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) G23A, Excision repair cross-complementing 2 (ERCC2) G23A, Excision repair cross-complementing 2 (ERCC2) 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

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
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        | His464His| T>C              | 13q33.1       | Exon 15      | rs17655        | C_____1891769_20 |
| XPG        | Asp1104His| G>C              | 13q33.1       | Exon 2       | rs1047768      | C_____1891769_20 |
| 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.
**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. 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 (χ²) test by comparing the observed frequencies with the expected frequencies. Chi-square test was also used to assess the differences in allele frequencies between...
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.

**XPDI G23A (rs1800975).** The XPDI 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 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 statistically divergent 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 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      |
|                  |    |                        | 50.8                 | 49.2    |
| Present study (SI) | 128 | 29.7                   | 42.2                 | 28.1    |
| CEU              | 226 | 37.2                   | 49.6                 | 13.3    |
| HCB              | 86  | 20.9                   | 60.5                 | 18.6    |
| JPT              | 168 | 29.8                   | 42.9                 | 27.4    |
| YRI              | 226 | 56.6                   | 40.7                 | 2.7     |
| GIH              | 176 | 30.7                   | 47.7                 | 21.6    |
| MEX              | 100 | 40.0                   | 42.0                 | 18.0    |

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, Gujarati 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      |
|                  |    |                        | 63.7                 | 36.3    |
| Present study (SI) | 128 | 43.0                   | 41.4                 | 15.6    |
| CEU              | 226 | 40.7                   | 52.2                 | 7.1     |
| HCB              | 86  | 83.7                   | 16.3                 | 0.0     |
| JPT              | 172 | 86.0                   | 12.8                 | 1.2     |
| YRI              | 226 | 64.6                   | 33.6                 | 1.8     |
| GIH              | 176 | 39.8                   | 48.9                 | 11.4    |
| MEX              | 100 | 62.0                   | 34.0                 | 4.0     |

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, Gujarati 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      |
|                  |    |                        | 52.0                 | 48.0    |
| Present study (SI) | 128 | 28.9                   | 46.1                 | 25.0    |
| CEU              | 226 | 17.7                   | 49.6                 | 32.7    |
| HCB              | 86  | 55.8                   | 34.9                 | 9.3     |
| JPT              | 172 | 68.6                   | 29.1                 | 2.3     |
| YRI              | 224 | 8.0                    | 42.0                 | 50.0    |
| GIH              | 176 | 38.6                   | 45.5                 | 15.9    |
| MEX              | 100 | 36.0                   | 52.0                 | 12.0    |

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, Gujarati 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      |
|                  |    |                        | 77.0                 | 23.0    |
| Present study (SI) | 128 | 59.4                   | 35.1                 | 5.5     |
| CEU              | 120 | 6.7                    | 40.0                 | 53.3    |
| HCB              | 90  | 15.6                   | 57.8                 | 26.7    |
| JPT              | 88  | 25.0                   | 54.5                 | 20.5    |
| YRI              | 120 | 28.3                   | 51.7                 | 20.0    |

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 |
|--------------|----|------------------------|----------------------|---------|
| Present study (SI) | 128 | GG 46.9 GA 38.3 AA 14.8 | G 66.0 A 34.0 | Ref. |
| CEU          | 224 | GG 38.4 GA 50.0 AA 11.6 | G 63.4 A 36.6 | 0.4846 |
| HCB          | 84  | GG 52.4 GA 40.5 AA 7.1  | G 72.6 A 27.4 | 0.1518 |
| JPT          | 172 | GG 52.3 GA 40.7 AA 7.0  | G 72.7 A 27.3 | 0.0788 |
| YRI          | 226 | GG 77.9 GA 22.1 AA 0.0   | G 88.9 A 11.1 | <0.0001 |
| GIH          | 176 | GG 34.1 GA 50.0 AA 15.9 | G 59.1 A 40.9 | 0.0824 |
| MEX          | 98  | GG 42.9 GA 49.0 AA 8.2   | G 67.3 A 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, Gujarati 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. 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. Moreover, XPA polymorphisms have a role as a predictive biomarker of response to platinum-based chemotherapy, especially in non-small-cell lung cancer.

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 and on South Indians by Vettriselvi et al. This polymorphism has been associated with an increased risk of cancers of the lung, bladder, prostate, and brain. A recent study also revealed that the XPD polymorphism can be useful as a biomarker for tamoxifen response in breast cancer patients.

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 subsets 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. This probably suggests that inter-ethnic variations exist in the distribution of XPG gene polymorphisms. XPG His46His has been associated with colon and prostate cancer. It also has a role in predicting response to platinum-based chemotherapy. The Asp1104His, on the other hand, has been associated with an increased risk of cutaneous melanoma and breast cancer. Other studies show weak or no association with cancer.

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%). A recent study from Northern India, evaluating the role of Arg399Gln in colorectal cancer, found a higher percentage of homozygous mutants than our study.

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.

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 further studies to establish the role of these SNPs in the development and drug resistance in cancer.
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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