Risk Modulation of Oral Pre Cancer and Cancer with Polymorphisms in XPD and XPG Genes in North Indian Population

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Abstract

**Background:** Environmental carcinogens cause DNA damages which if not repaired properly, may increase the risk of cancer. The Xeroderma pigmentosum group D (XPD) and group G (XPG) genes are essential genes for DNA repair and alteration in DNA repair causes cancer. The present study aimed to evaluate the relationship between XPD and XPG polymorphisms and risk of oral pre cancer and cancer. **Methods:** Present study genotyped 302 samples of oral diseases and 300 controls for XPD (A/C) and XPG (G/C) polymorphisms with PCR-RFLP method. **Results:** Our result showed that compared to AA genotype frequency of AC and CC genotype for XPD (A/C) polymorphism were significantly lower among cases than in control and are associated with decreased risk of oral diseases (OR= 0.621 and 0.603 respectively). In contrast with reference to GG genotype the frequency of CC genotype of XPG (G/C) was significantly higher in case than in control population (p value=0.004) and found to increase the risk of oral diseases (OR= 2.077). Particularly C allele for XPD A/C polymorphism was found to be associated with decreased risk of Lichen planus and increased risk of (OR = 0.470 and 1.541 respectively) oral cancer. While C allele of XPG G/C polymorphism significantly increased the risk of Oral Submucous Fibrosis and Leukoplakia (OR= 1.879 and 1.837 respectively) but not of Lichen planus and oral cancer. In combined genotype analysis from the aforesaid polymorphisms presence of C allele for XPD (A/C) polymorphisms were found to decrease the risk of oral diseases. However, the same C allele was observed to increase the chance of having high stage disease (OR= 5.71) with nodal involvement (OR= 6.78) once the cancer been initiated. **Conclusion:** This work shows association of XPD (A/C), XPG (G/C) polymorphisms with the development of pre oral cancer as well as oral cancer and its clinical courses.

**Keywords:** Oral pre cancer and cancer- XPD- XPG- PCR-RFLP- gene polymorphism

Introduction

Oral cancer, a form of head and neck cancer is present in the oral cavity. It is very frequent with 30,000 cases diagnose worldwide per year (Feraly et al., 2015). Around 75 percent of oral cancers are caused due to use of tobacco and excessive alcohol consumption. Poor oral hygiene, nutrition, and some chronic infections by fungus, bacteria and virus are among the other causes of oral cancer. In most of the cases oral cancer is preceded by pre malignant lesions such as Oral Submucous Fibrosis (OSMF), Leukoplakia and Lichen planus. OSMF is characterized by progressive development of fibrosis in oral submucosa with 5-10% of them develop to malignancy (Gupta PC et al., 1992). Leukoplakia appears as white patches while Lichen planus is chronic inflammation to mucous membrane of oral cavity.

Cancer is a complex disease related to environmental factors, genetic susceptibility and gene environment interactions. DNA damage caused by environmental factors, such as consumption of tobacco and alcohol, exposure to UV radiation are important risk factors for oral cancer (Wood et al., 2001). This exposures may results in DNA damages such as formation of DNA adducts and cross-links. Damaged DNA if not restored properly with DNA repair system (Cheng et al., 1998) can causes dis-regulation of cell growth and apoptosis which may lead to development of cancer including oral cancer (Kawakami et al., 2015).

DNA repair mechanism is a complex biological system, including five different pathways namely; nucleotide excision repair (NER), Double –strand break repair,
Base excision repair, Mismatch repair and Homologous recombination repair (Yang, 2012). Gene mutation in NER pathway can develop to several human diseases, including Xerodermapigmentosum (XP) (Spivak et al., 2015). The XP patients can be classified as 8 complementation groups, XPA through XPG. The XPG gene is located on chromosome 13 and synthesizes a DNA endonuclease of 1,186 amino acids. This enzyme is specific for single strand and cleaves the damaged DNA strand at the 3’end (O’Donovan et al., 1994). Any alteration in XPG gene can impair its DNA repair efficiency which can further cause genomic instability and carcinogenesis (Cheng et al., 2002). XPG gene harbored SNPs and many of those SNPs have been reported to alter the risk of different cancer including colorectal (Moreno et al., 2006), lung (Shen et al., 2005; Sakoda et al., 2012), gastric (He et al., 2012; Yang et al., 2012) and laryngeal (Abbasi et al., 2009).

Xerodermapigmentosum complementation group D (XPD) is involved in NER pathway through recognition and repair of thymidine dimers. The XPD gene contains 23 exons, encodes the 761-amino acid protein and is present in chromosome 19q13.3. The XPD protein is a part of transcription factor TFIIH and is involved in different functions including nucleotide excision repair (NER), transcription coupled repair, transcription, cell cycle regulation and apoptosis (Sturgis et al., 2000) and therefore, any sequence variation in XPD gene may lead to repair and transcription defects. Several SNPs been identified in XPD gene, and it is thought that certain XPD polymorphisms may be associated with the development of cancer (Goode et al., 2002).

In this study, we investigated the association between XPD (A/C, rs13181) and XPG (G/C, rs17655) polymorphisms with the risk of oral cancer and pre cancer.

Materials and Methods

Study Subjects

The study was evaluated on 602 subjects including 302 patients with previously treated and pathologically confirmed oral pre cancer and cancer who were registered at department of Oral Pathology and Microbiology, King George’s Medical University and 300 healthy controls. This study was approved by the Institutional Ethics Committee of the King George’s Medical University, Lucknow. An informed written consent was obtained from all subjects. Venous blood samples were collected in EDTA tubes and stored at −80°C, till DNA extraction. Genomic DNA extraction from blood samples was carried out by salting out method (Suguna et al., 2014).

Genotyping by RFLP

PCR-RFLP method was employed to determine the genotypes of XPD A/C and XPG G/C polymorphisms. PCR primers used for the amplification of XPD A/C and XPG G/C polymorphisms were same as used by Sanyal et al., (2004). PCR reactions were carried out with 10 ng of genomic DNA in 10 ul volume reactions containing 0.3 mM each primer, 0.11 mM each dNTP, 20 mMTris–HCl, 50 mM KCl, 2.0 mM MgCl₂, and 0.5 U TaqDNApolymerase (Sigma Aldrich, USA). PCR products were digested with Pst I and Nla III respectively to obtain genotypes for XPD and XPG polymorphisms. The digested PCR products were visualize on a 2% agarose gel stained with ethidium bromide. The genotype results were regularly checked and compared with known genotypes as controls.

Statistical analysis

The distributions of genotype were checked for the Hardy–Weinberg equilibrium (HWE) and any deviation from HWE was measured with Pearson chi-square test. Comparison between the genotype and allele frequencies among case and control were assessed by the chi-square test. Odds ratio (OR) was calculated to measure the chances of having diseases with the relative frequency of different genotypes and allele among the cases and controls. Odds ratio and p values were calculated with Epi-Info programme (http://www.cdc.gov/epiinfo/). P value <0.05 was considered to be significant.

Results

Demographics of the study population

The demographic profile including gender, age, habitual risk which may responsible for the development of oral cancer and pre oral cancer along with the tumor’s clinical parameters, are shown in Table 1. This study involved 302 oral cancer patient, including 203 (67%) male and 99 (33%) female. Calculated mean age of subject was 46.67. The mean age of controls [219 (73%) males and 81 (27%) females] was 38.02. Tobacco, smoking chewing and alcohol consumption have been observed.
Table 1. Demographic Parameters of Patient and Controls and Their Association with Risk of Oral Pre Cancer and Cancer

| Demographic Character | Cases (n=302) (%) | Control (n=300) (%) | P- value |
|-----------------------|------------------|---------------------|----------|
| Sex                   |                  |                     |          |
| Male                  | 203 (67)         | 219 (73)            | Ref      |
| Female                | 99 (33)          | 81 (27)             | 0.144    |
| Age distribution      |                  |                     |          |
| 10 – 40               | 89 (29)          | 160 (53)            | Ref      |
| 40-90                 | 213 (71)         | 140 (47)            | <0.0001* |
| Mean age              | 46.67            | 38.02               |          |
| Median age            | 47               | 37.5                |          |
| Habitual risk         |                  |                     |          |
| Alcohol consumption   |                  |                     |          |
| Yes                   | 41 (14)          | 11 (04)             | Ref      |
| No                    | 261 (86)         | 289 (96)            | <0.0001* |
| Smoking               |                  |                     |          |
| Yes                   | 141 (46)         | 78 (26)             | Ref      |
| No                    | 161 (54)         | 222 (74)            | <0.0001* |
| Tobacco chewing       |                  |                     |          |
| Yes                   | 134 (44)         | 73 (25)             | Ref      |
| No                    | 168 (56)         | 227 (75)            | <0.0001* |
| Type of oral cancer   |                  |                     |          |
| Leukoplakia           | 70 (23.33)       | -                    | -        |
| O.S.M.F               | 90 (30.00)       | -                    | -        |
| Lichen planus         | 70 (23.33)       | -                    | -        |
| Malignancy            | 72 (23.33)       | -                    | -        |
| TNM staging of oral cancer (Malignancy) | - | - | |
| Tumor Stage           |                  |                     |          |
| I                     | 8 (11)           | -                    | -        |
| II                    | 11 (15)          | -                    | -        |
| III                   | 18 (25)          | -                    | -        |
| IV                    | 35 (49)          | -                    | -        |
| Tumor T Status        |                  |                     |          |
| T1+T2                 | 10(13)           | -                    | -        |
| T3+T4                 | 62 (87)          | -                    | -        |
| Lymph Node            |                  |                     |          |
| N0                    | 25 (34)          | -                    | -        |
| N1+N2                 | 47 (66)          | -                    | -        |
| Metastasis            |                  |                     |          |
| M0                    | 54 (75)          | -                    | -        |
| M1                    | 18 (25)          | -                    | -        |
| Cell differentiated grade |            |                     |          |
| Grade 1               | 31 (45)          | -                    | -        |
| >Grade 1              | 39 (55)          | -                    | -        |

*, significant value

Genotypes of XPD and XPG polymorphisms and risk of oral diseases

The different genotype distribution and allele frequency for XPD A/C, XPG G/C polymorphisms both in control and cases are represented in Table 2. Both the case and control population were at Hardy-Weinberg equilibrium. With reference to the AA genotype frequency of AC and CC genotype for XPD (A/C) polymorphism was significantly low among cases of oral diseases and found to decrease the risk of oral diseases (OR=0.621 and 0.603 respectively). Compared to A allele a significant risk reduction was also observed with C allele (OR=0.758). In contrast with reference to GG genotype the frequency of CC genotype of XPG (G/C) was significantly higher in case than in control population (p value=0.004) and found to increase the risk of oral diseases (OR= 2.077). Increased risk of oral disease was also documented with C allele of XPG (G/C) polymorphism (OR= 1.425, p value= 0.003).

Since both XPD and XPG are proteins of NER pathway and functions in collaboration we hypothesized that combined genotypes from XPD A/C and XPG G/C polymorphisms might synergistically altered the risk of oral disease. Distribution of different combined genotypes from XPD (A/C) and XPG (G/C) polymorphisms are shown in Table 3. Compared to combined common allele genotype AA/GG the risk of oral disease were found to be significantly reduced with AA/CC, AC/GC, AC/CC and CC/CC genotype (OR=0.393, 0.377, 0.237 and 0.147 respectively).

Genotypes of XPD and XPG polymorphisms and risk of pre oral cancer and oral cancer

The study showed impact of XPD and XPG polymorphisms on the risk of oral disease. In order to investigate the association of them separately with pre oral cancer and oral cancer we further divided the case population into four groups: (i) patients with Oral Submucous Fibrosis (ii) patients with Lichen planus, (iii) patients with Leukoplakia and (ii) patients with oral cancer. The frequency of different genotypes and alleles for XPD A/C and XPG G/C polymorphisms among patients of different pre oral cancer diseases and oral cancer are listed in Table 4. Compared to AA genotype of XPD A/C polymorphism the risk of developing Lichen planus was lower with AC as well as CC genotypes (OR= 0.495 and 0.222 respectively) (Table 4). In contrast with reference to GG genotype the frequency of CC genotype of XPG (G/C) was significantly higher in case and control population were at Hardy-Weinberg equilibrium. With reference to the AA genotype frequency of AC and CC genotype for XPD A/C polymorphism was found to be significantly associated with high risk for oral cancer (OR= 2.708 and 1.541 respectively) (Table 4). In contrast no such association was observed with other pre oral cancer lesions namely OSMF and Leukoplakia.

For XPG G/C polymorphism the CC genotype as well as CC genotype of XPG (G/C) was significantly higher in case and control population were at Hardy-Weinberg equilibrium. With reference to the AA genotype frequency of AC and CC genotype for XPD A/C polymorphism was found to decrease the risk of oral diseases (OR=0.758). Increased risk of oral disease was also documented with C allele of XPG (G/C) polymorphism (OR= 1.425, p value= 0.003).

Genotypes of XPD and XPG gene polymorphisms in relation to different clinical parameters of patients with oral cancer

The distribution of different genotypes of XPD A/C and XPG G/C polymorphisms among different disease to be significantly associated with the development of oral diseases (p value <0.0001). Types of oral diseases included in this study are also mentioned in Table 1, which includes 23.33% leukoplakia, 30% OSMF, 23.33% lichen planus, and 23.33% malignancy.

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categories are shown in Table 5. Prevalence of patients with variant allele genotypes (A/C + C/C) for XPD (A/C) polymorphism were more (96%) among patients who had cancer with lymph node involvement (number of lymph node involved N1+N2+N3) compared to those who did not (76%). Similarly compared to patients with AA genotype, patients with variant allele genotypes (A/C + C/C) for XPD (A/C) polymorphism had developed high stage tumor at diagnosis (OR= 5.71, p value= 0.049; Table 5). Rest of the clinical parameters of oral cancer did not show any association with XPD, XPG genotypes Table 5.

**Discussion**

Oral cancer is the most commonly found cancer and has been prime health issue in the growing countries including India. Pre oral cancer develops into oral cancer and early treatment of oral lesion could therefore decrease prevalence of oral cancer. This could be achieved by identifying the SNP markers for pre and malignant oral lesion. In this study we investigated the relationship between genotypes of XPD (A/C) and XPG (G/C) polymorphism and risk of oral pre cancer and oral cancer.

| Combined genotype | Cases N (%) | Controls N (%) | p-value | Odds Ratio | 95% CI |
|-------------------|-------------|----------------|---------|------------|-------|
| AA/GG             | 29 (10.03)  | 14 (04.86)     | Ref     |            |       |
| AA/GC             | 40 (13.84)  | 28 (09.72)     | 0.477   |            |       |
| AA/CC             | 22 (07.61)  | 27 (09.37)     | 0.050*  | 0.393      | 0.168-0.921 |
| AC/GG             | 49 (16.95)  | 17 (05.90)     | 0.581   |            |       |
| AC/GC             | 50 (17.30)  | 64 (22.22)     | 0.014*  | 0.377      | 0.180-0.788 |
| AC/CC             | 29 (10.03)  | 59 (20.48)     | 0.0004* | 0.237      | 0.109-0.516 |
| CC/GG             | 20 (06.92)  | 06 (02.08)     | 0.57    |            |       |
| CC/GC             | 39 (13.49)  | 37 (12.84)     | 0.129   |            |       |
| CC/CC             | 11 (03.80)  | 36 (12.50)     | 0.0001* | 0.147      | 0.058-0.373 |

*, significant value

![Figure 2. 2.5% Agarose Gel Analysis of XPG (G/C) Polymorphism.](image)

Lane 1 50 bp Ladder. Lane 2,3,4,7,9,11,12 GG genotype 158bp. Lane 5,6,10 GC genotype 158,99,59bp. Lane 8 CC genotype 99,59bp.

Table 3. Distribution of Combined Genotype from XPD (A/C) and XPG (G/C) Polymorphism among the Subject of Oral Diseases and Controls

| Combined genotype | Cases N (%) | Controls N (%) | p-value | Odds Ratio | 95% CI |
|-------------------|-------------|----------------|---------|------------|-------|
| AA/GG             | 29 (10.03)  | 14 (04.86)     | Ref     |            |       |
| AA/GC             | 40 (13.84)  | 28 (09.72)     | 0.477   |            |       |
| AA/CC             | 22 (07.61)  | 27 (09.37)     | 0.050*  | 0.393      | 0.168-0.921 |
| AC/GG             | 49 (16.95)  | 17 (05.90)     | 0.581   |            |       |
| AC/GC             | 50 (17.30)  | 64 (22.22)     | 0.014*  | 0.377      | 0.180-0.788 |
| AC/CC             | 29 (10.03)  | 59 (20.48)     | 0.0004* | 0.237      | 0.109-0.516 |
| CC/GG             | 20 (06.92)  | 06 (02.08)     | 0.57    |            |       |
| CC/GC             | 39 (13.49)  | 37 (12.84)     | 0.129   |            |       |
| CC/CC             | 11 (03.80)  | 36 (12.50)     | 0.0001* | 0.147      | 0.058-0.373 |

*, significant value
| Genotype | XPD (A/C) Polymorphism | XPG (G/C) Polymorphism |
|----------|------------------------|------------------------|
| G        | 44.79%                 | 12.84%                 |
| C        | 55.21%                 | 87.16%                 |
| AC       | 3.82%                  | 3.82%                  |
| CC       | 44.79%                 | 87.16%                 |

Table 4. Distribution of Different Genotypes and Allele from XPD (A/C), XPG (G/C) Polymorphisms Among the Subjects of Oral Submucous Fibrosis, Lichen planus, Leukoplakia, and Oral Cancer.
Table 5. Association of Different Genotypes for XPD (A/C) and XPG (G/C) Polymorphism with Tumor Stage, Tumor T Status, Lymph Node, Metastasis and Grade in Oral Cancer Patients

|                        | XPD (A/C), XPG (G/C) Genotypes/Alleles | T3+T4 N (%) | T1+T2 N (%) | P-value | Odds Ratio | 95% CI |
|------------------------|----------------------------------------|-------------|-------------|---------|------------|-------|
| **Tumor T Status**     |                                        |             |             |         |            |       |
| XPD (A/C)              |                                        |             |             |         |            |       |
| AA                     | 03 (08)                                | 05 (15)     | Reference   | Reference | Reference  |       |
| AC+CC                  | 34 (92)                                | 28 (85)     | 0.583       | 2.024   | 0.444-9.222 |       |
| XPG (G/C)              |                                        |             |             |         |            |       |
| GG                     | 21 (58)                                | 12 (38)     | Reference   | Reference | Reference  |       |
| GC+CC                  | 15 (42)                                | 19 (62)     | 0.174       | 0.451   | 0.169-1.203 |       |
| **Lymph Node**         |                                        |             |             |         |            |       |
| N1+N2+N3               | N (%)                                  | N (%)       |             |         |            |       |
| XPD (A/C)              |                                        |             |             |         |            |       |
| AA                     | 02 (04)                                | 06 (24)     | Reference   | Reference | Reference  |       |
| AC+CC                  | 43 (96)                                | 19 (76)     | 0.038*      | 6.789   | 1.254-36.77 |       |
| XPG (G/C)              |                                        |             |             |         |            |       |
| GG                     | 23 (53)                                | 10 (42)     | Reference   | Reference | Reference  |       |
| GC+CC                  | 20 (47)                                | 14 (58)     | 0.5         | 0.621   | 0.226-1.704 |       |
| **Metastasis**         |                                        |             |             |         |            |       |
| M1                     | N (%)                                  | N (%)       |             |         |            |       |
| XPD (A/C)              |                                        |             |             |         |            |       |
| AA                     | 01 (06)                                | 07 (13)     | Reference   | Reference | Reference  |       |
| AC+CC                  | 16 (94)                                | 46 (87)     | 0.698       | 2.435   | 0.277-21.36 |       |
| XPG (G/C)              |                                        |             |             |         |            |       |
| GG                     | 11 (65)                                | 22 (44)     | Reference   | Reference | Reference  |       |
| GC+CC                  | 06 (35)                                | 28 (56)     | 0.232       | 0.428   | 0.136-1.341 |       |
| **Tumor stage**        |                                        |             |             |         |            |       |
| III+IV                 | N (%)                                  | N (%)       |             |         |            |       |
| XPD (A/C)              |                                        |             |             |         |            |       |
| AA                     | 03 (06)                                | 05 (26)     | Reference   | Reference | Reference  |       |
| AC+CC                  | 48 (94)                                | 14 (74)     | 0.049*      | 5.714   | 1.212-26.93 |       |
| XPG (G/C)              |                                        |             |             |         |            |       |
| GG                     | 26 (53)                                | 07 (39)     | Reference   | Reference | Reference  |       |
| GC+CC                  | 23 (47)                                | 11 (61)     | 0.451       | 0.562   | 0.187-1.694 |       |
| **Cell differentiated grade** |                                        |             |             |         |            |       |
| >Grade 1               | N (%)                                  | N (%)       |             |         |            |       |
| XPD (A/C)              |                                        |             |             |         |            |       |
| AA                     | 02 (05)                                | 06 (20)     | Reference   | Reference | Reference  |       |
| AC+CC                  | 38 (95)                                | 24 (80)     | 0.115       | 4.75    | 0.885-25.49 |       |
| XPG (G/C)              |                                        |             |             |         |            |       |
| GG                     | 20 (55)                                | 13 (48)     | Reference   | Reference | Reference  |       |
| GC+CC                  | 16 (45)                                | 14 (52)     | 0.743       | 0.742   | 0.272-2.022 |       |

*, significant value

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**Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Conflict of Interest**

None of the author had any conflict of interest

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