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RESEARCH

Genetic Variations in *XRCC1* Gene in Sporadic Head and Neck Cancer (HNC) Patients

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Abstract DNA repair gene polymorphisms have been implicated as susceptibility factors in cancer development. It is possible that DNA repair polymorphisms may also influence the risk of gene mutation. Polymorphisms in the DNA repair gene *XRCC1* have been indicated to have a contributive role in DNA adduct formation and an increased risk of cancer development. 300 head and neck cancer patients and 150 controls were included in this study. PCR-single-strand conformation polymorphism and DNA sequencing were used to analyze the whole exonic region of *XRCC1* in head and neck cancer patients. Sequence analysis revealed two missense and two silent mutations in our study. Frequency of silent mutations; Pro206Pro (rs915927) and Gln632Gln (rs3547) was calculated as 0.16 (16 %) and 0.30 (30 %) respectively. Whereas, the frequency of missense mutations; Arg399Gln (rs25487) and Tyr576Asn (rs2307177) was calculated as 0.27 (27 %) and 0.28 (28 %) respectively. In our study, incidence of these mutations was found higher in larynx cancer ($p<0.005$) as compared to oral cavity and pharynx cancer. Our finding suggests that the polymorphic *XRCC1* gene may contribute to risk of developing head and neck cancer. To our knowledge, this is the first report that *XRCC1* is associated with increased risk of head and neck cancer in a Pakistani population.

Keywords HNC · SSCP · DNA · Carcinogenesis · Mutational analysis · *XRCC1*

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Introduction

Head and neck cancer (HNC) includes the cancers of oral cavity, pharynx and larynx. It represents the sixth most common cancer in the world [1]. Head and neck carcinogenesis is associated with abnormalities in DNA repair, apoptosis, carcinogen metabolism and cell-cycle control [2]. This is one of the best models to investigate the relationship between gene and environment in base excision repair pathway [3]. Tobacco and alcohol consumptions are the main etiological factors in head and neck carcinogenesis [4]. Human papillomavirus (HPV) has also been described as an important etiologic factor in HNC. HPV infections have been found associated with a 3–6 fold increase in oropharyngeal carcinoma risk [5]. Earlier studies have shown that genetic susceptibility also plays an important role in the risk of developing this disease [6]. In Pakistan the situation seems alarmingly high [7] and head and neck cancer (HNC) has been ranked second in both genders showing similar rates in both sexes [7].

Base excision repair (BER) is the primary guardian pathway against damage that results from cellular metabolism, including reactive oxygen species, methylation, deamination and hydroxylation. Therefore, base excision repair is a universal event in cells and is relevant for preventing mutagenesis [8]. *XRCC1* protein is a key factor in the DNA base excision repair (BER) and single strand repair (SSBR) pathways [9, 10].

Association of *XRCC1* polymorphisms with different cancer types has been investigated, such as lung [11, 12], breast [13, 14], gastric [15], colon [16], head and neck [17], esophageal [18] and bladder cancer [19, 20]. Since HPV infection is considered an important etiologic factor in pathogenesis of different cancers including HNC, its association

has been studied in relation to XRCC1 polymorphisms. Majumder *et al* (2009) analyzed the interaction between the HPV infection and *XRCC1* polymorphisms in context of oral cancer. XRCC1 polymorphisms did not show association with the risk of the oral cancer in HPV-infected samples [21]. Several studies have observed that the contribution of XRCC1 polymorphisms to the development of oral cancer [21] and cervical cancer [22] may be concealed by HPV infection. Single nucleotide polymorphisms (SNP) in *XRCC1* have been found associated with head and neck cancer risk but the findings have been inconsistent in different populations [23]. Based on a study of selected genes and SNPs, it has been concluded that *XRCC1* may be important in head and neck carcinogenesis [17].

To date, the *XRCC1* polymorphic system and cancer susceptibility have been investigated in Caucasian, Asian and African populations, but no study has been reported for a Pakistani population with reference to HNC. In the present study, we performed a comprehensive analysis of all potentially hot spot and novel single nucleotide polymorphisms in *XRCC1* to investigate its association with head and neck cancer in a Pakistani population.

Materials and Methods

The present study was conducted with a prior approval from ethical committees of both COMSATS Institute of Information Technology Islamabad (CIIT) and hospitals. A total of 300 patients with histologically confirmed head and neck cancer were recruited from National Oncology and Radiotherapy Institute (NORI), Pakistan Institute of Medical Sciences (PIMS) and Military Hospital (MH). A total of 150 age, gender and ethnicity matched and cancer free healthy individuals were selected as controls. The inclusion criterion for the controls was absence of prior history of cancer or pre-cancerous lesions. Patients and controls suffering from any other familial disease (diabetes, blood pressure and cardiovascular impairment) were excluded from this study. After obtaining informed consent, all individuals were personally interviewed using the specifically designed questionnaire. Information on age, gender, ethnic group and detailed exposure data on smoking was recorded. This study has included three types of tobacco use which are paan, naswar and cigarettes. As intake of these agents varies from individuals to individuals, a broad definition of smoking was introduced here.

DNA Extraction and Polymerase Chain Reaction (PCR)

DNA was extracted from white blood cells, using standard phenol-chloroform extraction method [24] and stored at -20 °C for further processing. Human *XRCC1* exon sequence was taken from Ensembl. Primers were designed by using primer 3 software, and checked for specific amplification by using BLAST. Whole coding region and their exon intron boundaries of approximately 60 bp sequence of *XRCC1* were investigated to identify the novel and any splice site variation in parallel to previously reported mutations. Each PCR reaction was performed in a 20 μl reaction mixture containing approximately 20 ng of genomic DNA templates, 2 μl (10 mM) of each primer, 0.24 μl (25 mM) of dNTP, 2 μl (10x) PCR buffer and 0.2 μl (5u/μl) of Taq polymerase. PCR profile consisted of an initial melting step of 94 °C for 5 min, 35 cycles of 94 °C for 45 s, annealing temperature for 1 min and 72 °C for 1 min and a final extension step of 72 °C for 10 min and hold at 4 °C. PCR products were electrophoresed on a 2 % agarose gel and stained with ethidium bromide.

Mutational Screening, Sequencing and Data Analysis

Single stranded conformational polymorphism (SSCP) was used for the mutational analysis of the PCR products. Samples, displaying an altered electrophoretic mobility were reamplified in another reaction and were analyzed by direct sequencing to confirm and characterize the nature of mutations. Sequencing was carried out by Macrogen (Korea). Control (normal) samples were also sequenced along with cases to check the quality of sequencing. $\chi 2$-test and Fisher exact test were used to evaluate the differences in selected demographic variables, family history and smoking history by using the Graph Pad Prism 5 Demo and SPSS.

Results

The observed mean age of patients and controls is 38 (±16.35) and 35 (±32.23) years respectively. A significantly higher difference was observed in case of family history in cancer patients ($p<0.002$) when compared with controls (Table 1).

Germline Mutation Detection

All 17 exons of *XRCC1* were analyzed successfully for germline mutations. The combination of SSCP and sequence analysis revealed two silent mutations Pro206Pro and Gln632Gln in exon 7 and 17 respectively. In addition two missense mutations Arg399Gln and Tyr576Asn were also observed in exon 10 and exon 16 respectively. The overall frequency of these mutations was found 87 % (missense mutations 55 % and silent mutations 45 %, OR= 35.96, 95 % CI=24.18–53.49). No SNPs and splice site mutations were found in remaining exons (1, 2, 3, 4, 6, 8, 9, 11, 12, 13, 14, and 15) after sequencing.

Table 1 Demographic characteristics in Pakistani case–control study

Variables	Cancer cases[c]	Control[d]	p value	OR (95%CI)
1. Age (years)				
Mean (±S.D.)	38 (±16.35)	35 (±32.23)	0.86[a]	
<40	210 (70 %)	99 (66 %)	0.39[a]	0.83 (0.55-1.26)
>40	90 (30 %)	51 (34 %)		
2. Gender				
Male	152 (51 %)	78 (52 %)	0.84[a]	1.05 (0.71-1.56)
Female	148 (49 %)	72 (48 %)		
3. Family history				
Yes	25 (8.0 %)[e]	2 (1.0 %)[f]	<0.002[b]	0.15 (0.035-0.64)
No	275 (92 %)[e]	148 (99 %)[f]		
4. Smoking history[g]				
Never	171(57 %)	80 (53 %)	0.48[a]	0.86 (0.58-1.27)
<40	25(8.0 %)	18 (12 %)		
41-60	69(23 %)	37 (25 %)		
61-80	35(12 %0	15 (10 %)		

[a] For $\chi 2$ –Test

[b] For Fisher exact test

[c] Total number of cases 300

[d] Total number of control 150

[e] Family history of cancer patients

[f] Family history of controls

[g] Chewing tobacco, naswar, paan and cigarettes

Types of Germline Mutation

In case of silent mutations, [Pro206Pro (rs915927)] substitution of A→G was observed in 42 patients on exon 7, whereas no controls showed this mutation. In addition to this, a second silent mutation Gln632Gln (A to G transition, rs3547) was observed in exon 17 in 78 patients which was absent in controls. Two missense mutations (Arg399Gln and Tyr576Asn) were also observed. Arg399Gln (rs25487, exon 10) was observed in a total of 70 patients and Tyr576Asn (rs2307177, exon 16) in 72 patients. No missense mutation or silent mutation was observed in controls. Frequency of silent mutations,

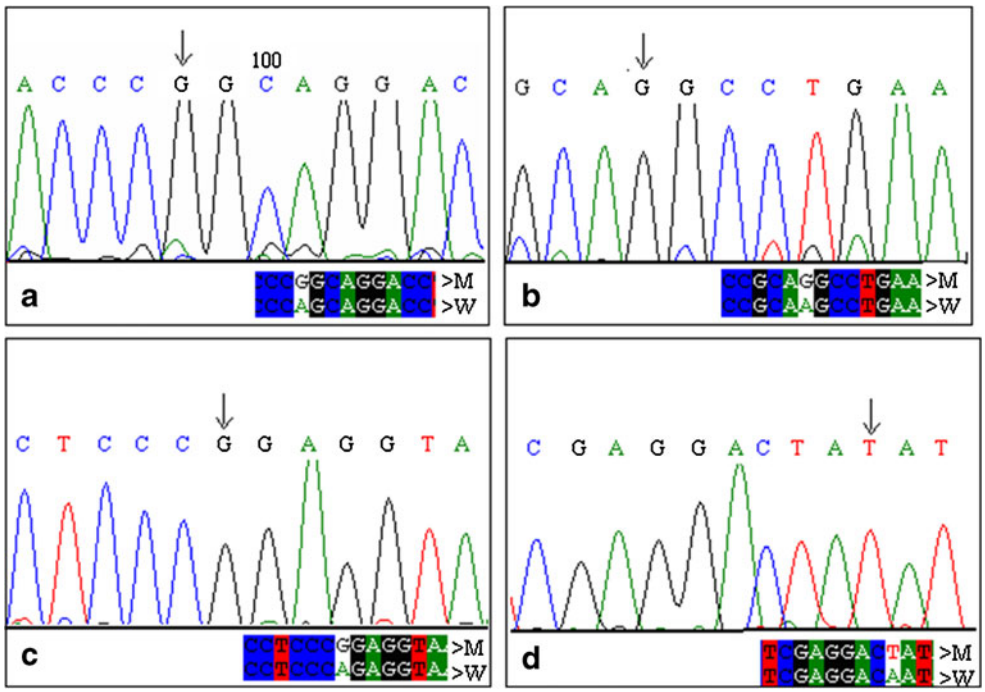

Fig. 1 Sequencing electropherogram of silent and missense mutations (**a**) Silent mutation, Pro206Pro (rs915927) on exon 7 showing A to G substitution resulting in change of DNA sequences from CCA to CCG encoding the same amino acid proline. (**b**) Silent mutation, Gln632Gln (rs3547) on exon 17 showing A to G substitution resulting in change of DNA sequence from CAA to CAG encoding the same amino acid glutamine. (**c**) Missense mutation, Arg399Gln (rs25487) on exon 10 showing A to G substitution resulting in change of DNA sequence from CAG to CGG encoding the amino acid arginine instead of glutamine. (**d**) Missense mutation, Tyr576Asn (rs2307177) on exon 16 showing A to T substitution changing the DNA sequence from AAT to TAT encoding the amino acid tyrosine, (M) variant sequence and (W) wild type sequence

Pro206Pro (rs915927) and Gln632Gln (rs3547) was 0.16 (16 %) and 0.30 (30 %), respectively. While the frequency of missense mutation was 0.27 (27 %) for Arg399Gln (rs25487) and 0.28 (28 %) for Tyr576Asn (rs2307177) (Fig. 1, Table 2).

Association of Germline Mutations with Other Parameters

In case of frequency of silent and missense mutations, no statistically significant difference in frequency of Pro206Pro was observed in males when compared with females ($p<0.66$). Similar trend was observed in smoking status ($p=0.04$). This A to G substitution is significantly higher in the patients with age group >40 years ($p<0.005$) when compared with patients of age group <40 years.

Gln632Gln silent mutation was found equally distributed in males and females ($p=1.00$) and smokers and non smokers ($p=1.00$). Similar trend was observed in age-groups ($p=1.00$). Arg399Gln missense mutation was observed significantly higher in the patients below the age of 40 years ($p<0.03$) and non-smokers ($p<0.015$). No statistically significant ($p=0.4$) difference in the frequency of A to G substitution was observed in case of gender (Table 2).

A significantly higher frequency of Tyr576Asn was observed in patients with age <40 years ($p<0.005$) compared with patients above 40 years. The difference in the frequency of this missense mutation was statistically non-significant ($P=0.8$ and $P=0.12$) for gender and smoking status as shown in Table 2.

Area of Cancer

As presented in Table 2, the association of mutations Pro206-Pro and Gln632Gln was found non-significant ($P=0.2$ and $P=0.3$) for different areas of HNC. However, significantly higher incidence of Arg399Gln and Tyr576Asn mutation was observed in the patients of larynx cancer when compared to patients of oral cavity and pharynx cancer ($p<0.001$).

Discussion

Among the identified four mutations from this study, three mutations Pro206Pro, Gln632Gln and Arg399Gln has extensively been studied in relation to different populations worldwide [25]. However, the role of Tyr576Asn has not been explored with reference to HNC [12]. Since these mutations were not detected in 150 healthy controls, these are likely to play a contributory role in cancer.

Our findings suggest that *XRCC1* Pro206Pro and Gln632Gln may contribute to genetic susceptibility of HNC cancer in a Pakistani population. *XRCC1* Pro206Pro on exon 7

Table 2 Frequency of silent, missense mutations and risk of Head and neck cancer

	Silent mutation, Pro206Pro(rs915927)	Silent mutation, Gln632Gln(rs3547)	Missense mutation, Arg399Gln (rs25487)	Missense mutation, Tyr576Asn(rs2307177)
Total patients	42	78	70	72
Allele Freq	A0.84, G0.16	A0.70, G0.30	A0.73, G0.27	A0.72,T0.28
Allele Freq [c] (Asian pop. HapMap pro)	A0.90, G0.10	ND	A0.274, G0.726	ND
OR(95%CI)	5.21(2.66-10.21)	6.11(3.64-10.25)	5.88(3.43-10.10)	5.94(3.48-10.13)
Gender				
Male	24(57 %), 0.66[a]	38(49 %), 1.00[a]	30(43 %), 0.4[a]	38(53 %), 0.8[a]
Female	18(43 %)	40(51 %)	40(57 %)	34(47 %)
Age				
<40	8(19 %),<0.005 [a]	40(51 %),1.00[a]	48(69 %), <0.03 [a]	53(74 %), <0.005 [a]
>40	34(81 %)	38(49 %)	22(31 %)	19 (26 %)
Smoking history				
History	31(74 %),<0.04 [a]	38(49 %),1.00 [a]	20(29 %), <0.015 [a]	26(36 %), 0.12[a]
No history	11(26 %)	40(51 %)	50 (71 %)	46(64 %)
Area of cancer				
Oral Cavity	13(31 %), 0.2 [a]	24(31 %),0.3 [a]	20(29 %), <0.0001 [a]	30(42 %),<0.001 [a]
Pharynx	8(19 %)	20(25 %)	6 (8 %)	6 (8 %)
Larynx	21(50 %)	34(44 %)	44 (63 %)	36(50 %)

ND not determined

[a] p value for $\chi 2$ –Test

[b] p value for Fisher exact test

[c] http://www.ncbi.nlm.nih.gov/SNP/ [27]

and Gln632Gln on exon 17 lie in regions of the human genome that are highly conserved with the mouse *XRCC1* gene [23]. The role of these mutations is yet to be explored; however these silent mutations can affect the timing of cotranslational folding and consequently function [23].

The other two observed missense mutations Arg399Gln and Tyr576Asn are equally present in male and female patients although higher in non smokers with larynx cancer. Arg399Gln is most extensively studied variant which falls within the BRCT 1 domain and changes the large, basic Arginine to a medium sized, polar Glutamine, resulting in destabilization of protein [24]. R399Q results in an increase in chromosomal deletions and this deletion would facilitate genetic instability and increase the risk of mutations observed in all type of cancers including head and neck cancer [26]. Tyr576Asn (rs2307177), a missense mutation is first time reported in association with head and neck cancer in this study.

Frequency of silent mutation observed in our study is 0.16 for Pro206Pro and 0.30 for Gln632Gln. There are only few studies in literature available concerning *XRCC1* Pro206Pro and Gln632Gln [20]. Frequency of SNPs in general population of Pakistan in context to this gene is not available up to best of author s' knowledge. The SNP frequency of Pro206-Pro has been reported as 0.15 in North Chinese population for lung cancer [25], 0.11 in cancer free Japanese population [27]. The frequency of Gln632Gln has been reported as 0.10 in Northern Chinese population for lung cancer [25] and 0.296 in cancer free Canadian population [27].

In current study the observed frequency of Arg399Gln is 0.27. This is higher than the frequency of same mutation reported in African American population for lungs cancer (0.169) [28], in Chinese population for nasopharyngeal cancer (0.25) [29], in Egyptian population for colorectal cancer (0.14) [30], in Korean population for lung cancer (0.22) [31] and in Chinese population for prostate cancer (0.20) [32]. Similar frequency was reported in Chinese population for gastric cancer (0.27) [33] and in Taiwan population for colorectal cancer (0.27) [34].

Frequency of Tyr576Asn in the present study is 0.28. There is no reported frequency of Tyr576Asn in relation to cancer or any other disease.

This study has the limitation that data included in this study were collected from only two main provinces of Pakistan due to accessibility limitations. Data collection from other provinces of the Pakistan, to build a substantially large study cohort, will be more helpful for studying the genomic instability in HNC.

In future studies, involvement of XRCC1 gene in HNC pathogenesis is planned to be extended further from germline screening to somatic mutations and expressional profiling both at transcript and translational levels. Epigenetic analysis of this gene including methylation of XRCC1 promoter region is also an interesting domain which will be explored in future studies.

Here we report the significant presence of Pro206Pro, Gln632Gln, Tyr576Asn and Arg399Gln genetic changes in head and neck cancer patients. The data suggests that a combination of silent mutations and missense mutations, or another mutation linked to it in the same gene or gene in vicinity, could conceivably play a role in the process of developing HNC cancer in a Pakistani population.

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