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ASSOCIATION BETWEEN GENETIC POLYMORPHISMS OF DNA REPAIR GENES (XPC, XPG) AND HEAD AND NECK CANCER SUSCEPTIBILITY IN INDIAN POPULATION: A HOSPITAL BASED CASE-CONTROL STUDY.

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ABSTRACT

Background: Smoking and alcohol related head and neck cancer is a major concern of health risk in rural parts of developing countries, such as India. In this study, we aimed to determine the frequency of polymorphisms in DNA repair gene, Xeroderma pigmentosum complementation group C (*XPC*) and Xeroderma pigmentosum complementation group G (*XPG*) in patients of oral cancer from western Maharashtra and to evaluate their association with oral cancer development. **Methods:** We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to analyze *XPC & XPG* gene polymorphisms in 320 patients with oral cancer and in 400 age and sex matched disease-free controls. **Results:** The result from our study showed that allele frequencies of selected genes were not statistically different between the groups for XPC Gln939, XPGAsp1104. XPC Intron 11 (OR= 4.65; 95% CI= (3.16-6.85); *p*= <0.0001) genotypes significantly increased the risk of head and neck cancer. **Conclusions:** This study indicates that polymorphisms in intron11 of XPC gene could play a role in modifying genetic susceptibility of individual to head and neck cancer in Maharashtra patients. The case-control study suggests that selected DNA repair genes represent genetic determinants in oral carcinogenesis along with other environmental risk factors in the unexplored rural Indian population.

KEYWORDS: Genetic polymorphisms, XPC, XPG, cancer risk, genotyping, PCR-RFLP

INTRODUCTION

Oral cancer is the most common malignancy worldwide and represents the leading cause of cancer death in men as well as women in the developing world (Chaturvedi et al 2013). Oral cancer specifies a subgroup of head and neck cancer (HNC) where cancer of the oral cavity, oropharynx and larynx constitute a major public health problem. In the Indian subcontinent HNC is the frequent malignancy, accounting up to 40-50% of all malignant cancers (Kulkarni MR 2013, Prasad LK 2014). It is generally assumed that among the major documented risk factors associated with HNC are tobacco smoking, alcohol consumption followed by oral health or exposure to environmental carcinogens and uptake of drugs (Marcu et al 2009, HariRam et al 2011). These carcinogens can cause DNA damage, introducing bulky adducts, crossloinks and single or double strand breaks. DNA repair is the primary defense mechanism against these mutagenic exposures. There are four major DNA repair pathways in human cells which play a pivotal role in maintenance of genomic integrity, such as base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double strand break repair (DSBR) (Wood et al 2001). In addition, over hundred genes are involved in the different DNA repair pathways, but it is not yet clear which DNA repair pathway genes or Enzymes are more important for protection against HNC. It is also believed that along with the environmental risk factors, the host factors including individual's genetic susceptibility and possible gene environment interactions are contributing to the development of oral cancer (Scully and Bagan 2009). Though the genetic factors are considered of great importance to cancer risk through the modulation of DNA repair but the genomic etiology of HNC is largely unknown.

The NER pathway is an important mechanism which involved in removal of variety of bulky DNA lesions such as ultra violet light induced pyrimidine dimmer, photoproducts, chemical adducts, crosslinks and in the maintenance of genomic stability through DNA damage

repair (Marteijn et al 2014). XPC and XPG are major components of the NER pathway (Min and Pavletich 2007]. The XPC gene spans 33 kb on chromosome 3 and contains 16 exons and 15 introns encoding a 940 amino acid protein uniquely involved in global genome repair (Khan et al 2002). *XPG* gene express proteins having roles in the NER pathway that can repair bulky lesions. Hundreds of polymorphisms in DNA repair genes associated with cancer risk have been identified. Some of them are XRCC, XPD, XPC and XPG which have been frequently studied and there is a growing body of evidence that polymorphisms of these genes may have some significance. Previous studies on XPC and XPG suggested that polymorphisms of those genes were associated with an increased risk of many human malignancies including stomach, colorectal, prostate and bladder cancer (Francisco et al 2008, Du 2014, Mirecka et al 2014, Yu et al 2014, Chen et al 2016), but some of studies on XPC and XPG and cancer risk produced contradictory and inconclusive results (Kumar et al 2003, Garcia-Closas et al 2006, Crew et al 2007, Ding et al 2011, Xu et al 2014. Also, the earlier observations were not consistent in terms of their roles in oral cancer susceptibility and therefore the influence of the polymorphisms of XPC and XPG genes on DNA repair capacity and the exact biological effect is still unclear. In former studies we have shown that polymorphisms in BER pathway genes especially XRCC1, XRCC4, XRCC5, XRCC7, hOGG1 and NER pathway genes plays an important role in susceptibility of HNC in rural population of western Maharashtra. In continuation with this, we also hypothesized that the inherited polymorphisms in XPC or XPG of NER pathway genes may contribute to genetic susceptibility to HNC. To test this hypothesis we focused on genetic polymorphisms of NER pathway genes especially XPC and XPG to evaluate their role in HNC if any. We performed a hospital based case-control study using a PCR-RFLP assay to genotype the polymorphisms of selected DNA repair genes in relation to HNC susceptibility in a rural population of western Maharashtra from India. We determined the genotypic frequency of polymorphisms of the (A) XPC A2920C at codon939 of the exon 15 (B) XPC C-A polymorphism of intron 11 and (C) XPG at codon 1104 using the restriction enzymes HaeIII, PvuII and NlaIII respectively.

MATERIALS AND METHODS

Study subjects

This was a hospital based case-control study conducted in rural areas of western Maharashtra from India. Study participants included 320 patients, who were newly diagnosed with head & neck cancer and 400 healthy, cancer free, age and sex matched individuals were selected as controls living in the same residential areas as the cases. All cases ranged in age from 30 - 80 years (Mean ± SD) 54.42 ±12.95 were recruited immediately after being diagnosed. Trained interviewers used a structured questionnaire to collect personal interview data from the participants regarding demographic factors and known risk factors including occupational history, dietary habits, smoking and drinking status and individual family history of diseases, including cancer.

Genomic DNA isolation from whole blood

Five milliliter (mL) of whole blood from patients and normal age matched controls was collected in sterile purple top vacutainer after receiving informed consent. Genomic DNA extraction was carried out from the peripheral blood sample using Purelink genomic DNA extraction and purification Kit (Invitrogen, Life technologies) following the manufacturer's instructions.

Genotyping assays

Genotyping of XPC and XPG genes were performed by PCR-RFLP methods with appropriate primer sets (Table 1). The primers were designed to amplify the regions of DNA that contain polymorphic sites of interest: (A) XPC C-A polymorphism of intron 11 (B) XPC A2920C at codon 939 of the exon 15 and (C) XPG at codon1104 of the exon 15. The PCR amplification were carried out separately under different conditions in 20 micro liter (µL) reaction mixtures containing 1X PCR buffer (10 mili molar (mM) Tris-HCl (pH 9.0), 50 mM KCl 1.5 mM MgCl2, 0.01% gelatin), 0.2 mM each dNTP, 10 picomole (pmol) of each primer listed in Table-1, 1U *Taq DNA* polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA template. The reaction mixtures were subjected to PCR amplification with a Master Cycler Gradient PCR (Eppendorf). After performing PCR programme for each of the reactions, the PCR products were analyzed by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer. The agarose gels were stained with ethidium bromide (10 mg/mL) and visualized under UV Transilluminator and photographed in gel documentation system (BioRad Laboratories). After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme as shown in table-1 for genotyping. Ten micro liters (µL) of the PCR products were digested at 37°C overnight with specific restriction enzymes in 20 µL reaction mixtures containing buffer supplied with each restriction enzyme. After the overnight incubation, digestion products were then separated on a 2-3% low EEO agarose (GeNei) gel at 100 V for 30 min stained with ethidium bromide and photographed with gel documentation system.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS 11.5 for windows software. The associations between the XPC and XPG genotypes and risk of HNC with or without smoking and drinking history were studied using odds ratio (OR). Both the univariate and multivariate logistic regression analyses were employed to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to determine the cancer risk associated with genotypes.

Table I. Details of PCR and RFLP procedures and expected products of XPC & XPG genes.

Gene	Primers Forward/Reverse	PCR conditions	PCR Product	Restriction enzyme	Restriction products
XPC A2920C Lys939Gln codon 939 Ex-15	5'-GGA GGT GGA CTC TCT TCT GAT G-3' 5'-TAG ATC CCA GCA GAT GAC C-3'	95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 52^0C- 45 sec, 72^0C- 30 sec, 72^0C- 5 min	765 bp	1U of PvuII	A/A: 765 bp A/C: 765bp, 585bp, 180 bp C/C: 585bp, 180 bp
XPC Intron 11 C-A	5'-GCC AAA TGC TGA CTT GCT CAC CGG-3' 5'-GCC ACG CGG TGT AGA TTG GG-3'.	95^0C- 5 min, 35 cycles of 95^0C- 60 sec, 58^0C- 30 sec, 72^0C- 30 sec, 72^0C- 5 min	128 bp	1U of HaeIII	WT allele:104bp, 24bp Variant allele:128bp
XPG C3507G His1104 Asp codon1104 Ex-15	5'-GAC CTG CCT CTC AGA ATC ATC-3' 5'-CCT CGC ACG TCT TAG TTT CC-3'	95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 55^0C- 45 sec, 72^0C- 30 sec, 72^0C- 5 min	271 bp	1U of NlaIII	G/G: 271bp G/C: 271bp, 227bp, 44bp C/C:227bp,44bp

RESULTS

Characteristics of the study subjects

During the study period, 320 patients with oral cancer met the eligibility criteria for this study and 400 controls were selected to match these cases. The characteristics of age and sex matched cases and controls are presented in Table 2. The (Mean ± SD) age in years was 54.42 ±12.95 for the cases and 52.84 ± 12.94 (P<0.05) for the controls (Table 2), however there was no significant difference in mean age between cases and controls. Also, there was no significant difference in males of cases (62.50%) and of controls (65.00 %). There were more smokers (78.13%) and drinkers (68.75%) in cases as compared to controls 20.0 % and 12.50) respectively enrolled in this study.

Table: 2 Distribution comparisons of selected demographic characteristics of head and neck cancer cases and healthy controls from rural areas of Maharashtra in India.

Variable	Cases N=320		Controls N=400		*P*-Value based on $\chi 2$
Age (Mean ± SD) years	54.42 ±12.95		52.84 ± 12.94		
	No.	(%)	No.	(%)	
≤ 50	122	38.13	184	46.00	<0.05
51-60	86	26.87	100	25.00	
61-70	84	26.25	86	21.50	
>70	28	8.75	30	7.50	
Sex					0.44
Male	200	62.50	260	65.00	
Female	120	37.50	140	35.00	
Tobacco smoking Status					**<0.001**
Smokers	253	78.13	80	20.00	
Non smokers	67	21.87	320	80.00	
Alcohol status					**<0.001**
Drinkers	220	68.75	50	12.50	
Non-drinkers	100	31.25	350	87.50	
Diet					0.04
Vegeterian	90	28.13	140	35.00	
Non-vegeterian	10	3.12	20	5.00	
Mixed	220	68.75	240	60.00	
Education					0.73
High School	205	64.06	180	45.00	
High School graduate (12 y)	70	21.88	120	30.00	
College /Graduate	45	14.06	100	25.00	
Economic status					0.56
Middle	112	35.00	148	37.10	
Poor	208	65.00	251	62.90	

Family history of Cancer					
Yes	20	6.25	0	0.00	0.2
No	300	93.75	400	100	

Association of polymorphisms in XPC , XPG gene and smoking , drinking status in cases of HNC and age and sex matched controls

We investigated the distribution and association between the previously described polymorphisms of codon 939 and intron 11 of XPC and codon 1104 of XPG genes in relation with tobacco, alcohol consumption from rural Maharashtrian population.

(A) Analysis of the XPC A2920C Lys 939 Gln of exon 15 and Intron 11.

The amplification of XPC exon 15 resulted in the product of 765bp. The PCR amplified products upon treatment with PvuII yielded wild type Lys/Lys alleles of 765bp fragment, and the polymorphic Gln/Gln allele produces two fragment of 585 & 180bp. The frequency of *XPC 2920*AA homozygotes was 53.13% in cases and 55.00 % in controls whereas the frequency of 2920CC allele was lower but not significantly in the cases (08.75 %) than in the controls (08.50 %). The frequency of *XPC2920 AC* heterozygotes was 38.12 % in cases and 36.50 % in controls (Table-3). Whereas, the frequency of wild type allele of *XPC intron 11* was 30.00% in cases and 65.00 % in controls whereas the frequency of variant allele was significantly higher in the cases (34.38 %) than in the controls (16.00 %). The frequency of heterozygote alleles was 35.62 % in cases and 19.00 % in controls. Compared to wild type genotype, the variant genotype was associated with oral cancer risk (0R=4.65; 95% CI= (3.16-6.85) of HNC (Table 3). Compared with combined group of Heterozygote and variant genotypes remained associated with increased risk of HNC. The variants of the DNA repair gene XPG are extremely high and contribute significantly to the risk of HNC in the rural population of western Maharashtra.

(B) Analysis of the XPG C3507G His1104 Asp of exon 15

The frequency of *XPG 3507CC* wild type homozygotes was 63.75 % in cases and 51.50 % in controls whereas *XPG 3507GG* variant homozygotes was 02.50 % in cases and 05.50 % in controls. We investigated the relationship between smoking and the risk for head and neck cancer, independent of genotype. We also investigated the association between the polymorphisms and alcohol consumption (Table-4). We did not find any significant difference in genotype or allele frequencies in patients with cancer and controls.

Table: 3 The genotype frequencies of *XPC & XPG* gene variants in untreated HNC patients and controls.

GENE	Genotype	CASES (n= 320) (%)	CONTROL (n = 400) (%)	Odds' Ratio (OR) (95% CI)	*P* value	Adjusted Odds Ratio (95% CI)	*P* value
XPC A2920C Lys939Gln codon 939 Ex-15	A/A	170 (53.13)	220 (55.00)	1		1	
	A/C	122 (38.12)	146 (36.50)	1.08 (0.79-1.47)	0.62	0.77 (0.54-1.09)	0.14
	C/C	28 (08.75)	34(08.50)	1.06 (0.62-1.82)	0.81	0.79 (0.43-1.44)	0.45
	A/C+ C/C	150 (46.87)	180 (45.00)	1.07 (0.80-1.44)	0.61	1.22 (0.89-1.69)	00.20
XPC Intron 11 C-A	WT allele	96 (30.00)	260 (65.00)	1		1	
	HT allele	114 (35.62)	76 (19.00)	4.06 (2.79-5.89)	**<0.0001***	0.24 (0.16-0.36)	<0.0001*
	VT allele	110 (34.38)	64 (16.00)	**4.65 (3.16-6.85)**	**<0.0001***	0.19 (0.13-0.29)	<0.0001*
	HT+VT allele	224 (70.00)	140 (35.00)	4.33 (3.16-5.93)	**<0.0001***	.4.41 (3.20-6.07)	<0.0001*
XPG His1104 Asp C3507G codon1104 Ex-15	C/C	204(63.75)	206 (51.50)	1		1	
	C/G	108 (33.75)	172 (43.00)	0.63 (0.46-0.86)	0.003	1.57 (1.12-2.18)	0.007
	G/G	8 (02.50)	22 (05.50)	0.36 (0.15-0.84)	0.01	3.0 (1.24-7.48)	0.01
	C/G+ G/G	116 (36.25)	194 (48.50)	0.60 (0.44-0.81)	0.001	0.61 (0.43-0.82)	0.002

*: Indicates significant Odds Ratio ($p<0.05$)
p value determined based on $\chi 2$

Table 4: Stratification analysis of the demographic factors including age, tobacco smoking and alcohol drinking and distribution of genotypes with odds ratio of the XPC & XPG genes in the patients with HNC and the control group from rural population of western Maharashtra.

Gene	Genotype	Demographic Factors							
		Age (Cases/Control)		Sex (Cases/Control)		Smoking status (Cases/Control)		Drinking status (Cases/Control)	
		≤ 50 N=106/147	> 50 N=214/253	Male N=200//261	Female N=120/139	Smokers N=249/80	Nonsmokers N=71/320	Drinkers N=220/50	Non-drinkers N=100/350
XPC A2920C Lys939Gln codon 939 Ex-15	A/A	56/86	114/136	110/138	60/84	133/43	37/179	115/24	55/198
	A/C+ C/C	50/61	100/117	90/123	60/55	116/37	34/1341	105/26	45/152
	OR (95% CI)	1.25 (0.16-2.68)	1.01 (0.76-1.46)	0.91 (0.63-1.32)	1.52 (0.93-2.50)	1.01 (0.61-1.67)	1.16 (0.69-1.96)	0.84 (0.45-1.55)	1.06 (0.68-1.66)
	P value	0.36	0.98	0.65	0.0.09	0.95	0.58	0.58	0.10
XPC Intron 11	WT allele	30/97	66/163	54/167	42/93	75/48	21/212	67/31	29/229
	HT/VT	75/50	148/60	146/94	78/46	174/32	50/108	153/19	71/121

C-A	allele								
	OR (95% CI)	4.91 (2.85-8.46)	6.09 (4.02-9.22)	4.80 (3.21-7.17)	3.75 (2.24-6.28)	3.48 (2.06-5.87)	4.67 (2.67-8.18)	3.72 (1.96-7.06)	4.63 (2.85-7.52)
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
XPG His1104 Asp C3507G codon1104 Ex-15	C/C	64/81	140/127	130/122	74/86	157/40	47/168	138/31	66/177
	C/G+ G/G	42/66	74/126	70/139	46/53	90/40	24/152	82/19	34/173
	OR (95% CI)	0.80 (0.48-1.33)	0.53 (0.36-0.77)	0.47 (0.32-0.69)	1.00 (0.61-1.66)	0.58 0.35-0.97)	0.56 (0.32-0.96)	0.96 (0.51-1.82)	0.52 (0.33-0.83)
	P value	0.40	0.001	0.001	0.97	0.03	0.03	0.92	0.006

DISCUSSION

In the present study, we conducted a case-control study to investigate the association between polymorphisms in the XPC, XPG genes and the development of HNC in a Maharashtrian population, and we found that contribution of the XPC intron 11 variant to the development of oral cancer. Most of the reports indicate that *XPC* polymorphisms modulate the risk for lung, head and neck, breast and bladder cancer. We didn't observe that *XPC* Lys939Gln was associated with increased HNC risk but interestingly observed polymorphisms in intron 11 of XPC gene. Although some studies showed the *XPC* Lys939Gln polymorphism significantly elevated the human bladder cancer risk, a recent pooled data meta-analysis indicated that the *XPC* Lys939Gln polymorphism was not related to cancer risk (Stern et al 2009). A meta-analysis of 34 case-control studies by (Zhang et al 2008) showed *XPC* Lys939Gln allele C associated with lung, breast, bladder, colorectal, esophageal, and other cancer risks. Previous studies also have reported that XPG gene polymorphisms are associated with several kinds of cancer in different ethnicities, such as HNC, gastric, bladder, colon and prostate cancer. Ma et al. (2012) reported that XPG gene polymorphisms affect the risk of HNC in an American population. He et al. (2012) reported that genetic variants of XPG contribute to the risk of gastric cancer. Zhang et al. (2014) reported that the XPG polymorphism was significantly correlated with prostate cancer susceptibility in a Chinese population. Zhu et al. (2012) suggested that XPG variant genotypes were associated significantly with esophageal cancer risk in a Chinese population. However, Meta analysis by Liu et al. (2014) reported that the XPG polymorphism was not associated with bladder cancer risk. Also, Steck et al. (2014) did not find significant association between XPG gene polymorphisms and colon cancer risk. Meta-analysis conducted by Xu et al. (2014) suggested that the XPG polymorphism is not associated with breast cancer risk. Thus, several previous studies have reported the association between XPC and XPG gene polymorphisms and the development of different cancer, but the results are inconclusive.

However, no information is available on the association of polymorphisms of NER pathway genes including XPC and XPG and their susceptibility to oral cancer from rural population of Maharashtra where the rate of tobacco and alcohol consumption is very high. Therefore in this study, we determined the relationship between the development of HNC and genetic polymorphisms in XPC & XPG genes from a pool of unexplored rural Maharashtrian population. Such genotyping analysis of NER pathway genes will enhance our ability to identify those individuals most susceptible to head & neck carcinogenesis in the rural Indian population.

CONCLUSION

The study suggests that functional XPC or polymorphisms could play an important role in the development of HNC in a Maharashtrian population. Thus this analysis of correlation of DNA repair genes and HNC may provide a deeper insight into the genetic and environment factors to cancer risk in the rural unexplored population but larger scale studies, including more detailed environmental exposure status and more detailed patient clinical information, are needed to verify these findings.

Conflict of Interest: None declared

Ethical approval: The study protocol was approved by the Institutional Ethics Committee of Krishna Institute of Medical Sciences for the use of human subjects in research

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