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Original Research

Are XPD and XPG gene variants related to the mechanism of oral squamous cell carcinoma?

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Abstract: Oral cavity cancers have anatomically a big part of the body system and include several types of cancer. The aim of the study is to investigate the relation between XPG and XPD gene variants in the DNA repair system and oral squamous cell cancers. A total of 111 patients with a pathologic diagnosis of oral squamous cell carcinoma and a control group of 148 healthy volunteers who presented to Istanbul Faculty of Medicine, Department of Otolaryngology & Head and Neck Surgery and Dentistry Faculty were included in the study. Isolation of DNA was achieved using an Invitrogen Purelink Genomic DNA Kit. XPD alleles of Lys751Gln (rs13181) and XPG Asp1104His (rs17655) loci from genomic DNA samples were reproduced using polymerase chain reaction. A statistically significant difference in XPD genotype distribution between control and patient groups was determined (P=0.019). XPD Lys+ was significantly more common in the patient group than in the control group, and a two-fold increased risk for disease was determined. XPD Gln/Gln+ was significantly more common in the control group than in the patient group, and a two-fold decrease in risk for disease was determined (P=0.045). In the other region of the study, there was no statistically significant difference in terms of disease development between XPG genotypes. In conclusion, Lys751Gln polymorphism in the XPD gene could play a role in oral squamous cell development. It is important to increase the numbers of subjects in patient groups and healthy controls in studies to increase the possibility of determining XPD's potential as a molecular risk factor.

Key words: Oral squamous cell cancer; XPG; XPD; DNA repair; PCR-RFLP.

Introduction

Oral cavity tumors are the 6th most commonly encountered cancers worldwide, constituting 2-4% of all cancers (1-5). The World Health Organization (WHO) classified oral cavity squamous cell carcinoma as a preventable cancer (6), which prompted further investigations into subjects such as early diagnosis methods and response to therapy; radiation, ultraviolet rays, and X-rays; exposure to chemicals and environmental agents; and existence of free radicals produced as by-products of metabolism that can be effective in cancer growth by causing DNA injury and triggering genomic instabilities, replication errors, mutation, and cell death. Independent from the cause of disease, the diagnosis and treatment of these cancers are some of the most important aspects of human health. Alternative treatment methods should be investigated due to delays in diagnosis and low success rates in therapy.

Oral cavity cancers are classified as epidermoid carcinomas, salivary gland carcinomas, lymphomas, sarcomas, melanomas, metastatic tumors, and multiple myelomas (7). Squamous cell carcinoma is the most commonly encountered subtype of epidermoid carcinoma seen in the oral squamous epithelia, which is characterized by malignant and localized growth, and high potential for metastasis (7, 8). A dramatic rate of exposure to carcinogens, mainly tobacco and alcohol, has been determined in up to 90% of head and neck cancers, including oral cavity cancers (7-24). Further investigations of the carcinogens in tobacco has established that they affect and subsequently change oncogenes and tumor suppressor genes and their functions, and hence trigger cancer growth (25, 26).

Cancer is the leading disease associated with failures in damage repair and blocking cell division. DNA repair mechanisms attempt to repair damage caused by endogenous and/or exogenous causes. Defects in these mechanisms and uncorrected mistakes can lead to genomic instability, and thus accelerate the cancer process. There are 6 main DNA repair mechanisms known in cells. Nucleotide excision and repair (NER) is one such DNA repair mechanism, which repairs damage to cyclobutane pyrimidine dimers caused by ultraviolet rays. The XPG gene, one of the genes that works in the NER mechanism, is located in the 19q22-q33 region of the chromosome, consists of 15 exons, and is approximately 32 kilobases (kb) (27, 28). The other gene, the XPD

gene, is located in the 19q13.3 region of the chromosome, consists of 23 exons, and it is approximately 19 kb (29, 30).

In our study, we aimed to find the roles of XPG and XPD gene polymorphisms in oral squamous cell carcinoma formation.

Materials and Methods

Samples

A total of 111 patients with a pathologic diagnosis of oral squamous cell carcinoma and a control group of 148 healthy volunteers who presented to Istanbul Faculty of Medicine, Department of Otolaryngology & Head and Neck Surgery and Dentistry Faculty, were included in the study.

Ethics committee approval was granted by Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee, and written informed consent was obtained taken from each subject included in the study.

Isolation of DNA and PCR Protocols

Isolation of DNA was achieved using an Invitrogen Purelink Genomic DNA Kit. XPD alleles of Lys751Gln (rs13181) and XPG Asp1104His (rs17655) loci from genomic DNA samples were reproduced using polymerase chain reaction. The nucleotide series of the primers used for reproduction of the polymorphic region of the investigated genes and the protocol for PCR are listed in Table 1 and Figure 1-2. The collected products of XPD and XPG were cut using PstI and Hsp92 restriction enzymes and studied in 3% agarose gel using electrophoresis.

Statistical methods

Statistic analyses of the study data were performed using the SPSS 11.0 program. A value of $p<0.05$ was accepted as statistically significant. The frequency of variations of genotypes and alleles between the groups were compared by using the Chi-square and Fisher test. Student's t-test and ANOVA were used to determine the effects of the genotypes and alleles on activity.

Results

The demographic data of the study group are given in Table 2. There was no significant difference in age distribution between the control and study groups. However, there was a significant difference in tobacco use between the two groups (χ^2=27.12, P<0.001, OR=3,8, 95 CI%: (2.30-6.53)).

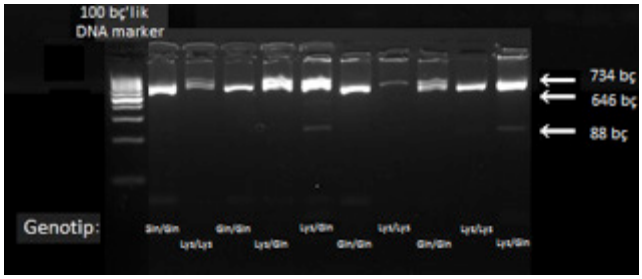

Figure 1. Gel view of XPD Lys751Gln polymorphism.

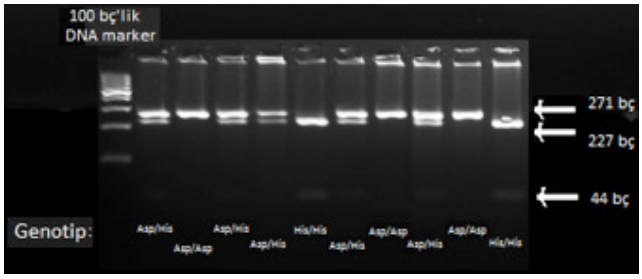

Figure 2. Gel view of XPG Asp1204His polymorphism.

There was no statistically significant difference in distribution of XPG genotype and alleles between the control and patient groups (Table 3).

A statistically significant difference in XPD genotype distribution between the control and patient groups was determined (P=0.019 ^{2}=7.94) (Table 4). XPD Lys+ was significantly more common in the patient group than in the control group, and a two-fold increase in risk for disease was determined (P=0.045, χ^2=4.02, OR=2.12, 95% CI: (1.00-4.47). XPD Gln/Gln+ was significantly more common in the control group than in the patient group, and a two-fold decrease in risk for disease was determined (P=0.045, χ^2=4.02, OR=0.47, 95% CI: (0.22-0.99)).

XPD Lys/Gln was significantly more common in the patient group than in the control group (61.31% vs. 44.6%, respectively), and a 1.9-fold increase in risk for disease was determined (P=0.008, χ^2=7.05, OR=1.96, 95% CI: (1.19-3.2)).

There was no statistically significant difference between XPG genotypes and stage and differentiation of disease and tumor size (Table 5). However, advanced stage disease was approximately 1.9 times

Table 1. Primer sequences of reproduced polymorphic region and PCR Protocols.

Gene Parts	Primers	PCR Protocols
XPD Lys751Gln rs13181	Forward primer: 5'-CCTCTCCCTTTCCTCTGTTC-3' Backward primer: 5'-CAGGTGAGGGGGGACATCT-3'	95° C→5 minutes 94° C→1 minutes 60° C→1 minutes 72° C→ 1 minutes 72° C→ 10 minutes Cycle: 35
XPG Asp1104His rs17655	Forward primer: 5'-GACCTGCCTCTCAGAATCATC-3' Backward primer: 5'-CCTCGCACGTCTTAGTTTCC-3'	95° C→5 minutes 94° C→1 minutes 62° C→1 minutes 72° C→ 1 minutes 72° C→ 10 minutes Cycle: 35

Table 2. Demographic data of the study group.

	CONTROL n=148	OSCC n=111	p
Age	56.37±12.86	56.24±13.61	0.938
Sex (Female/Male)	70/78	43/68	0.169
Tobacco use (Positive/Negative %)	70.3/29.7	37.8/62.2	<0.001
Alcohol consumption (Positive/Negative %)		71.2/28.8	
Cigarettes smoked per day (%)			
≤20		52.9	
>20		47.1	
Duration of smoking (%)			
≤20 years		30.9	
>20 years		69.1	
Duration of alcohol consumption (%)			
≤20 years		35.0	
>20 years		65.0	
Oral hygiene (Positive/Negative%)		58.6/41.4	
Mechanical trauma (Positive/Negative%)		58.6/41.4	
Lymph node metastasis			
Negative		62.3	
≤3cm		17.0	
3-6 cm		20.8	
Tumor size (%)			
<4cm		67.5	
≥4 cm		32.5	
Location of the Tumor			
Oral tongue		50.0	
Lip		9.4	
Floor of Mouth		12.3	
Gingiva alveolar crest		13.2	
Retromolar trigon		7.5	
Hard palate		3.8	
Buccal		3.8	
Stage (%)			
Early		42.5	
Advanced		57.5	
Stage			
T1N0M0:		21.7	
T2N0M0:		20.8	
T3N0M0, T1-3N1M0:		23.6	
T4N0-1M0,T0-4N2M0, T0-4N3M0,T0-4N0-3M:		34.0	
Differentiation			
Good		28.6	
Intermediate		61.0	
Poor		10.5	
Keratinization (Positive/Negative %)		28.8/71.2	

Table 3. XPG genotype distribution in control and patient groups.

XPG	CONTROL n=148		PATIENT n=111		P
GENOTYPES	n	%	n	%	
Asp/Asp	80	54.1	60	54.1	0.934
His/His	11	7.4	7	6.3	
Asp/His	57	38.5	44	39.6	
ALLELES					
Asp	217	73.31	164	73.87	0.885
His	79	26.68	58	26.12	

Table 4. XPD genotype distribution in the control and patient group.

XPD	CONTROL n=148		PATIENT n=111		P
GENOTYPES	n	%	n	%	
Lys/Lys	54	36.5	32	28.8	0.019
Gln/Gln	28	18.9	11	9.9	
Lys/Gln	66	44.6	68	61.3	
ALLELES					
Asp	174	58.78	132	59.45	0.877
Glu	122	41.21	90	40.54	

Table 5. Relations of XPG genotype differentiation of the disease and tumor size.

STAGE	EARLY STAGE GRADE 1-2 %	ADVANCED STAGE GRADE 3-4 %
Asp/Asp	44.8	55.2
His/His	28.6	71.4
Asp/His	41.5	58.5
DIFFERENTIATION	**POOR**	**GOOD**
Asp/Asp	9.1	90.9
His/His	14.3	85.7
Asp/His	12.9	87.1
TUMOR SIZE	**<4 cm**	**≥4 cm**
Asp/Asp	65.9	34.1
His/His	57.1	42.9
Asp/His	71.9	28.1

Table 6. Relation between XPD genotypes and stage, differentiation and tumor size.

STAGE	EARLY STAGE GRADE 1-2 %	ADVANCED STAGE GRADE 3-4 %
Lys/Lys	35.5	64.5
Gln/Gln	30.0	70.0
Lys/Gln	47.7	52.3
DIFFERENTIATION	**POOR**	**GOOD**
Lys/Lys	4.2	95.8
Gln/Gln	10.0	90.0
Lys/Gln	14.6	85.4
TUMOR SIZE	**<4 cm**	**≥4 cm**
Lys/Lys	60.0	40.0
Gln/Gln	80.0	20.0
Lys/Gln	68.0	31.0

more frequent in individuals with the His/His genotype (P=0.44, OR=1.92, 95% CI: (0.35-10.37)). Furthermore, tumors sized ≥4 cm were approximately 1.6 times more frequent in individuals with the His/His genotype (P=0.54, OR=1.62, 95% CI: (0.33-7.83)).

There was no statistically significant differences between XPD genotypes and stage of disease, differentiation, and tumor size (Table 6). However, individuals with the Lys/Lys genotype had a 1.5-fold greater risk for advanced stage disease (P=0.35, OR=1.50, 95% CI: (0.63-3.58)); a 3.6-fold greater tendency for good differentiation (P=0.20, OR=3.68, 95% CI: (0.43-31.17)), and a 1.6-fold greater risk for tumors ≥4 cm (P=0.34, OR=1.60, 95% CI: (0.60-4.28)). Also, tumors sized ≥4 cm were observed approximately 2 times more frequently in individuals with the Lys+ genotype (P=0.36, OR=2.08, 95% CI: (0.41-10.56))

In individuals with the Gln/Gln genotype, the frequency of tumors sized ≥4 cm was found approximately 2 times less (P=0.36, OR=0.48, 95% CI: (0.09-2.43)).

Discussion

Deficiencies and loss of DNA repair mechanisms may increase the risk for disease (29, 31). In recent studies that researched the relation between cancer and DNA repair gene polymorphisms, an association between repair gene polymorphisms was discovered. These polymorphisms can trigger diseases by changing the capacity of DNA repair, causing genetic instabilities, and causing defects in protein activity (32,33). Using this knowledge, the role of DNA repair genes such as XPG and XPD in the carcinogenesis of oral squamous cell carcinoma, which accounts for the majority of oral cavity carcinomas, was studied for the first time in the literature.

In our study, we found a statistically significant difference in XPD genotype distribution between the control and patient groups. We also found statistically significantly high ratios of XPD Lys+ and Lys/Gln genotypes in the patient group, and an increase in risk for disease in individuals with this polymorphism. The XPG gene

is a DNA helicase that works in the 5'-3' direction, which plays a role in nucleotide excision repair of damage due to chemical carcinogens such as polycyclic aromatic hydrocarbons, aromatic amines and N-nitrose; it is thought that polymorphisms of this gene can cause decreased transcription and thus decrease DNA repair capacity (29, 30, 34).

In a study of the healthy population by Salah et al., an interaction in codon 751 XPD substrate was shown, which led to the belief that any changes in this substrate residue could cause changes in function thereby decreasing DNA repair capacity. In the same study, a T-G polymorphism of the XPD gene that caused changes in the configuration of coded proteins, and an interaction between the helicase activator p44 protein of TFIIH complex, a local change at the C-terminal end domain of Lysine (K) at codon 751 to Glutamine (Q), that caused changes in the ATP-binding part of the XPD were observed. These results show the harmful effects of the Lys751>Gln polymorphism and association with cancer risk (30, 35). Relevant to literature, in our thesis study, an increased risk for oral squamous cell carcinoma in individuals with XPD Lys+ and XPD Lys/Gln was observed.

In a study by Bau et al. on the XPA and XPD DNA repair mechanism genes in a Taiwanese population, no statistically significant relation between XPA A-23G and XPD Lys751Gln was found (36). It is known that DNA mechanisms can show changes with genetic and environmental factors, thus in our study it was observed that XPD Lys751Gln gene could be relevant in the Turkish population. Further studies with advanced analysis and larger subject groups are needed before these genes can be used as indicators of oral cancer risk factors in the Turkish population.

In a study by Kietthubthew et al. on oral squamous cell carcinoma and DNA repair genes in patients from Thailand, a positive risk between XRCC1, XRCC3, and XPD genes, and an inclination to disease was found (37). Wang et al. studied the effects of polymorphisms of DNA repair genes in patients with oral premalignant lesions, and changes in XPA (A23G), XPD (Lys751Gln), and XPC (Ala499Val) were found to be statistically significant (38). If premalignant lesions are not excised surgically, the risk of progression to oral cell squamous cell carcinoma is almost inevitable. Accordingly, taking Wang et al's study and our thesis together, further studies of XPD Lys751Gln must be supported.

In our study, there was no statistically significant difference in the XPG polymorphism between the patient and healthy groups in terms of genotypes and alleles. XPG is an endonuclease enzyme responsible for XP complementation group 64. It has two important roles in NER; it has a role in catalyzing the excision of 5 damaged nucleotides at the 3' end of DNA, and facilitates non-enzymatically in detaching the 5' end of DNA. Polymorphisms in the promoter area decrease transcription and thus decrease the capacity for DNA repair (27,28).

Our study is the first study to inquire about the effect of XPG and XPD gene polymorphisms on oral squamous cell carcinoma in the Turkish population; a potential increase in risk due to polymorphism was observed. It is thought that defects and changes in bases that code XPD, a very potent protein in DNA repair, play a role in disease development.

As a result, it is thought that the Lys751Gln polymorphism in the XPD gene contributes to the development of oral squamous cell carcinoma. It is important to increase the numbers of subjects in patient groups and healthy controls in studies to increase the possibility of determining XPD's potential as a molecular risk factor indicator, and to deepen our understanding of the molecular structure of oral squamous cell carcinoma.

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Interest conflicts
The authors declare that they have no conflict of interest.

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