RESEARCH ARTICLE

DNA Repair Gene Polymorphisms at XRCC1, XRCC3, XPD, and OGG1 Loci in the Hyderabad Population of India

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Abstract

Background: DNA repair is one of the crucial defense mechanism against mutagenic exposure. Inherited SNPs of DNA repair genes may contribute to variation in DNA repair capacity and susceptibility to cancer. Due to the presence of these variants, inter-individual and ethnic differences in DNA repair capacity have been established in various populations. India harbors enormous genetic and cultural diversity. Materials and Methods: In the present study we aimed to determine the genotypes and allele frequencies of XRCC1 Arg399Gln (rs25487), XRCC3 Thr241Met (rs861539), XPD Lys751Gln (rs13181), and OGG1 Ser326Cys (rs1052133) gene polymorphisms in 186 healthy individuals residing in the Hyderabad region of India and to compare them with HapMap and other populations. Results and Conclusions: The genotype and allele frequency distribution at the four DNA repair gene loci among Hyderabad population of India revealed a characteristic pattern. Comparison of these gene polymorphisms with other populations revealed a distinctiveness of Hyderabad population from the Deccan region of India. To the best of our knowledge, this is the first report of such DNA repair gene polymorphisms in the Deccan Indian population.

Keywords: DNA repair - genotyping - XRCC3 - XRCC1 - XPD - OGG1 - Deccan, India

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Introduction

Genetic variation plays a critical role in most diseases, however gene-environment interactions may also be important in various ways, either by risk due to an individual's or population genotype, or differential gene risk based on exposure (Gangwar et al., 2002; Iannuzzi et al., 2002). Exposure of cells to physical and chemical agents, including ionizing radiation and other toxic chemicals, results in DNA damage, potentially causing loss of genetic integrity and elevated cancer risk. The integrity of the damaged DNA is typically restored by the action of certain DNA repair enzymes (Charames and Bapat, 2003; Vettriselvi et al., 2007). Hence, the integrity, preservation and stability of the human genome depends on the DNA repair mechanism which is essential to cellular and physiological processes. Any harmful mutations in the DNA repair mechanism genes can lead to genomic instability eventually causing cancer and ageing. Genetic polymorphisms in DNA repair genes may influence inter-individual variation in DNA repair capacity by altering the functional properties of DNA repair enzymes and thus modulate susceptibility to cancer (Lunn et al., 1999).

X-ray repair cross-complementing group 1 (XRCC1, 19q13.2) gene synthesize a protein implicated in single-strand breaks (SSB) repair including base excision repair (BER) of affected bases as a result of endogenous and exogenous oxidants (Skjelbred et al., 2006). It interacts with human polynucleotide kinase enzyme as well as with DNA polymerase-b, poly (ADP-ribose) polymerase and DNA ligase IIIα (Pramanik et al., 2011). Several mutations in XRCC1 have been reported to disrupt the protein function by altering binding sites or catalytic domain of the protein (Caldecott, 2003). The Arg399Gln polymorphism alters Arginine to Glutamine substitution at codon 399 of exon 10 (C>T, rs25487) and is located in the conserved residue of the poly (ADP-ribose) polymerase-binding domain of XRCC1 (Pramanik et al., 2011). The association between the XRCC1 and various types of cancers such as lung cancer (Ratnasinghe et al., 2001), breast cancer (Moullan et al., 2003) and head and neck cancer (Sturgis et al., 1999) has previously been studied.

X-ray repair cross-complementing group 3 (XRCC3) gene, a member of the RecA/Rad51-related protein complex responsible for the homologous recombinational repair (HRR) of double-strand DNA and is necessary for the stability of the genome (Cui et al., 1999; Brenneman et al., 2000; Griffin et al., 2000). The C>T transition is the most often occurring polymorphism in the XRCC3 gene at codon 241 causing an amino acid change (Thr

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to Met) (Pramanik et al., 2011). The carriers of the Met allele showed a relatively high DNA adducts level in lymphocytes, which could be associated with reduced DNA repair capacity (Matullo et al., 2001a; 2001b). An association between XRCC3 241Met allele and cancer has been observed in various studies including investigations of bladder cancer (Matullo et al., 2001a), breast cancer (Kuschel et al., 2002), and colorectal (Krupa et al., 2011), lung cancer (Improta et al., 2008) and astrocytomas and glioblastomas (Custodio et al., 2012).

Xeroderma pigmentosum complementation group D (XPD) gene encodes an ATP-dependent DNA helicase located at 1.8 Mb downstream of XRCC1 on chromosome 19q13.3. XPD is a vital component of the Transcription Factor IIH that is involved in nucleotide excision repair (NER) of UV induced damage and removal of bulky DNA adducts (Chen and Kadlubar, 2003). The Lys751Gln (T>G, rs13181) polymorphism at codon 751 of exon 23 causes a non-synonymous substitution that changes Lysine to Glutamine. The Lys751Gln polymorphism in XPD gene is critical and alters the conformation of the respective amino acid in the important domain of the protein that plays a role in protein interaction (Benhamou and Sarasin, 2002). The 751Gln variant has been implicated in several case-control association studies i.e. esophageal cancer (Yuan et al., 2011), lung cancer (Zhan et al., 2010), breast cancer (Samson et al., 2011), and melanoma patients (Kertat et al., 2008).

The human 8-oxoguanine glycosylase 1 (hOGG1) synthesized by the 8-oxoguanine DNA glycosylase (OGG1) gene is located at chromosome 3p26.2, a region that often shows loss of heterozygosity in several human cancers (Shinmura and Yokota, 2001; Kohno et al., 2006). The OGG1 is involved in the repairs of 8-oxoguanine (8-oxoG), a highly mutagenic guanine base lesion formed due to the action of reactive oxygen species (ROS) on the DNA. The OGG1 gene belongs to the base excision repair pathway and has a DNA glycosylase/AP-lyase activity, catalyzing the excision of 8-oxoG. Several polymorphisms in the OGG1 gene have previously been reported, however most of the studies have focused on the Ser326Cys polymorphism causing a substitution of Serine to Cysteine at codon 326 of exon 7 (C>G, rs1052133). The OGG1 326Cys allele is associated with a higher risk of developing many different types of cancers including lung (Kohno et al., 2006), and orolaryngeal cancers (Elahi et al., 2002).

The present study was performed to investigate the allele and genotype frequencies of four non-synonymous SNPs, rs25487 (XRCC1), rs861539 (XRCC3), rs13181 (XPD), and rs1052133 (OGG1) in the Hyderabad region population of India and to compare them with HapMap and other populations.

Materials and Methods

Study population

The study involved 186 subjects (age range 25-70 years) from Hyderabad region of India. Unrelated healthy subjects from the general population belonging to the same geographical region with similar ethnicity were used for this study. Hospital ethical committee approved the study and informed consent was obtained from the participating volunteers.

DNA extraction

Approximately 3 ml of blood samples were collected in sterile tubes containing ethylenediaminetetracetic acid (EDTA) from all subjects enrolled in the study. Genomic DNA was isolated from blood samples using QIAmp kit (QIAmp DNA blood Mini Kit, Qiagen, Valencia, CA) following the manufacturer's instructions. After extraction and purification, the DNA was quantitated on a NanoDrop 8000, to determine the concentration and its purity was examined using standard A260/A280 and A260/A230 ratios (NanoDrop 8000) (Sambrook et al., 1989).

Genotyping

SNPs in four DNA repair genes XRCC1 (Arg399Gln, rs25487), XRCC3 (Thr241Met, rs861539), XPD (Lys751Gln, rs13181), and OGG1 (Ser326Cys, rs1052133) were genotyped using TaqMan allelic discrimination assay (Livak, 1999). For each sample, 5 ng DNA per reaction was used with 5.6 μL of 2X Universal Master Mix and 200 nM primers (Applied Biosystems, Foster City, CA, USA). All genotypes were determined by endpoint reading on an ABI 7500 (Applied Biosystems, Foster City, CA, USA). Primers and probe mix were purchased directly through the assays-on-demand service of Applied Biosystems. Five percent of the samples were randomly selected and subjected to repeat analysis as a quality control measure for verification of genotyping procedures.

Statistical analysis

Chi square (χ^2) test was used to compare the observed genotype distributions of the XRCC1, XRCC3, XPD and OGG1 polymorphisms with their expected values. The allele and genotype frequencies of polymorphisms in the Hyderabad region population of India (HYB) were compared with some of the populations of the HapMap database (www.hapmap.org) for example, Utah residents with Northern and Western European ancestry from the CEPH collection (CEU), Gujarati Indians in Houston, Texas (GIH), Han Chinese in Beijing, China (CHB), Yoruba in Ibadan, Nigeria (YRI), Maasai in Kinyawa, Kenya (MKK), and Japanese in Tokyo, Japan (JPT) and some other populations selected from literature e.g., Eastern Saudi population in Saudi Arabia (Jeddah) (Harithy and Ghazzawi et al., 2011), Eastern Indian population in India (EInd) (eastern Indian ethnicity from Calcutta, West Bengal state) (Majumder et al., 2005; 2007), South Indian population in India (SInd) (South Indian ethnicity from Chennai, Tamil Nadu state) (Vettriselvi et al., 2007; Wang et al., 2010), North Indian population in India (NInd) (North Indian ethnicity from Lucknow, Uttar Pradesh state) (Gangwar et al., 2009; Srivastava et al., 2009) and Central Indian population in India (Central Indian ethnicity from Vidarbha region, Maharashtra state). Pair-wise Chi square (χ^2) tests were performed between Hyderabad region population of India (HYB) and other populations using the allele frequencies in a 2×2 contingency table to study if the central region

of Deccan region population (HYB) shows significant differences compared to other populations.

Results

The allele and genotype frequencies of rs25487 (Arg399Gln, XRCC1), rs861539 (Thr241Met, XRCC3 gene), rs13181 (Lys751Gln, XPD gene), and rs1052133 (Ser326Cys, OGG1gene) polymorphisms in Hyderabad population from Deccan region of India are summarized in Table 1. The observed genotype frequencies did not show any significant departure from Hardy-Weinberg expectations for all four polymorphic loci that were observed in this study.

Allele and genotype frequencies of XRCC1 Arginine399Glutamine (C>T)

The observed Arg/Arg, Arg/Gln and Gln/Gln genotype frequencies were 0.371, 0.527 and 0.102, respectively (Table 2). The Arg (wild-type) and Gln (variant) allele frequencies were 0.634 and 0.366, respectively. All the HapMap populations including CEU, CHB, MKK, JPT, YRI,GIH and JPT including other EInd, SInd, NInd, Jeddha populations were selected for this study. The variant allele frequency varied from 0.11 among YRI to 0.602 among NInd. Except CBH and GIH all the other populations were found to be not significantly different from HYB when pair-wise Chi-square (χ^2) test was used for analysis (Table 2).

Allele and genotype frequencies of XRCC3 Threonine241Methionine (G>A)

The observed Thr/Thr, Thr/Met and Met/Met genotype frequencies were 0.557, 0.346 and 0.097, respectively (Table 3),where as the Thr (wild-type) and Met (variant) allele frequencies were 0.73 and 0.27, respectively. The variant allele frequency varied from 0.07 (CHB) to 0.43 (CEU). The HYB and CEU, CHB, JPT,YRI, SInd, and EInd, populations differed significantly based on pair-wise Chi-square (χ^2) test (Table 3).

Allele and genotype frequencies of XPD Lysine751Glutamine (T>G)

The observed Lys/Lys, Lys/Gln and Gln/Gln genotype frequencies were 0.527, 0.387 and 0.086, respectively (Table 4). The Lys (wild-type) allele frequency was 0.72, whereas the Gln (variant) allele frequency was 0.28. The variant allele frequency varied from 0.076 in JPT to 0.642 in GIH. The CHB, JPT, YRI, MKK, and GIH populations differed significantly with HYB population based on Pair-wise Chi-square (χ^2) (Table 4).

Table 1. Distribution of Genotypes and Allele Frequencies on XRCC1, XRCC3, XPD and OGG1 Loci among Deccan Region Population

Genotype (SNP ID)	Total subjects	Allele frequency		HWE P-value
Arg/Gln		Wild type	Variant	0.0639
(rs25487)		(Arg)	(Gln)	
Arg/Arg	69	0.63	0.37	
Arg/ Gln	98			
Gln/ Gln	19			
Thr241Met		Wild type	Variant	
(rs861539)		(Thr)	(Met)	0.0944
Thr/ Thr	103	0.72	0.28	
Thr/ Met	64			
Met/ Met	18			
Lys751Gln		Wild type	Variant	
(rs13181)		(Lys)	(Gln)	
Lys/ Lys	98	0.72	0.38	0.5945
Lys/ Gln	72			
Gln/Gln	16			
Ser326Cys		Wild type	Variant	
(rs1052133)		(Ser)	(Cys)	
Ser/ Ser	70	0.63	0.37	0.3958
Ser/ Cys	90			
Cys/ Cys	22			

Table 2. Allele and Genotype Frequencies of XRCC1 Arg399Gln in Hyderabad Deccan and Other Populations

Population	Genotype Freq (No)			Allele frequency		Pairwise χ^2 test value between
	Arg/ Arg	Arg/ Gln	Gln/ Gln	Wild type	Variant Gln	HYB & other
	Freq (No)	Freq (No)	Freq (No)	Arg		populations
CEU (n=224)	0.38 (86)	0.5 (112)	0.110 (26)	0.63	0.37	0.0001[a]
CHB (n=83)	0.55 (48)	0.38 (30)	0.060 (4)	0.75	0.25	4.65
JPT (n=172)	0.52 (90)	0.4 (70)	0.070 (12)	0.73	0.27	3.49[a]
YRI (n=226)	0.78 (176)	0.22 (50)	0	0.89	0.11	36.51
MKK (n=286)	0.32 (92)	0.66 (188)	0.021 (6)	0.82	0.18	0.12[a]
Jed (n=65)	0.523 (34)	0.38 (25)	0.090 (6)	0.72	0.28	1.39[a]
GIH (n=176)	0.159 (28)	0.500 (88)	0.341 (60)	0.409	0.591	18.4
SInd (n=255)	0.357 (91)	0.471 (120)	0.172 (44)	0.592	0.408	0.80[a]
NInd (n=209)	0.387 (81)	0.431 (90)	0.182 (38)	0.182	0.602	0.41[a]
EInd (n=385)	0.44 (170)	0.465 (179)	0.093 (36)	0.67	0.33	0.87[a]
MAH (n=215)	0.386 (83)	0.507 (109)	0.107 (23)	0.64	0.36	0.01[a]
HYB (n=186)	0.371 (69)	0.527 (98)	0.102 (19)	0.634	0.366	ref

Table 3. Allele and Genotype Frequencies of XRCC3 Thr241Met in Hyderabad Deccan and Other Populations

Population	Genotype Freq (No)			Allele frequency		Pairwise χ^2 test value between
	Thr/ Thr	Thr/ Met	Met/ Met	Wild type	Variant Met	HYB & other
	Freq (No)	Freq (No)	Freq (No)	Thr		populations
CEU (n=226)	0.31 (70)	0.52 (118)	0.17 (38)	0.57	0.43	11.18
CHB (n=82)	0.85 (70)	0.15 (12)	0	0.93	0.07	13.3
JPT (n=172)	0.79 (136)	0.20 (34)	0.01 (2)	0.89	0.11	14.59
YRI (n=224)	0.67 (150)	0.321 (72)	0.009 (2)	0.83	0.17	6.07
MKK (n=286)	0.64 (182)	0.31 (90)	0.05 (14)	0.79	0.21	2.58[a]
GIH (n=176)	0.602 (106)	0.330 (58)	0.068 (12)	0.767	0.233	0.66[a]
SInd (n=291)	0.677(197)	0.292 (85)	0.031 (9)	823	0.177	5.86
NInd (n=250)	0.636 (159)	0.32 (80)	0.044(11)	0.796	0.204	2.61[a]
EInd (n=348)	0.63 (220)	0.34 (120)	0.03 (8)	0.8	0.2	3.92
MAH (216)	0.634 (137)	0.338 (73)	0.028 (6)	0.803	0.197	3.03[a]
HYB (n=185)	0.557 (103)	0.346 (64)	0.097 (18)	0.73	0.27	

*CEU-Utah residents with Northern and Western European ancestry from the CEPH collection; CHB-Han Chinese in Beijing, China; JPT-Japanese in Tokyo, Japan; YRI: Yoruba in Ibadan, Nigeria, MKK: Maasai in Kinyawa, Kenya, Jed: Saudi population residing in Jeddah region of western Saudi Arabia (Harithy and Ghazzawi et al. 2011); GIH- Gujarati Indians in Houston, Texas; SInd-South Indian population in India (Vettriselvi et al., 2007); NInd-North Indian population in India (Gangwar et al., 2009); EInd-Eastern Indian population from Calcutta, India (Majumder et al., 2007); MAH- Maharashtrian population residing in Vidarbha region of central India; HYB- Hyderabad population residing in Deccan region of South India; [a]Chi-square test statistic value less than 3.841 at 5% significance level, so populations are not significantly different from HYB

Table 4. Allele and Genotype Frequencies of XPD Lys751Gln in Hyderabad Deccan and Other Populations

Population	Genotype Freq (No)			Allele frequency		Pairwise χ^2 test value between
	Lys/Lys	Lys/Gln	Gln /Gln	Wild type	Variant Gln	HYB & other
	Freq (No)	Freq (No)	Freq (No)	Lys		populations
CEU (n=226)	0.4 (92)	0.522 (118)	0.071 (16)	0.668	0.332	1.30[a]
CHB (n=82)	0.76 (62)	0.24 (20)	0	0.82	0.12	7.95
JPT (n=172)	0.860 (148)	0.128 (22)	0.012 (2)	0.924	0.076	59.33
YRI (n=226)	0.65 (146)	0.34 (76)	0.01 (4)	0.82	0.18	29.74
MKK (n=286)	0.67 (192)	0.29 (82)	0.04 (12)	0.81	0.19	35.18
GIH (n=176)	0.114 (20)	0.489 (86)	0.398 (70)	0.358	0.642	17.27
SInd (n=255)	0.51 (130)	0.408 (104)	0.082 (21)	0.665	0.335	1.41[a]
NInd (n=209)	0.435 (91)	0.46 (96)	0.105 (22)	0.713	0.287	0.02[a]
EInd (n=388)	0.49 (190)	0.407 (158)	0.103 (40)	0.69	0.31	0.44[a]
MAH (n=215)	0.512 (110)	0.377 (81)	0.111 (24)	0.7	0.3	0.20[a]
HYB (n=186)	0.527 (98)	0.387 (72)	0.086 (16)	0.72	0.28	--

Table 5. Allele and Genotype Frequencies of OGG1 Ser326Cys in Hyderabad Deccan and Other Populations

Population	Genotype Freq (No)			Allele frequency		Pairwise χ^2 test value between
	Ser/ Ser	Ser/ Cys	Cys/ Cys	Wild type	Variant Cys	HYB & other
	Freq (No)	Freq (No)	Freq (No)	Ser		populations
CEU (n=116)	0.621 (72)	0.310 (36)	0.069 (8)	0.776	0.224	6.84
CHB (n=90)	0.244 (22)	0.511 (46)	0.244 (22)	0.5	0.5	4.32
JPT (n=88)	0.182 (16)	0.59 (52)	0.227 (20)	0.477	0.523	5.82
YRI (n=118)	0.746 (88)	0.22 (26)	0.034 (4)	0.856	0.144	17.82
NInd (n=204)	0.55 (112)	0.146 (85)	0.034 (7)	0.757	0.243	7.18
MAH (n=218)	0.413 (90)	0.495 (108)	0.092 (20)	0.66	0.34	0.35[a]
HYB (n=182)	0.464 (70)	0.404 (90)	0.132 (22)	0.632	0.368	

*CEU-Utah residents with Northern and Western European ancestry from the CEPH collection; CHB-Han Chinese in Beijing, China; JPT-Japanese in Tokyo, Japan; YRI: Yoruba in Ibadan, Nigeria, MKK: Maasai in Kinyawa, Kenya, Jed: Saudi population residing in Jeddah region of western Saudi Arabia (Harithy and Ghazzawi et al. 2011); GIH- Gujarati Indians in Houston, Texas; SInd-South Indian population in India (Vettriselvi et al., 2007); NInd-North Indian population in India (Gangwar et al., 2009); EInd-Eastern Indian population from Calcutta, India (Majumder et al., 2007); MAH- Maharashtrian population residing in Vidarbha region of central India; HYB- Hyderabad population residing in Deccan region of South India; [a]Chi-square test statistic value less than 3.841 at 5% significance level, so populations are not significantly different from HYB

Allele and genotype frequencies of OGG1 Ser326Cys (C>G)

The observed Ser/Ser, Ser/Cys and Cys/Cys genotype frequencies were 0.464, 0.404 and 0.132, respectively (Table 5). The Serine (wild-type) and Cysteine (variant) allele frequencies were 0.632 and 0.368, respectively. The variant allele frequency differed from 0.144 (YRI) to 0.523 (JPT). There were no allele and genotype frequency data available for the MKK,GIH populations in the HapMap and SInd, EInd, among the Indian populations (Table 5). Except with MAH population, the HYB population differed significantly from all the other populations used in this study based on pair-wise Chi-square (χ^2) test (Table 5).

Discussion

The aim of this study was to investigate the polymorphisms in healthy individuals for three genes XRCC1, XRCC3, XPD and OGG1 DNA repair genes and compare their frequencies with other populations. Polymorphism in genes that are involved in carcinogen metabolism and DNA repair mechanism have been reported to be a source of inter-individual variability in human response to carcinogens. Although several studies have been carried out that deal with the heritable polymorphisms among genes responsible for carcinogen metabolism in recent years; however very few reports in relation to the DNA repair capacity and development of cancer in different populations have been published (Friedberg et al., 1995; Vettriselvi et al., 2007; Pramanik et al., 2011). Individuals generally differ widely in their capacity to repair damaged DNA as a result of external agents like exposure to sunlight and tobacco smoke as well as endogenous oxidation reactions. Hence the present study was performed to determine the genotype distribution of DNA repair genes XRCC1, XRCC3, OGG1 and XPD among the ethnic population living in Hyderabad, Deccan region of India. The is the first report that deals with the frequency distribution of DNA repair genes XRCC1, XRCC3, OGG1 and XPD in the central region population of Hyderabad region.

In the present study XRCC1 Arg399Gln genotype frequencies showed a significant deviation in the HYB compared to the CHB and GIH populations (Table 2). However, similarities were found in the HYB and among CEU, JPT, YRI, MKK, Jed, SInd, NInd, EInd and MAH populations. No significant difference was observed between HYB and other Indian populations. This could be due to the fact that the samples drawn from populations from these Indian regions comprised of individuals that were randomly selected and did not represent any particular ethnic group.

Apart from the XRCC1 locus, allele frequency and genotype distribution of the SNPs in the XRCC3, XPD and OGG1 loci varied more significantly between different populations. Interestingly SInd and EInd populations significantly differed from HYB population with XRCC3 loci. The populations CHB, JPT, YRI were significantly different from HYB for the XRCC3, XPD and OGG1 loci. Whereas HYB population differed significantly from CHB population for all the DNA repair gene loci. Contrary to this, the MAH population did not show any significant difference with the HYB population for all the loci.

Establishing the baseline frequency of the various DNA repair alleles within a population may help to find out ethnic based risk against environmental insults and susceptibility to carcinogenesis. In addition to their role in cancer risk, DNA repair polymorphisms may also influence a response to survival and/or treatment. Therefore, the polymorphisms in the genes involved in the DNA repair mechanism may play a role in pharmacogenetics by altering the repair capability as a result of cytotoxic or radiation therapy. Further studies on the phenotypic effects of these polymorphisms in random individuals of distinct ethnic origin based on life style and environmental exposures will generate a clear picture, not only of the functional effects of the various genotypes but also about the gene environment interactions.

In conclusion, our study could provide a preliminary basis for cancer risks assessment that are associated with polymorphisms among these DNA repair genes by

performing genetic epidemiological studies in the Deccan region population of India. Furthermore, our results indicate a distinct molecular profile of polymorphisms for the DNA repair genes XRCC1, XRCC3, OGG1 and XPD loci for HYB compared to other populations.

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