Nigeria; CHD – Chinese in Metropolitan Denver, Colorado.

Table-2: Comparison of the genotype and allele frequencies of XRCC1 codon 194 polymorphism with other populations and HapMap populations

frequencies were found to be significantly different from those observed among all other populations while being similar to North Indian studies.

XRCC1 Arg399Gln G>A (rs25487): The frequencies were 36% for GG, 45% for GA, and 19% for AA genotypes (Table 1). The A allele frequency was calculated to be 42%, and the G allele frequency was 58%. A comparative table of polymorphisms of DNA repair gene XRCC1-399 has been summarized in (Table 4).[9,10-38] The minor allele frequency varied from 14% in Egypt to 91% in LWK. The allele frequencies were found to be statistically divergent from NInd (Delhi), China, Egypt, Taiwan and all populations compared from HAPMAP.

DISCUSSION

DNA-repair enzymes are required for elimination of DNA

Study Population	N	XRCC1 Genotypes of Codon 280			Allele Frequency		Pairwise χ^2 test	References
		GG (%)	GA (%)	AA (%)	Wild (G)	Variant (A)		
PS (SInd)	225	90 (40)	85 (38)	50 (22)	0.59	0.41	-	-
NInd	150	88 (59)	28 (19)	64 (22)	0.68	0.32	1.75[a]	Kiran et al. (2010)[10]
NInd (MP)	250	120 (48)	78 (31)	52 (21)	0.64	0.36	0.53[a]	Nishank (2015)[13]
CEU	226	-	20 (09)	206 (91)	0.04	0.96	70.10	HapMap
HCB	84	-	18 (21)	66 (79)	0.11	0.89	50.64	HapMap
JPT	172	02 (01)	24 (14)	146 (85)	0.08	0.92	58.38	HapMap
YRI	226	-	08 (04)	218 (96)	0.06	0.94	64.02	HapMap
ASW	98	-	06 (06)	92 (94)	0.03	0.97	73.31	HapMap
CHB	82	-	14 (17)	68 (83)	0.09	0.91	55.7	HapMap
CHD	170	-	22 (13)	148 (87)	0.06	0.94	64.02	HapMap
GIH	176	02 (01)	30 (17)	144 (82)	0.10	0.90	53.13	HapMap
LWK	180	-	02 (01)	178 (99)	0.01	0.99	80.10	HapMap
MEX	98	02 (02)	10 (10)	86 (88)	0.07	0.93	61.15	HapMap
MKK	286	-	18 (06)	268 (94)	0.03	0.97	73.31	HapMap
TSI	176	02 (01)	32 (18)	142 (81)	0.10	0.90	53.13	HapMap

[a]Chi-square test at 5% significance level, indicating these studies are not significantly different from present study.
Abbreviations: N - number of subjects; SInd - South Indian; NInd - North Indian; MP – Madhya Pradesh; CEU - Utah residents with Northern and Western European ancestry; HCB - Han Chinese in Beijing, China; JPT - Japanese in Tokyo, Japan; YRI - Yoruba in Ibadan, Nigeria; ASW – African ancestry in Southwest USA; CHB – Han Chinese in Beijing, China; CHD – Chinese in Metropolitan Denver, Colorando. GIH - Gujarat Indians in Houston, TX; LWK – Luhya in Webuye, Kenya; MEX - Mexican ancestry in Los Angeles, CA; MKK – Maasai in Kinyawa, Kerala; TSI – Toscans in Italy.

Table-3: Comparison of the genotype and allele frequencies of XRCC1 codon 280 polymorphism with other populations and HapMap populations

damage which are caused by the endogenous metabolic processes or due to environmental carcinogens. Aberrant functions of these enzymes are obvious to endorse carcinogenesis. Genes involved in the base excision repair (BER) and nucleotide excision repair (NER) pathways have been widely studied worldwide for cancer risk. XRCC1, a noteworthy part in the BER pathway, is encoded by X-ray repair cross-complementary 1 (XRCC1) and involved in single-strand break repair. It has been studied for three polymorphisms in Indians, codons 399, 194 and 280. All three polymorphisms have been found to be associated with increased cancer risk, reduced cancer risk or for no risk at all. This is due to marked differences in the distribution of DNA repair gene polymorphisms between various ethnicities. Therefore, the data from 'normal healthy' populations are of special interest for the adequate evaluation of the relevance of the investigated genetic markers in susceptibility, manifestation, prognosis or treatment of diseases. Several studies have been reported from some specific ethnics.[10,11,21,31,32] The present study was aimed to determine the frequency of genetic polymorphisms in the XRCC1 genes in a South Indian healthy population. Genotype and allele frequencies of the three different polymorphisms in DNA repair genes were reported.

In our study, the allele frequencies of XRCC1 194 C>T showed a significant deviation when compared to all other populations and HapMap. The frequencies of codon 194 were lesser for the wild (20%) and higher for the variant genotype. The same was observed in one of the studies from North Indian population.[10] Various reports from different populations throughout the world reported that frequencies of homozygous wild genotype (CC) of codon 194 lie in the range of 38% in China[15] to 95% in Poland.[16] The variant allele (T) frequency varied from 3% among healthy individuals in Poland[16] to 59% in North Indians.[10] The genotype distribution (33%) for the variant form (TT) of XRCC1 codon 194 observed in our study was much higher as compared to its total absence in Poland[16], Brazilians[21,22], Americans[23], and Egyptians.[25] However, the codon 194 heterozygous genotype (CT) (47%) in our study matched with that of the North Indian population (45%)[10] and Chinese population (49%).[15] Pair wise Chi-square (χ^2) test revealed a significant difference between healthy individuals among present study and all other comparative data from different populations,[9,11-26] except North Indian population.[10]

The XRCC1 codon 280 gene polymorphism frequencies in South Indians was comparable to the populations such as North Indians, CEU, HCB, JPT, YRI, ASW, CHB, CHD, GIH, LWK, MEX, MKK, and TSI. It showed a significant deviation from all populations except the two North Indian studies.[10,13] Surprisingly, total absence of wild form of XRCC1 codon 280 was observed in CEU, HCB, YRI, ASW, CHB, CHD, LWK, and MKK. In contrast, our data showed a relatively higher frequency (40%).

The observed frequency for codon 399 variant allele (T) in present work (42%) was found to be comparable to that reported in the above-mentioned studies. The variant allele frequency varied from 14% among Egyptians[25] to 56% in Northern part of India (Delhi).[29] A study from the India (Delhi)[29] with 100 healthy volunteers found the minor allele frequency to be 56%, higher than the present study population (42%). Whereas, a recent study from North-East India,[28] reported the variant allele frequency to be 32%, lower than the present study population.

Study Population	N	XRCC1 Genotypes of Codon 399			Allele Frequency		Pairwise χ^2 test	References
		GG (%)	GA (%)	AA (%)	Wild (G)	Variant (A)		
PS (SInd)	225	82 (37)	100(44)	43(19)	0.58	0.42	-	-
NInd	150	48 (32)	74 (49)	28 (19)	0.56	0.44	0.08[a]	Kiran et al. (2010)[10]
NInd	209	81 (39)	90 (43)	38 (18)	0.60	0.40	0.08[a]	Gangwar et al. (2008)[11]
NInd (Lucknow)	250	102 (40)	109 (44)	39 (16)	0.63	0.37	0.52[a]	Mittal et al. (2012)[12]
NInd (MP)	250	105 (42)	113 (45)	32 (13)	0.65	0.35	1.04[a]	Nishank (2015)[13]
NInd (Kashmir)	150	75 (50)	30 (20)	45 (30)	0.60	0.40	0.08[a]	Sameer et al. (2013)[27]
North-East Ind	120	56 (47)	52 (43)	12 (10)	0.68	0.32	2.15[a]	Seram Anil and Sankar (2016)[28]
NInd (Delhi)	100	12 (12)	65 (65)	23 (23)	0.44	0.56	3.92	Uppal et al. (2014)[29]
SInd (TN)	263	62 (23)	128 (49)	73 (28)	0.48	0.52	2.01[a]	Sujitha et al. (2016)[30]
SInd	255	91 (36)	120 (47)	44 (17)	0.59	0.41	0.02[a]	Vettriselvi et al. (2007)[31]
SInd	128	60 (47)	49 (38)	19 (15)	0.66	0.34	1.36[a]	Srinivasa Rao et al. (2014)[32]
China	216	121 (56)	86 (40)	9 (4)	0.76	0.24	7.33	Gong et al. (2015)[14]
China	141	56 (40)	73 (52)	12 (8)	0.66	0.34	1.36[a]	Zhang et al. (2005)[15]
Poland/ Finland	298	138 (47)	129 (43)	31 (10)	0.68	0.32	2.15[a]	Forsti et al. (2004)[16]
Spain	996	433 (44)	453 (45)	110 (11)	0.66	0.34	1.36[a]	Figueroa et al. (2007)[17]
France	312	127 (41)	146 (47)	39 (12)	0.64	0.36	0.76[a]	Moullan et al. (2003)[18]
Italy	124	53 (43)	58 (47)	13 (10)	0.66	0.34	1.36[a]	Matullo et al. (2006)[19]
Europe	1094	484 (44)	482 (44)	128 (12)	0.66	0.34	1.36[a]	Matullo et al. (2006)[19]
USA	182	77 (42)	78 (43)	27 (15)	0.64	0.36	0.76[a]	Van Gils et al (2002)[20]
Brazil	262	119 (45)	107 (41)	36 (14)	0.66	0.34	1.36[a]	Duarte et al. (2005)[21]
Brazil	58	25 (43)	23 (40)	10 (17)	0.63	0.37	0.52[a]	Rossit et al. (2002)[22]
North America	169	65 (38)	83 (49)	21 (12)	0.63	0.37	0.52[a]	Lunn et al. (1999)[9]
Taiwan	120	63 (53)	51 (43)	6 (5)	0.74	0.26	5.70	Lunn et al. (1999)[9]
North America	300	120 (40)	150 (50)	30 (10)	0.65	0.35	1.04[a]	Smith et al. (2003)[24]
Egypt	50	37 (74)	9 (18)	2 (4)	0.86	0.14	19.44	Abdel-Rahman et al. (2000)[25]
China	166	94 (57)	59 (36)	13 (8)	0.74	0.26	5.70	Shen et al. (2000)[26]
Taiwan	729	384 (53)	291 (40)	54 (7)	0.73	0.27	4.98	Yeh at al. (2005)[33]
Korea	135	81 (60)	48 (36)	6 (4)	0.78	0.22	9.19	Park et al. (2002)[34]
USA Caucasians	437	179 (41)	203 (46)	55 (13)	0.64	0.36	0.76[a]	Rybicki et al. (2004)[35]
Germany Caucas	246	113 (46)	110 (45)	23 (9)	0.68	0.32	2.15[a]	Sanyal et al. (2004)[36]
USA	538	225 (42)	227 (42)	86 (16)	0.63	0.37	0.52[a]	Andrew et al. (2006)[37]
Taiwan	282	152 (54)	109 (39)	21 (7)	0.73	0.27	4.98	Cho et al. (2003)[38]
CEU	224	26 (12)	112 (50)	86 (38)	0.37	0.63	8.84	HapMap
HCB	84	06 (07)	34 (41)	44 (52)	0.27	0.73	19.66	HapMap
JPT	172	12 (07)	70 (41)	90 (52)	0.27	0.73	19.66	HapMap
YRI	226	-	50 (22)	176 (78)	0.11	0.89	48.88	HapMap
ASW	98	02 (02)	32 (33)	64 (65)	0.18	0.82	33.96	HapMap
CHB	82	04 (05)	30 (37)	48 (58)	0.23	0.77	25.42	HapMap
CHD	170	08 (05)	84 (49)	78 (46)	0.29	0.71	17.11	HapMap
GIH	176	28 (16)	88 (50)	60 (34)	0.41	0.59	5.78	HapMap
LWK	180	02 (01)	30 (17)	148 (82)	0.09	0.91	53.89	HapMap
MEX	98	08 (08)	48 (49)	42 (43)	0.33	0.67	12.60	HapMap
MKK	286	06 (02)	92 (32)	188 (66)	0.18	0.82	33.96	HapMap
TSI	176	16 (09)	94 (53)	66 (38)	0.36	0.64	9.72	HapMap

[a]Chi-square test at 5% significance level, indicating these studies are not significantly different from present study.
Abbreviations: *N* - number of subjects; SInd - South Indian; NInd - North Indian; MP – Madhya Pradesh; TN – Tamil Nadu; USA – United States of America; CEU - Utah residents with Northern and Western European ancestry; HCB - Han Chinese in Beijing, China; JPT - Japanese in Tokyo, Japan; YRI - Yoruba in Ibadan, Nigeria; ASW – African ancestry in Southwest USA; CHB – Han Chinese in Beijing, China; CHD – Chinese in Metropolitan Denver, Colorando. GIH - Gujarat Indians in Houston, TX; LWK – Luhya in Webuye, Kenya; MEX - Mexican ancestry in Los Angeles, CA; MKK – Maasai in Kinyawa, Kerala; TSI – Toscans in Italy.

Table-4: Comparison of the genotype and allele frequencies of XRCC1 codon 399 polymorphism with other populations and HapMap populations

Pair wise Chi-square (χ^2) test revealed a significant difference between healthy individuals among present study and among North India (Delhi),[29] China,[14,26] Egypt,[25] Taiwan,[9,33,37] Korea.[34] The importance of this DNA repair gene is mainly associated with several types of diseases including cancers. Various types of carcinoma were also investigated, namely esophageal cancer, prostate cancer, colorectal cancer, lung cancer, hepatocellular carcinoma and uterine leiomyoma to investigate the association between XRCC1 codon 194, 280, 399 and cancer.

CONCLUSION

India is a nation derived from various ethnic groups. It is believed to be most diverse because of different socio-cultural traditions. Hence, genetic differences are common among various groups within India, and the South Indian population represents a

genetically distinct group. The divergence in allele frequencies observed among these studies might be due to ethnic differences, heterogeneity of study populations and different sample sizes. However, the data at the population level are very scanty. A Proper understanding of the evolutionary processes involved in determining the pattern of genetic diversity, including variation influencing disease, across different populations may be important in identifying genes/ alleles that cause disease. Hence further studies are needed at the population level from different regions of the country to observe the variations in DNA repair gene which may be helpful in elucidating crucial determinants in environmental exposure and cancer, which could have future indications for preventive and early intervention strategies for various diseases.

ACKNOWLEDGEMENTS

The authors were thankful to the respondents of North Coastal Andhra Pradesh, who volunteered to be the research subjects, and support for their help in data and sample collection.

REFERENCES

1. Lodish H, Berk A, Matsudaira P, Kaiser C. A, Krieger, M, Scott M. P, Zipursky S. L and Darnell J, Molecular Biology of the Cell. 2004;963.
2. Charames GS, Bapat B. Genomic instability and cancer. Curr Mol Med. 2003;3:589-96.
3. Wood RD, Mitchell M, Lindahl T. Human DNA repair genes. Mutat. Res. 2005;577:275-283.
4. Mohrenweiser, H. and Jones, I. Variation in DNA repair is a factor in cancer susceptibility: a paradigm for the promises and perils of individual and population risk estimation. Mutation Research. 1998;400:14-23.
5. Thompson L. H, Brookman K. W, Jones N. J, Allen S. A and Carrano A. V. Molecular cloning of the human XRCC1 gene, which corrects defective DNA strand break repair and sister chromatid exchange. Mol Cell Biol. 1990;10:6160-6171.
6. Audebert M, Salles B and Calsou P. Involvement of poly (ADP-ribose) polymerase-1 and XRCC1/DNA ligase III in an alternative route for DNA double-strand breaks rejoining,‖ Journal of Biological Chemistry. 2004;279:55117–55126.
7. Shen, M., Jones, I. and Mohrenweiser, H. Non-conservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer Research. 1998;58:604-608.
8. Nasiri, H., Forouzandeh, M., Rasaee, M.J., Rahbarizadeh, F. Modified salting-out method: high-yield, high-quality genomic DNA extraction from whole blood using laundry detergent. J. Clin. Lab. Anal. 2005;19:229–232.
9. Lunn R.M, Langlois R. G, Hsieh L.L, Thompson C. L and Bell D. A. XRCC1 polymorphisms, effects on aflatoxin B1–DNA adducts and glycophorin A variant frequency. Cancer Res. 1999;59:2557–2561.
10. Kiran M, Saxena R, Kaur J. Distribution of XRCC1 genotypes in north Indian population. Indian J Med Res. 2010;131:71–75.
11. Gangwar R, Manchanda PK, Mittal RD. Implications of XRCC1, XPD and APE1 gene polymorphism in North Indian population: a comparative approach in different ethnic groups worldwide. Genetica. 2008;136:163–169.
12. Mittal Rama Devi, Raju Kumar Mandal, Ruchika Gangwar. Base excision repair pathway genes polymorphism in prostate and bladder cancer risk in North Indian population. Mechanisms of Ageing and Development. 2012;133:127–132.
13. Nishank, S. Distribution of DNA Damage Repair Gene Polymorphism hOGG1, XRCC1 and p53 among Sickle Cell Disease Patients in India. Mediterranean Journal of Hematology and Infectious Diseases. 2015;7:e2015046.
14. Gong Y, Qi M, Chen J, Fang R, Mai C, Chen, T., Tang, Y. XRCC1 Arg194Trp and Arg399Gln polymorphisms and risk of extrahepatic cholangiocarcinoma: a hospital-based case-control study in China. International Journal of Clinical and Experimental Medicine. 2015;8:19339–19345.
15. Zhang Z, Wan J, Jin X et al. Genetic polymorphisms in XRCC1, APE1, ADPRT, XRCC2, and XRCC3 and risk of chronic benzene poisoning in a Chinese occupational population. Cancer Epidemiol Biomarkers Prev. 2005;14U8O:2614–2619.
16. Forsti A, Angelini S, Festa F et al. Single nucleotide polymorphisms in breast cancer. Oncol Rep. 2004;11:917–922.
17. Figueroa JD, Malats N, Real FX et al. Genetic variation in the base excision repair pathway and bladder cancer risk. Hum Genet. 2007;121:233–242.
18. Moullan N, Cox DG, Angele S, Romestaing P, Gerard JP, Hall J. Polymorphisms in the DNA repair gene XRCC1, breast cancer risk, and response to radiotherapy. Cancer Epidemiol. Biomark. Prev. 2003;12:1168-1174.
19. Matullo G, Dunning AM, Guarrera S et al. DNA repair polymorphisms and cancer risk in non-smokers in a cohort study. Carcinogenesis. 2006;22:997–1007.
20. Van Gils CH, Bostick RM, Stern MC et al. Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the XRCC1 gene. Cancer Epidemiol Biomarkers Prev. 2002;11:1279–1284.
21. Duarte MC, Jucimara Colombo, Andréa Regina Baptista Rossit and Ana Elizabete Silva. Polymorphisms of the DNA repair genes XRCC1 and XRCC3 in a Brazilian population. Genetics and Molecular Biology. 2005;28:397-401.
22. Rossit ARB, Cabral IR, Hackel C, et al. Polymorphisms in DNA repair gene XRCC1 and susceptibility to alcoholic liver cirrhosis in older Southeastern Brazilians. Cancer Lett. 2002;180,173-182.
23. David-Beabes GL, Lunn RM, London SJ. No association between the XPD (Lys751Gln) polymorphism or the XRCC3 (Thr241Met) polymorphism and lung cancer risk. Cancer Epidemiol Biomarkers Prev. 2001;10:911–12.
24. Smith TR, Millera MS, Lohmanc K, Langec EM, Casec LD, Mohrenweiser HW and Hu JJ. Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer. Cancer Lett. 2003;190:183-190.
25. Abdel-Rahman SZ, Soliman AS, Bondy ML, et al. Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene XRCC1 are associated with increased risk of early-onset colorectal carcinoma in Egypt. Cancer Lett. 2000;159:79-86.
26. Shen H, Xu Y, Qian Y, Yu R, Qin Y, Zhou L, et al. Polymorphisms of the DNA repair gene XRCC1 and risk of gastric cancer in a Chinese population. Int J Cancer. 2000;88:601-06.
27. Sameer A. Arg399Gln polymorphism of XRCC1 gene and risk of colorectal cancer in Kashmir: a case control study. Oncol Lett. 2013;5:959–963.

28. Seram Anil Singh, Sankar Kumar Ghosh. Polymorphisms of XRCC1 and XRCC2 DNA Repair genes and Interaction with Environmental Factors Influence the Risk of Nasopharyngeal Carcinoma in Northeast India. Asian Pac J Cancer Prev. 2016;17:2429-2437.
29. Uppal V, Mehndiratta M, Mohapatra D, et al. XRCC-1 Gene Polymorphism (Arg399Gln) and Susceptibility to Development of Lung Cancer in Cohort of North Indian Population: A Pilot Study. J Clin Diagn Res. 2014;8:CC17-20.
30. Sujitha SP, Nair A, Banerjee M, Lakshmanan S, Harshavaradhan S, Gunasekaran S, et al.5-Hydroxytryptamine (serotonin) 2A receptor gene polymorphism is associated with schizophrenia. Indian J Med Res. 2014;140:736–43.
31. Vettriselvi V, Vijayalakshmi K, Solomon PFD, Venkatachalam P. XRCC1 and XPD gene polymorphisms in a South Indian population. Asian Pac J Cancer Prev. 2007;8:283–286.
32. Srinivasa Rao et al. Allele and Genotype Distributions of DNA Repair Gene Polymorphisms in South Indian Healthy Population. Biomarkers in Cancer. 2014;6:29–35.
33. Yeh CC, Sung FC, Tang R, Chang-Chieh CR, Hsieh LL. Polymorphisms of the XRCC1, XRCC3, and XPD genes, and colorectal cancer risk: a case-control study in Taiwan. BMC Cancer. 2005;28:5-1.
34. Park JY, Lee SY, Jeon HS, Bae NC, Chae SC, Joo S, Kim CH, Park JH, Kam S, Kim IS et al. Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. Cancer Epidemiol Biomarkers Prev. 2002;11:23–27.
35. Rybicki BA, Conti DV, Moreira A et al. DNA repair gene XRCC1 and XPD polymorphisms and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2004;13:23–29.
36. Sanyal S, Festa F, Sakano S et al. Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis. 2004;25:729–734.
37. Andrew AS, Nelson HH, Kelsey KT et al. Concordance of multiple analytical approaches demonstrates a complex relationship between DNA repair gene SNPs, smoking and bladder cancer susceptibility. Carcinogenesis. 2006; 27:1030–1037.
38. Cho EY, Hildesheim A, Chen CJ et al. Nasopharyngeal carcinoma and genetic polymorphisms of DNA repair enzymes XRCC1 and hOGG1. Cancer Epidemiol Biomarkers Prev. 2003;12:1100–1104.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 24-11-2016; **Published online**: 31-12-2016