

# Role of xpd gene in development of squamous cell carcinoma



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“ ROLE OF XPD GENE IN DEVELOPMENT OF SQUAMOUS CELL CARCINOMA OF HEAD AND NECK ”

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### **ABSTRACT**

In the present global health, cancer is emerging as the most dangerous death causing disease. Head and neck cancer has become one of the common ailments today and considered as a complex disease. Squamous cell carcinoma of head and neck accounts for 3.5% of all the registered cancer in Korea during 2001. It is the sixth most common cancer worldwide with approximately 48,010 new cases expected in United States during 2009.

The significance of DNA repair for moderating the cancer risk of humans originated from the observation that persons with skin cancer-susceptible disease xeroderma pigmentosum (XP) have defective nucleotide excision repair (NER). XP is a genetically complex disease that includes eight diverse complementation groups.

### **INTRODUCTION**

The vast majority of head and neck cancer are squamous cell carcinomas of the head and neck. It is the sixth most common and also the seventh leading cause of deaths due to cancer worldwide. Squamous cell carcinoma of the head and neck is a disease which includes cancers of the oral cavity, hypopharynx, oropharynx, and larynx. It represents a therapeutically challenging, behaviorally heterogeneous category of disease. Together environmental and genetic risk factors contribute to the etiology of head and

neck cancer, thus it is considered as a complex disease. Epidemiological studies have described that alcohol consumption and tobacco use are amongst the most known risk factors. Infection with high-risk types of human papilloma viruses (HPVs) has also been known as an increasingly important risk factor for HNC, especially for oropharyngeal squamous cell carcinoma. Another important risk factor for HNC is the family history of cancer, genetic factors may contribute to HNC susceptibility. It is associated with low survival and high morbidity when diagnosed in advanced stage, accounting for nearly 500, 000 newly diagnosed cancer cases per year. Epidemiological studies have shown that head and neck occurs through a complex multistage process that may involve exposure to a combination of carcinogens from cigarette smoking, tobacco chewing and alcohol consumption. Individuals differ widely in their capacity to repair DNA damage on exposure to exogenous sources like alcohol, tobacco smoke and to endogenous reactions involving oxidants. Previous case shows the control studies of several phenotypic and genotypic assays support hypothesis and concludes that genetic susceptibility or predisposition plays an important role in HNSC. It has been hypothesized that susceptibility to disease development is based on inherited differences in the DNA repair and cell cycle control, or a combination of these. The major research focus in the gene - environment interactions in relation to HNC has been involved on genes in repair enzymes for alcohol and tobacco smoke.

## **HEAD AND NECK SQUAMOUS CELL CARCINOMA: Diversity**

There is a remarkable diversity in the array of tumor morphologies and anatomy, including 10 anatomic sub-sites of the head and neck, which is a challenge for all members of the multidisciplinary researchers to define the extent of a patient's disease. While the majority pathology consists of squamous cell carcinoma (SCC), there are many other pathologic diagnoses. Accordingly, a wide range of advanced treatments are offered, mostly in combination, like radiation including Modulated Radiation Therapy, and surgery with or without reconstruction. Historically, the treating teams have to join the anatomic and morphologic considerations of a patient's disease to identify the treatment options.

Clinicians also need to consider set of issues, for molecular determinants of head and neck cancer. In this section we will see to highlight the spectrum of these targets mostly to impact clinical and patients in the upcoming year.

We will touch briefly on somatic aberrations that predispose to tumorigenesis, both genetic and epigenetic, as well and a number of specific cancer pathways as targets of tumorigenesis. We will consider the role of developing molecular diagnostics in the management of patient care. The likelihood of genetic liability due to the polymorphisms and phenotypic dissimilarities in the DNA repair enzymes or the metabolic enzymes that defend against the carcinogens in tobacco or alcohol have expected much attention in efforts to determine the causes of HNC. The greater frequency of SCCHN in the first-degree relations of HNC patients and the earliest onset of squamous cell carcinoma of head and neck in a subcategory of patients

gives support for such genetic liability. It shows that genetic changes in DNA repair ability and that are the result of genetic polymorphisms effect the risk of environmental carcinogenesis. The significance of DNA repair for moderating the cancer risk of humans originated from the observation that persons with skin cancer-susceptible human disease xerodermapigmentosum (XP) have defective nucleotide excision repair (NER). XP is a genetically complex disease that includes eight diverse complementation groups.

## **XPD GENE**

XPD protein is one of nine subunits that comprise transcription factor IIH (TFIIH), and TFIIH is a basal transcription aspect that participates in NER and transcription initiation. The role of TFIIH in NER is to open the impaired DNA to permit damage-specific nucleases to cut both sides of the damage site. XPD protein has single strand DNA-dependent ATPase and DNA helicase actions and this protein is to participate in DNA unwinding during nucleotide excision repair. Mutations in the XPD gene lead to repair and transcription defects. In adding to these point mutations, variations in the XPD sequence are initiated in general. These variants are called single nucleotide polymorphisms with a highly variable frequency above 1%. 17 polymorphisms in the XPD recognized, and it is supposed that certain XPD polymorphisms may be associated with the susceptibility to increasing cancer. Polymorphisms in the XPD gene have been studied in relation to the risk for head and neck cancer or lung cancer. Sturgis et al. reported that the XPD +35931A> C and A SNPs are associated with a slightly increased risk of head and neck cancer. In a study on larynx, oral cavity and lung cancer,

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Buch et al. reported that XPD +23591G> A and XPD +35931A> C SNPs are associated with a statistically significant increased risk of HNC. However, in another study, the variant genotype of XPD showed no association with the risk of head and neck cancer. Similar contradictory results have been reported by studies on lung cancer. No genetic study of XPD polymorphism has been HNC performed in a sample of the Korean population. In this study, we investigated frequencies of XPD SNPs in the SCCHN patients and controls in a sample of the Korean population.

## **RISK FACTORS FOR DEVELOPMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA**

The most well known risk factor for developing head and neck cancer is the deleterious effects of tobacco. HNSCC was one of the first carcinomas to be linked with p53 mutations initiated by tobacco usage. Use is synergistic in causing HNSCC. There are other cultural habit-forming risk factors that have a relationship with HNSCC. Betel nut, a fruit that is the basic component of a stimulant chew, is used by an estimated 200 to 400 million throughout South-east Asia. Betel nut in Asian medicines is used to treat a variety of complaints from headaches to rheumatism. The odds ratio of emerging leukoplakia and sub mucous fibrosis using betel nut is five compared to one in non-chewers. The duration and frequency of betel nut use increases the risk of developing cancer signifying a dose-response relation. Tobacco smoke is associated with structural changes in DNA, particularly those induced by oxidative damage. Damage induced by BDPE and other such carcinogens can be repaired through the nucleotide excision repair system (NER). Along with the NER the base excision repair system is another set of multi-step

enzymatic complexes involved in the repair of nonspecific DNA damage, containing gamma and ultraviolet radiation, cross linking. So, individual variations in NER/BER are one of the factors that may influence tobacco smoking related cancer risks like HNSCC. Interestingly, several studies have demonstrated that sequence variations in NER/BER genes contribute to HNSCC susceptibility. The ERCC1 gene product is a key enzyme in the NER system, and one particular polymorphism at the ERCC1 gene may affect its mRNA constancy, resulting in impaired DNA repair capacity. Two single nucleotide polymorphisms (SNPs) in the XPD gene also part of the NER cascade been linked with suboptimal DNA repair capacity.

## **MARIJUANA**

Marijuana is the most frequently used illegal drug in the United States and the second most generally smoked substance after tobacco[17]. Habitual marijuana smoking exhibits with similar signs and symptoms associated with chronic tobacco use[18, 19]. Also, the carcinogenic properties of marijuana smoke are similar to those of tobacco and numerous studies parallel the usage of cannabinoids to cancer development[. Marijuana has been presented to induce cytogenic changes containing of chromosomal breaks, deletions, and translocations in mammalian cells in vivo. Recently, there was not enough confirmation to suggest a causative relation with oropharyngeal HNSCC especially those caused by tobacco use. 24 However, HNSCC caused by human papilloma virus (HPV) may be associated with tobacco use.

## **CAUSES**

Squamous cell carcinoma is believed to be induced by environmental

carcinogens. Tobacco smoking and alcohol consumption are accepted as <https://assignbuster.com/role-of-xpd-gene-in-development-of-squamous-cell-carcinoma/>

major risk factor. The possibility of genetic susceptibility due to the polymorphism and phenotypic variation in the DNA repair enzymes and the metabolic enzymes that defend against the carcinogen in tobacco or alcohol.

## **STUDY POPULATION**

This case-control study was executed at the Department of Otolaryngology-Head and Neck Surgery, Hanyang University Hospital, Seoul, Korea, from 1997 to 2004. The patient group contained 290 pathologically verified; there were 148 cases of larynx cancer, 56 cases of oral cancer, 42 cases of oropharynx cancer, and four cases of cancer. The control group consisted of 358 patients with chronicotitis media, chronic sinusitis or chronic tonsillitis, and had no past of previous malignant disease. The patient group contained 252 males and 38 females with a mean age range, 28 to 90 yr), and the control group contained 339 males and 19 females with a mean age of 38. 8 yr (range, 21 accepted by The Institutional Review Board of Hanyang University Hospital

## **RESULT**

The estimates of SCCHN in subgroups rendering to the smoking and alcohol consumption status are précised. The patient and control groups were categorized as non-smokers, light-smokers or heavy smokers. The light smoker group was defined as having a smoking history of more than 20 pack per year and the heavy smoker as having more than or equal to 20 pack per year. There were no statistically important differences in the risk of SCCHN according to status. The patient and control groups were also classified according to alcohol consumption into non-drinkers, social drinkers or heavy-drinker. The social drinker group was defined as those who consumed <https://assignbuster.com/role-of-xpd-gene-in-development-of-squamous-cell-carcinoma/>



alcohol less than 2 times per week and the heavy drinker group was defined as those consumed alcohol more than 2 times per week. There were no statistically significant variances in the risk of SCCHN according to the drinking status. We also analyzed the XPD polymorphisms and the risk of SCCHN according to the tumor sub-site (oral cavity, larynx, hypopharynx and oropharynx.)

## **DISCUSSION**

DNA repair systems play a significant role not only in ensuring cellular existence, but also in preventing the development of cancer. At least four DNA repair pathways, with nucleotide excision repair, base excision repair, mismatch repair and double strand DNA break repair are involved in the repair of specific types of DNA damage. Aberrant DNA repair is related with the development of some cancer types. The nucleotide excision repair pathway is the most adaptable mechanism and it is mainly involved in protection against the geno-toxic damage induced by UV- radiation or chemical carcinogens. In nucleotide excision repair, the injured part of a DNA strand is excised and then the gap is occupied by repair replication using the complementary strand. This “ cut and patch” mode consists of five main steps- Recognition of the injured DNA site, Incision of the injured DNA strand on both sides of the defect, Deletion of the damaged strand containing the lesion, DNA replication to substitute the excised region using the complementary strand as a template, Ligation to link the 3’ end of the repair patch to the contiguous parental strand. Defects in the NER pathway are accountable for several human syndromes, including Cockayne syndrome,

trichothiodystrophy and xerodermapigmentosum, which are all categorized by defective repair of UV-damaged DNA and an increased risk of skin cancer.

## **CONCLUSION**

Cancer is generally a disease of DNA, the risk for any individual of developing a tumor based on his or her genomic makeup cannot be explicitly determined given our current scope of knowledge. The kinds of genetic damage experienced are primarily to DNA in the form deletions, amplifications, or focal damaging mutations; though other mechanisms are increasingly noted to be significant including epigenetic changes to chromatin. Definitely most scientists and clinicians emphasize models of carcinogenesis similar to the ones just described, heavily focused on molecular events and cancer pathways.

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