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Biomarkers in Cancer

Allele and Genotype Distributions of DNA Repair Gene Polymorphisms in South Indian Healthy Population

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ABSTRACT: Various DNA repair pathways protect the structural and chemical integrity of the human genome from environmental and endogenous threats. Polymorphisms of genes encoding the proteins involved in DNA repair have been found to be associated with cancer risk and chemotherapeutic response. In this study, we aim to establish the normative frequencies of DNA repair genes in South Indian healthy population and compare with HapMap populations. Genotyping was done on 128 healthy volunteers from South India, and the allele and genotype distributions were established. The minor allele frequency of Xeroderma pigmentosum group A (*XPA*) G23A, Excision repair cross-complementing 2 (*ERCC2*)/Xeroderma pigmentosum group D (*XPD*) Lys751Gln, Xeroderma pigmentosum group G (*XPG*) His46His, *XPG* Asp1104His, and X-ray repair cross-complementing group 1 (*XRCC1*) Arg399Gln polymorphisms were 49.2%, 36.3%, 48.0%, 23.0%, and 34.0% respectively. Ethnic variations were observed in the frequency distribution of these polymorphisms between the South Indians and other HapMap populations. The present work forms the groundwork for cancer association studies and biomarker identification for treatment response and prognosis.

KEYWORDS: *XPA*, *XPD*, *XPG*, *XRCC1*, DNA repair

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Introduction

The human genome is vulnerable to structural and chemical damage by various environmental and endogenous noxious stimuli. The integrity and stability of the genome are of paramount importance to its function as any alteration would result in malfunctioning of downstream pathways that could lead to disease or dysfunction. Alteration in the genome is a key step for cancer initiation and progression. Hence, it is not surprising that the human genome has more than 130 genes involved in recognizing and repairing DNA defects.[1] These genes control various DNA repair pathways involved in maintaining the genomic integrity. Polymorphisms in the genes coding for DNA repair proteins result in decreased removal of DNA damaged products, thereby, increasing the risk of developing cancer and age-related disorders.[2]

The nucleotide excision repair (NER) pathway is a complex and versatile DNA repair mechanism that rectifies various DNA defects caused by ultraviolet (UV)-induced lesions and bulky chemical adducts, and drug-induced DNA damage.[3] Various proteins are involved in the functioning of the NER pathway, and variants in the genes encoding for these proteins have been studied. Seven complementation groups (*XPA–XPG*) have been described, and they code for proteins involved in the NER pathway.[4]

The Xeroderma pigmentosum group A (*XPA*) gene codes for a protein that, along with the replication protein A (RPA) and Xeroderma pigmentosum group C (XPC), is involved in the initial sensing of the damage in the DNA strands,[5] and, hence, is called the *damage recognition factor*. A polymorphism in the *XPA*, the G23A polymorphism, is located in the 5′ untranslated region and is four nucleotides upstream of the start codon. Mutations in this region are known to cause low levels of protein expression because of the differential binding of the 40S ribosome to the promoter region.[6] The Xeroderma pigmentosum group D (*XPD*), also known as the Excision repair cross-complementing 2 (*ERCC2*), codes for a protein that forms three of the nine subunits that constitute the transcription factor IIH (TFIIH).[7] TFIIH is involved in the transcription of the DNA during the DNA repair process. Mutations in the *XPD* can diminish the activity of these proteins and result in an abnormal DNA repair process. A total of 17 single nucleotide polymorphisms (SNPs) of *XPD* have been described, of which the Lys751Gln (rs13181) results in an amino acid change and, consequently, can affect protein function.[8] The *XPG* gene codes for an endonuclease that helps in the nicking of damaged DNA fragments and plays a pivotal role in the NER pathway.[9] Two important SNPs in the *XPG* gene are the *XPG* His46His (rs1047768) and *XPG* Asp 1104His (rs17655). Mutations of the genes encoding proteins in the NER pathway have been studied and found to be associated with various cancers.

The X-ray repair cross-complementing group 1 (*XRCC1*) gene codes for a scaffolding protein that plays a role in the base excision repair (BER) pathway. DNA repair is brought about by its complex interactions with DNA polymerase-β, poly (ADP-ribose) polymerase, and DNA ligase III.[10,11] *XRCC1* is required for the efficient repair of single-strand breaks (SSBs).[12] SSBs occur in the cell because of the oxidative damage produced by the reactive oxygen species (ROS), because of the anomalous activity of certain enzymes involved in DNA replication, or during repair of DNA by other repair pathways.[13] Genetic alterations of the *XRCC1* may result in a dysfunctional protein with impaired repair capacity, thus, increasing risk of cancer in an individual. A common genetic variant of *XRCC1*, Arg-399Gln, has been implicated in various cancers.[14]

Apart from conferring increased susceptibility to cancer risk, mutations in the DNA repair pathway also alter the sensitivity to cancer chemotherapy.[15] Platinum-based chemotherapeutic agents, which includes cisplatin, carboplatin, and oxaliplatin, are commonly used as first-line chemotherapeutic agents for many cancers. The platinum compounds form DNA adducts and cause cell death. Efficient NER of the DNA damage decreases the efficiency to cause tumor cell death and might result in resistance to these compounds, whereas a deficiency in the DNA repair will increase the efficiency.[16]

India is a country with a vast population derived from various ethnic groups. Hence, genetic differences are common among various groups within India, and the South Indian population represents a genetically distinct group.[17] Such genetic differences within populations can confound genotype–phenotype association studies and are the major reasons for the conflicting results. In this study, we aim to establish the normative frequency of five SNPs of genes involved in DNA repair pathways, viz, *XPA* G23A (rs1800975), *ERCC2/XPD* Lys751Gln (rs13181), *XPG* His46His (rs1047768), *XPG* Asp1104His (rs17655), and *XRCC1* Arg399Gln (rs25487) (details of the polymorphisms are shown in Table 1). We also aim to evaluate the similarity or dissimilarity between various HapMap populations such as 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), GIH (Gujarat Indians in Houston), and MEX (Mexican ancestry in Los Angeles, CA).

Methodology

Study subjects. The study was carried out on 128 healthy individuals between 18 and 70 years of age. Unrelated individuals from the general population, residing in the Southern states of India (Tamil Nadu, Kerala, Karnataka, and Andhra Pradesh) for three consecutive generations and speaking a Dravidian language (Tamil, Malayalam, Kannada, and Telugu), were selected for the study. The study subjects comprised 73 males and 55 females, and the mean age (±SD) was 34.8 (±14.5) years. Ethical approval was obtained from the Institute Ethics Committee, JIPMER (Jawaharlal Institute of Postgraduate Medical Education and Research), Pondicherry, India. Written informed consent was obtained from all subjects participating in the study. The study was in compliance with the good clinical practice according to the principles of the Declaration of Helsinki.

Table 1. Characteristic features, rs IDs, and assay IDs of the DNA repair gene polymorphisms studied.

GENE	SNP	BASE PAIR CHANGE	GENE LOCATION	SNP LOCATION	rs ID	ASSAY ID
XPA	G23A	G>A	9q22.3	5′ UTR	rs1800975	C____482935_1_
ERCC2/XPD	Lys751Gln	A>C	19q13.3	Exon 23	rs13181	C___3145033_10
XPG	His46His	T>C	13q33.1	Exon 2	rs1047768	C___1891769_20
XPG	Asp1104His	G>C	13q33.1	Exon 15	rs17655	C____1891743_10
XRCC1	Arg399Gln	G>A	19q13.2	Exon 10	rs25487	C____622564_10

Abbreviations: SNP, single nucleotide polymorphism; 5′ UTR, untranslated region; Lys, lysine; Gln, glutamine; His, histidine; Asp, aspartate; Arg, arginine.

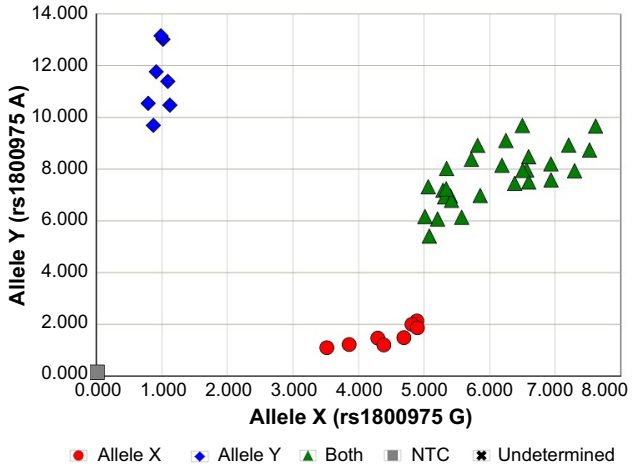

Figure 1. Allelic discrimination plot of *XPA* G23A (rs1800975) polymorphism.

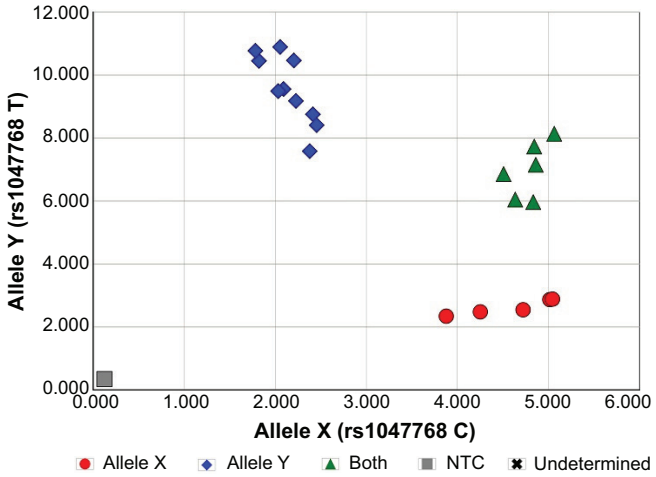

Figure 3. Allelic discrimination plot of *XPG* His46His (rs1047768) polymorphism.

DNA extraction. Approximately 5 mL of venous blood was collected from each study subject in tubes containing 100 µL of 10% ethylene diaminetetraacetic acid (EDTA). Genomic DNA was extracted using the standard phenol–chloroform extraction method.[18] The isolated DNA was stored at –20°C until genotyping.

Genotyping. Five SNPs in DNA repair genes—*XPA* G23A (rs1800975), *ERCC2/XPD* Lys751Gln (rs13181), *XPG* His46His (rs1047768), *XPG* Asp1104His (rs17655), and *XRCC1* Arg399Gln (rs25487)—were genotyped by RT-PCR (Real time polymerase chain reaction) (Applied Biosystems 7300) using TaqMan SNP genotyping assay kits (Table 1). Genomic DNA was diluted to 50 ng/µL, and 2.5 µL was used for RT-PCR. In all, 5 µL of TaqMan Universal PCR master mix and 0.25 µL of TaqMan genotyping assay were added to the diluted DNA, and deionized water was added to make up the final volume to 10 µL. The thermocycler was set at 50°C for two minutes and at 95°C for 10 minutes to activate polymerase AmpliTaq Gold. In all, 40 cycles of denaturation (92°C for 15 seconds) and annealing–extension (60°C for 1 minute) were used to amplify the DNA sequence. Allelic discrimination was done by 7300 sequence detection software (SDS), version 1.4. The allelic discrimination plots of the five SNPs are shown in Figures 1–5. For quality control, 10% of the samples were reanalyzed, and the results were found to be 100% concordant.

Statistical analysis. The genotype and allele frequencies were determined by direct gene count method. The genotype frequencies were tested for Hardy–Weinberg equilibrium using the chi-square (χ^2) test by comparing the observed frequencies with the expected frequencies. Chi-square test was also used to assess the differences in allele frequencies between

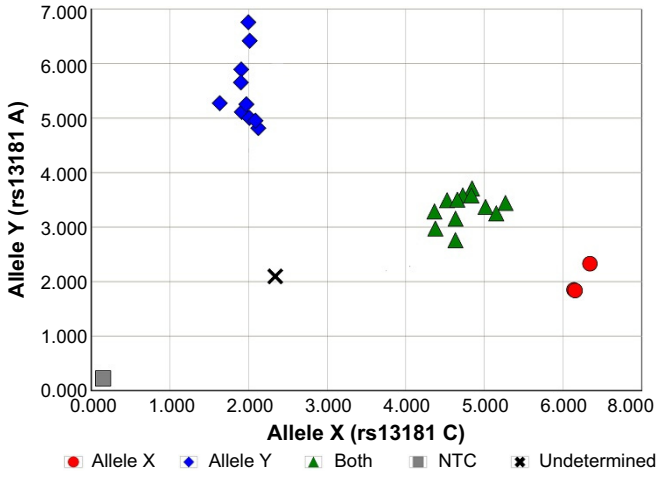

Figure 2. Allelic discrimination plot of *ERCC2/XPD* Lys751Gln (rs13181) polymorphism.

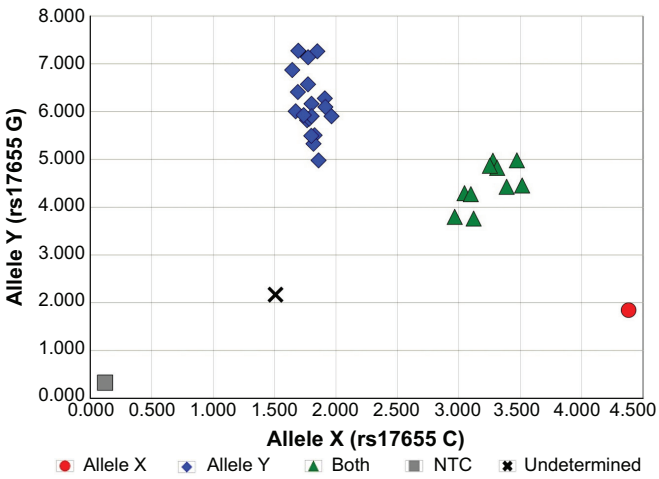

Figure 4. Allelic discrimination plot of XPG Asp1104His (rs17655) polymorphism.

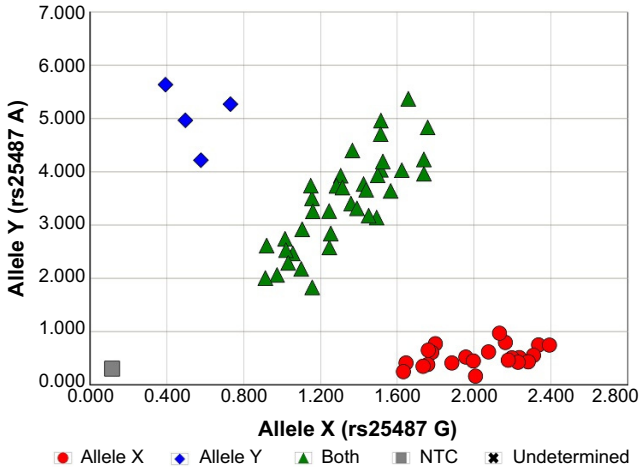

Figure 5. Allelic discrimination plot of *XRCC1* Arg399Gln (rs25487) polymorphism.

the study population and populations of different ethnicities. Statistical analysis was performed using GraphPad InStat 3.

Results

The observed allele frequencies of all the five SNPs were in Hardy–Weinberg equilibrium. Gender-wise stratification of the genotype and allele frequencies of the five SNPs was done and is shown in Table 2. The allele frequencies did not differ significantly between males and females.

***XPA* G23A (rs1800975).** The *XPA* G23A had G allele frequency of 50.8% and A allele frequency of 49.2%. The heterozygous genotype GA was seen in 42.2% while the homozygous genotypes GG and AA were seen in 29.7% and 28.1%, respectively (Table 3). The allele frequencies were significantly different from those observed among the CEU, YRI, and MEX. They were similar to the HCB, JPT, and GIH.

***ERCC2/XPD* Lys751Gln A>C (rs13181).** The observed genotype and allele frequencies of *ERCC2/XPD* Lys751Gln are shown in Table 4. The genotype frequencies of AA, AC, and CC were 43.0%, 41.4%, and 15.6%, respectively. The minor allele C had a frequency of 36.3%, highest among the populations compared. The allele frequencies observed in South Indians were significantly different from HCB, JPT, YRI, and MEX populations, while being similar to CEU and GIH. The C allele was as low as 7.6% in the JPT.

***XPG* His46His T>C (rs1047768).** The genotype and allele frequencies of *XPG* His46His are shown in Table 5. T allele and C allele had frequencies of 52.0% and 48.0%, respectively. The TT and CC genotypes were seen in 28.9% and 25.0%, respectively, while the heterozygous TC was present in 46.1%. The allele frequencies were found to be significantly different from all the populations compared.

***XPG* Asp1104His G>C (rs17655).** The genotype and allele frequencies of *XPG* Asp1104His are shown in Table 6. The GG and GC genotypes were seen in 59.4% and 35.1%, respectively, while the homozygous mutant CC was observed in 5.5%. The allele frequencies of G and C alleles were 77.0% and 23.0%, respectively. The allele frequencies of the South Indian population studied differed significantly from all the populations compared.

***XRCC1* Arg399Gln G>A (rs25487).** The genotype frequencies of GG, GA, and AA of *XRCC1* Arg399Gln were 46.9%, 38.3%, and 14.8%, respectively (Table 7). The G allele frequency was calculated to be 66.0%, and the A allele frequency was 34.0%. The allele frequencies were found to be statistically divergent from YRI. The minor allele frequency varied from 11.1% in YRI to 40.9% in GIH.

Table 2. Gender-wise genotype and allele frequency distribution of DNA repair gene polymorphisms in the study population.

SNP	GENOTYPE FREQUENCY (%)			ALLELE FREQUENCY (%)		*P* VALUE
rs13181	**AA**	**AC**	**CC**	**A**	**C**	
Male (73)	39.7	41.1	19.2	60.3	39.7	0.1928
Female (55)	47.3	41.8	10.9	68.2	31.8	
rs25487	**GG**	**GA**	**AA**	**G**	**A**	
Male (73)	46.6	39.7	13.7	66.4	33.6	0.8693
Female (55)	47.3	36.4	16.4	65.5	34.5	
rs1800975	**GG**	**GA**	**AA**	**G**	**A**	
Male (73)	30.1	43.8	26.0	52.1	47.9	0.6387
Female (55)	29.1	40.0	30.9	49.1	50.9	
rs1047768	**TT**	**TC**	**CC**	**T**	**C**	
Male (73)	30.1	41.1	28.8	50.7	49.3	0.6399
Female (55)	27.3	52.7	20.0	53.6	46.4	
rs17655	**GG**	**GC**	**CC**	**G**	**C**	
Male (73)	63.0	32.9	4.1	79.5	20.5	0.2740
Female (55)	54.5	38.2	7.3	73.6	26.4	

Table 3. Comparison of the genotype and allele frequencies of *XPA* G23A polymorphism with HapMap populations.

POPULATION	N	GENOTYPE FREQUENCY (%)			ALLELE FREQUENCY (%)		*P* VALUE
		GG	GA	AA	G	A	
Present study (SI)	128	29.7	42.2	28.1	50.8	49.2	Ref.
CEU	226	37.2	49.6	13.3	61.9	38.1	0.0038
HCB	86	20.9	60.5	18.6	51.2	48.8	0.9383
JPT	168	29.8	42.9	27.4	51.2	48.8	0.9214
YRI	226	56.6	40.7	2.7	77.0	23.0	<0.0001
GIH	176	30.7	47.7	21.6	54.5	45.5	0.3585
MEX	100	40.0	42.0	18.0	61.0	39.0	0.0294

Abbreviations: *N*, number of subjects; SI, South Indian; 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; GIH, Gujarat Indians in Houston, TX; and MEX, Mexican ancestry in Los Angeles, CA.

Table 4. Comparison of the allele and genotype frequencies of *ERCC2/XPD* Lys751Gln (A>C) polymorphism with HapMap populations.

POPULATION	N	GENOTYPE FREQUENCY (%)			ALLELE FREQUENCY (%)		*P* VALUE
		AA	AC	CC	A	C	
Present study (SI)	128	43.0	41.4	15.6	63.7	36.3	Ref.
CEU	226	40.7	52.2	7.1	66.8	33.2	0.3975
HCB	86	83.7	16.3	0.0	91.9	8.1	<0.0001
JPT	172	86.0	12.8	1.2	92.4	7.6	<0.0001
YRI	226	64.6	33.6	1.8	81.4	18.6	<0.0001
GIH	176	39.8	48.9	11.4	64.2	35.8	0.8925
MEX	100	62.0	34.0	4.0	79.0	21.0	0.0004

Abbreviations: *N*, number of subjects; SI, South Indian; 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; GIH, Gujarat Indians in Houston, TX; and MEX, Mexican ancestry in Los Angeles, CA.

Table 5. Comparison of the genotype and allele frequencies of *XPG* His46His (T>C) polymorphism with HapMap populations.

POPULATION	N	GENOTYPE FREQUENCY (%)			ALLELE FREQUENCY (%)		*P* VALUE
		TT	TC	CC	T	C	
Present study (SI)	128	28.9	46.1	25.0	52.0	48.0	Ref.
CEU	226	17.7	49.6	32.7	42.5	57.5	0.0151
HCB	86	55.8	34.9	9.3	73.3	26.7	<0.0001
JPT	172	68.6	29.1	2.3	83.1	16.9	<0.0001
YRI	224	8.0	42.0	50.0	29.0	71.0	<0.0001
GIH	176	38.6	45.5	15.9	61.4	38.6	0.0205
MEX	100	36.0	52.0	12.0	62.0	38.0	0.0318

Abbreviations: *N*, number of subjects; SI, South Indian; 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; GIH, Gujarat Indians in Houston, TX; and MEX, Mexican ancestry in Los Angeles, CA.

Table 6. Comparison of the genotype and allele frequencies of *XPG* Asp1104His (G>C) polymorphism with HapMap populations.

POPULATION	N	GENOTYPE FREQUENCY (%)			ALLELE FREQUENCY (%)		*P* VALUE
		GG	GC	CC	G	C	
Present study (SI)	128	59.4	35.1	5.5	77.0	23.0	Ref.
CEU	120	6.7	40.0	53.3	26.7	73.3	<0.0001
HCB	90	15.6	57.8	26.7	44.4	55.6	<0.0001
JPT	88	25.0	54.5	20.5	52.3	47.7	<0.0001
YRI	120	28.3	51.7	20.0	54.2	45.8	<0.0001

Abbreviations: *N*, number of subjects; SI, South Indian; CEU, Utah residents with Northern and Western European ancestry; HCB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan; and YRI, Yoruba in Ibadan, Nigeria.

Table 7. Comparison of the genotype and allele frequencies of *XRCC1* Arg399Gln (G>A) polymorphism with HapMap populations.

POPULATION	N	GENOTYPE FREQUENCY (%)			ALLELE FREQUENCY (%)		*P* VALUE
		GG	GA	AA	G	A	
Present study (SI)	128	46.9	38.3	14.8	66.0	34.0	Ref.
CEU	224	38.4	50.0	11.6	63.4	36.6	0.4846
HCB	84	52.4	40.5	7.1	72.6	27.4	0.1518
JPT	172	52.3	40.7	7.0	72.7	27.3	0.0788
YRI	226	77.9	22.1	0	88.9	11.1	<0.0001
GIH	176	34.1	50.0	15.9	59.1	40.9	0.0824
MEX	98	42.9	49.0	8.2	67.3	32.7	0.7662

Abbreviations: *N*, number of subjects; SI, South Indian; 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; GIH, Gujarat Indians in Houston, TX; and MEX, Mexican ancestry in Los Angeles, CA.

Discussion

The aim of the present study was to investigate the frequency of genetic polymorphisms in the *XPA, XPD, XPG*, and *XRCC1* genes in a South Indian healthy population. We report the genotype and allele frequencies of five different polymorphisms in DNA repair genes.

In our study, the allele frequencies of *XPA* G23A showed a significant deviation from the CEU, YRI, and MEX. The presence of G allele has been shown to decrease the risk of lung cancer among non-Caucasians, while this effect was not seen in the Caucasians.[19] Further, ethnic specific differences were observed in its association with head and neck and colorectal cancers, a protective effect of the G allele being greater in the Asian population.[20] Moreover, *XPA* polymorphisms have a role as a predictive biomarker of response to platinum-based chemotherapy, especially in non-small-cell lung cancer.[21,22]

The *ERCC2/XPD* Lys751Gln polymorphism frequencies showed a significant deviation from the populations of HCB, JPT, YRI, and MEX. The minor allele frequency was found to be similar to a study on the Northern Indian population by Gangwar et al[23] and on South Indians by Vettriselvi et al.[24] This polymorphism has been associated with an increased risk of cancers of the lung,[25] bladder,[26] prostate,[27] and brain.[28] A recent study also revealed that the *XPD* polymorphism can be useful as a biomarker for tamoxifen response in breast cancer patients.[29] Recently, we established the frequency distribution of another polymorphism *ERCC2/XPD* Asp312Asn and two important polymorphisms of the *ERCC1* in South Indian population.[30]

We report, to the best of our knowledge, for the first time in South Indian population, the allele and genotype frequencies of *XPG* His46His and Asp1104His. We observe the allele frequencies of both the SNPs to be completely deviant in the rest of the populations from the HapMap such as the CEU, HCB, JPT, and YRI. Heterozygous genotype of the *XPG* His46His was observed in a larger group of subjects similar to other populations, unlike the HCB or JPT. The present study population also had almost equal frequencies of both the alleles. Interestingly, the GG genotype of the *XPG* Asp1104His was higher in our population, quite contrary to the rest of the populations compared with. CC was the major genotype in CEU, while the heterogeneous genotype GC was major genotype in HCB, JPT, and YRI. Very few studies evaluating *XPG* gene polymorphisms are available from India, and a North Indian study reported the heterogeneous genotype to be the commonest genotype in the healthy population.[31] This probably suggests that inter-ethnic variations exist in the distribution of *XPG* gene polymorphisms. *XPG* His46His has been associated with colon[32] and prostate cancer.[31] It also has a role in predicting response to platinum-based chemotherapy.[33,34] The Asp1104His, on the other hand, has been associated with an increased risk of cutaneous melanoma[35] and breast cancer.[36] Other studies show weak or no association with cancer.[37,38]

The *XRCC1* Arg399Gln gene polymorphism frequency in South Indians was comparable to the populations such as CEU, HCB, JPT, GIH, and MEX. However, it showed a significant deviation from YRI. A study from the northern part of India of 150 healthy volunteers found the minor allele frequency to be 43%, higher than the present study population (34%).[39] A recent study from Northern India, evaluating the role of Arg399Gln in colorectal cancer, found a higher percentage of homozygous mutants than our study.[40] Arg399Gln has been found to be associated strongly with hepatocellular carcinoma in the Asian population and breast cancer in Indians.[41] Various studies have shown its association with the risk of lung cancer,[42,43] glioma,[28,44] endometrial carcinoma,[45] breast cancer,[46] etc.

We did not find a difference in the distribution of these polymorphisms between the genders, and the differential risk that these genotypes confer on males and females might be because of the dietary habits and interaction with other environmental factors as explained by Wang et al.[47]

To the best of our knowledge, this is the first study to establish the frequency distribution of *XPA* and *XPG* gene polymorphisms in South Indian population. To conclude, we report the frequency distribution of five SNPs in DNA repair pathways, and the present work forms the groundwork

for cancer association studies and biomarker identification for treatment response and prognosis.

Author Contributions

Conceived and designed the experiments: KSR, BD, KG, and SAD. Recruitment of healthy volunteers and DNA extraction: ASA and KSR. Genotyping: GU and KSR. Analyzed the data: KSR and AP. Wrote the manuscript: AP, KSR, and SAD. All authors reviewed and approved the final manuscript.

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