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An Insight Of DNA Repair Gene Polymorphism In Oral Premalignant Disorders Associated With Habitual Risk Factors

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Abstract
Background: Oral potentially malignant disorders (OPMD) of the oral mucosa are one of the increased risks of oral cancer transformation. This is primarily caused by habitual risk factors such as tobacco (smoking and smokeless), betel quid chewing and alcohol consumption, which are the most important etiologic factors. Multiple studies have assessed the correlation of increased oral cancer and oral potentially malignant disorder with polymorphism in DNA repair genes.
Highlight: This review explores the genetic perspectives of the OPMD with special emphasis on DNA repair genes polymorphism associated with the risk exposures. The base Excision Repair (BER) pathway plays an important role in repairing damaged base pairs caused by oxidative stress due to tobacco carcinogens. Adenosine diphosphate ribosyl transferase (ADPRT), x-ray repair cross-complementing 1 (XRCC1), and apurinic/apyimidinic endonuclease (APE1), MGMT and other repair gene polymorphisms are involved with OPMD associated with habitual risk factors.
Conclusion: Genetic differences between various ethnicities and differences in the carcinogenesis of OPMD development in various countries could partially explain the discrepant of these gene-environmental lifestyle habits. An understanding of DNA repair genetic variants associated with habitual risk factors contribute to more accurate identification and establishing tailor-made prevention measures.

Keywords: *DNA repair; Gene polymorphism; Risk factor; Oral premalignant disorder*

1. Introduction

Oral cancer has shown alarming prevalence globally, affecting human populations residing in both more developed and less developed countries. It is the sixth most prevalent cancer in the world and the incidence of oral cancer in the Indian subcontinents is the second-highest among all men's cancers[1]. It is noteworthy that oral potentially malignant disorders (OPMDs), a well-established pre-cancer stage, which includes common lesions such as leukoplakia, erthyroplakia and oral sub-mucous fibrosis. Disorders such as oral leukoplakia and oral

submucous fibrosis (OSF) have been shown to have a high rate of transformation to oral cancer [2].Effectively addressing such premalignant disorders at an early stage facilitates to arrest progression into OSCC.

2. OPMD associated with habitual risk factors (Tobacco use- Betel Quid Chewing-Alcohol consumption)

OPMD is primarily caused by habitual risk exposures [3] that are associated with oral carcinogenesis. This includes several chronic habits such as tobacco ((tobacco smoking, smokeless betel quid chewing tobacco and alcohol consumption), which is the primary etiology for oral cancer incidences worldwide [4,5],areca nut and alcoholic products (alone or in combinations) [6,7]. In the South Asian region, over one-third of the tobacco consumed is smoke-free[3]related to high-risk habits such as tobacco and alcohol use in young individuals. The prevalence of OSF in India varying between 0.03 and 3.2% [8]is mainly due to chewing of tobacco/pan masala and paan [betel leaf with areca nut], and so on are prevalent in different parts of the world. [9].Arecanut is the fourth commonly used psychoactive substance utilized around the world, after tobacco, alcohol, and caffeine-containing beverages. In India, tobacco-related cancers are expected to constitute 30% of the total cancer burden, which is likely to increase in the future[10]. It is noteworthy that numerous OSCC develops from potentially malignant disorders (PMDs).Correct genetic diagnosis and timely treatment of OPMDs may help prevent malignant transformation in oral lesions. Lack of awareness about signs and symptoms of OPMDs among the general population are believed to be responsible for the diagnostic delay of these entities[11].

3. Genetic variationsin OPMD associated with habitual risk factors

Cancer and oral premalignant disorders are largely carcinogen induced environmental factors, genetic susceptibility and gene-environment/habitual risk exposure interactions. According to the somatic mutation theory to explain carcinogenesis, cancer is considered a genetic accident, resulting from the progressive accumulation of random mutations of DNA [12]. Studies have demonstrated direct lesion tissue genetic damage in leukoplakia with accumulated frequency of loss of heterozygosity that contain known or presumptive tumor suppressor genes is an early predictor of consequent progression of oral premalignant lesions[13] influence on the use of tobacco has been strongly implicated by cross-sectional studies in twins, association studies, and numerous other genetic epidemiology data [14,15] and it isalso recognized that the use of tobacco is often accompanied by alcohol consumption[16].An individual's physiological responses to environmental factors such as consumption of tobacco and alcohol stimuli modulate genetic variations there by leading to oral cancer [17]. The progressive accumulation of genetic lesions after long term betel-quid (BQ) exposure result in DNA damages such as the formation of DNA adducts and cross-links. Damaged DNA if not restored properly with DNA repair system [18] can cause deregulation of cell growth and apoptosis which may lead to the development of cancer including oral cancer[19].

4. DNA damage and repair of OPMD related to habitual risk factors

Carcinogens in way of life hazard exposure sinduce a wide range of DNA lesions such as ribose sugar damage, apurinic/apyrimidinic (AP) sites, modified guanine bases (O^6-mG and 8-oxoG), and bulky DNA base adducts to more pernicious lesions such as DNA crosslinks and strand breaks and DNA alterations like alkylative and oxidative base products, abasic sites, strand breaks, and misincorporated nucleotides. The bulky DNA adducts are formed by the covalent bonding of the chemical carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and aromatic amines, to various sites on DNA bases. These adducts moreover incorporate exocyclic DNA bases such as the etheno, propano, and benzetheno adducts formed by individual bifunctional compounds [20]. These bulky adducts frame a major class of DNA damage starting from exposure to cigarette smoke, significantly disrupting the DNA helix and block Watson-Crick base pairing[21]. They form highly mutagenic DNA adducts such as PAH-DNA adducts [22] and exocyclic DNA adducts[20]. Some of them may not be repaired (e.g., benzo[c]phenanthrene N^6-dA adducts) or only poorly repaired (e.g., two dibenzo[a,l]pyrene-induced DNA adduct[23], thereby the high levels of these bulky adducts are associated with an increased risk of cancers.

Depending on the type of damage inflicted on the DNA helix, numerous repair strategies have evolved to re-establish lost information.DNA repair mechanism is a complex biological system, including five different pathways such as base excision repair (BER), nucleotide excision repair (NER), double strand break repair (DSBR), mismatch repair (MMR),homologous recombination (HR) and non-homologous end-joining (NHEJ).They are active throughout different stages of the cell cycle, allowing the cells to repair the DNA damage[24]. NER is the major repair pathway for different duplex-distorting bulky DNA lesions such as those induced by carcinogen (PAHs).BER pathway evolved to cope with the high level of spontaneous decay products that are formed in DNA, as well as those damages created by reactive oxygen species (ROS) from carcinogens. The BER pathway handles the largest number of cytotoxic and mutagenic base lesions that are associated with the risk of oral cancer[25]. It specifically removes alterations of a single base that has been methylated, oxidized,or reduced and thus rectifies single-strand interruptions in DNA. Small alkylated and oxidized lesions are excised by the BER pathway which repairs single-ring exocyclic DNA adducts. Hence DNA repair genes play a vital role in the maintenance of the genomic integrity and protect the cells from DNA damage. Therefore, the alteration of DNA repair genes might increase the risk of cancer [26].The exfoliated buccal cells of smokers has a high number of micronuclei [27] likewise the buccal smears of precancerous and cancerous oral lesions also has high levels of micronuclei counts [28]. Other abnormalities evident in buccal cells from smokers include condensed chromatin, karyorrhexis, karyolysis and pyknosis[29]. The buccal cellsof oral leukoplakia patients possess a higher degree of genetic damage manifested in the form of multiple micronuclei per cell in more number of subjects as well as a significant increase in the total number of micronucleated cells. The multiple micronucleation within the target tissue demonstrated an extensive genetic damage, thereby chromosomal instability which might be a hallmark of human tumors [30].The overall cellular repair capacity in response to tobacco and other carcinogen exposure is critically related to the levels of DNA base pair adducts in the genome or mutations in specific genes.

In India and many Southeast Asian countries, the high incidence of oral cancer was associated with the habit of areca quid chewing was due to low frequencies of p53 gene mutation in the exons 5–9 [31].This p53 mutation was infrequent in areca quid/tobacco chewing-associated oral cancers from Papua-New Guinea and in a Sri Lankan population[32]. There isan alternative mechanism of p53 inactivation other than mutations. The mechanism might be either inactivation by revoking particular DNA binding resulting in p53sequestering or other genes related to oral cancer with the association of p16/pRb pathway, p21ras, cyclin D1, CD44v7-8, c -myc, N-myc and Ki-ras[33].The metabolites produced by the consumption of alcohol and tobacco usage lead to an increase in the oxidative stress and DNA strand interruption. Eventually, it is the impaired or poor repair of bulky DNA adducts and oxidized bases and this is most important in the etiology of alcohol and tobacco-related cancer including oral and OPMD. The understanding of DNA damage recognition and repair mechanism is important to gain insight into the specific roles of carcinogen DNA adducts in the development of oral cancer and OPMD.

5. DNA repair gene polymorphism of OPMD related to habitual risk factors

Individual variation and its relevance as a predisposition risk factor have been gaining importance by different distributions of genetic variants (single nucleotide polymorphisms, SNPs) in a population [34]. Allelic association is a powerful method for detecting genetic influence on complex traits such as tobacco and alcohol consumption. The alleles representing different functional activities have a significant impact and cause variation in the ability to metabolize carcinogens and/or viable repair of the damage caused by them [35].The role of individual variability in DNA repair, including polymorphism in repair genes is highly related to the increased oral leukoplakia and cancer risk and tobacco users [36, 37,38]. Therefore, the identification of individuals carrying SNPs that alter the DNA repair efficiency has substantial preventive implications for long term risk assessment for the development of cancer risk. Several DNA damage, and its repair gene polymorphism in OPMD associated with habitual risk factors are shown in figure.1. The Base Excision Repair(BER) pathway plays an important role in repairing damaged base pairs caused by oxidative stress due to tobacco carcinogens[39]. The multifunctional DNA repair gene apurinic/apyrimidinic endonuclease 1 (APE1) is an important member of the BER pathway. Tobacco contains various carcinogens that cause DNA damage, including oxidative injuries that are removed effectively by the base-excision repair (BER) pathway, in which adenosine diphosphate ribosyl transferase

(ADPRT), x-ray repair cross-complementing 1 (XRCC1), and apurinic/apyimidinic endonuclease (APE1) play key roles within the base excision repair pathway but only the ADPRT polymorphism shown the main impact on smoking and drinking status in squamous cell carcinoma of the head and neck (SCCHN)risk. Genetic variations in genes encoding for these DNA repair enzymes alter the repair functions. Thus, it is possible that there may be some locus-locus interactions that might have masked the main effects of certain genotypes of these genes[40].

The common known allelic variants ofAPE1 gene include a G > T polymorphism in exon 5 was associated with hypersensitivity to cancer risk[41].APE1polymorphisms significantly correlated with a hig hrisk proportion for OPMD malignant transformation in Taiwan subjects who had smoking, betel quid chewing and alcohol drinking had overall low survival in oral cancer patients. But in the Indian population, APE1polymorphisms were not associated with an increased risk of oral cancer, but the interaction betweenAPE1 and transcription-coupled nucleotide excision repair- XPD gene polymorphisms increased the oral cancer risk [42]). Another report suggested that the 148Glu allele decreased the capacity to repair oxidative damage to DNA[43]. The development of OPMD and oral cancer was associated with the use of alcohol, betel quid, and cigarette[44]. Exposure to oral carcinogens decreased APE1function of the Glu/Glu genotype and the subjects with APE1 (Glu/Glu + Glu/Asp) genotypes had a higher rate of malignant transformation from OPMD to oral cancer compared to those with Asp/Asp genotypes. This altered BER pathway activity and accumulation of unrepaired DNA intermediates led to malignant transformation. Choudhury et al., 2014reported the interaction of tobacco and polymorphisms of X-ray repair cross-complementing 1 and 2 (XRCC1 and XRCC2)genes and the cross-talk between these two DNA repair genes might modulate susceptibility towards OPMD and HNSCC[45]. The distribution of polymorphic variant in XRCC1 and XPD from South Indian population was associated with increased risk of oral cancer and smokers and betel quid chewers [46].Cases with the record of alcohol intake habits, tobacco smoking and chewing habits had polymorphic XRCC-1 hetero (CT) genotype variant and mutant (TT) genotype variants, which demonstrated the role of gene-ecological interconnection in modifying the vulnerability of loco-regionally progressed cancer. The polymorphism causing the change in amino acid location in the DNA repair gene and led to debilitation of DNA resolution process and hence these polymorphisms could cause malignancy in a person with the history of alcohol and tobacco substance use[38]. Susceptibility to oral cancer and patients with precancerous lesions showed genetic polymorphisms among Indians who had tobacco exposure as a risk modulator reported that theGSTM1null genotype as a risk factor and GSTT1 null genotype emerged as a protective factor and increased vulnerability to buccal mucosa cancer among individuals carrying these hereditary markers[47,48]. The DNA repair protein O^6 -methylguanine-DNA-methyltransferase- MGMT, a specific DNA repair enzyme that plays an important role in genome stability. This removed the alkylating lesions expression from leukoplakia when compared with early squamous cell carcinoma. There was a significant relationship between smoking and the loss of MGMT protein expression. Loss of MGMT expression might be considered an early event in oral carcinogenesis with possible prognostic implications[49]. The discrepancies of DNA repair genes among various ethnicities of OPMD associated with habitual risk factors are listed in Table1 and 2. The polymorphic alleles of DNA repair genes XPD **(**xeroderma pigmentosum group D)in tobacco use HNC(54) and hOGG1 (8-oxoguanine DNA-glycosylase 1) that excises 7,8-dihydro-8-oxoguanine (8oxoG) from DNA showed Cys polymorphism with significant G allele heterogeneity associations with an increased risk of HNC in Caucasian populations(56). A report stated that there was a different malignant transformation rate in OPMD patients with different characteristics, for example, a Taiwan cohort study reported malignant transformation rates in OPMD patients of 2.1% had lichen planus and 5.4% epithelial dysplasia with oral submucous fibrosis. Among Caucasian population, inherited MLH1 (mutL homolog 1) anomalies of DNA mismatch repair (MMR) pathway were essential determinants and important predictors of smokers of HNSCC(63). Information on DNA damage and associated genetic variants of DNA repair genes associated OPMD, directly affect oral mucosa, which could provide a more rational basis for developing smoking, chewing or drinking cessation programs. This includes identification of persons at high risk and the introduction of suitable interventions to prevent smoking-related, chewing-related or drinking-related diseases. An early DNA repair gene (primary target for carcinogen) variant diagnosis of OPMD is of excellent significance for cancer detection and prevention in the initial stage, the potential for remission is of a higher percentage. An understanding of genes

associated with habitual risk factors will contribute to more accurate risk identification and establishing tailor-made prevention measures.

6. Conclusion

This review discuss the current knowledge about the DNA damage caused by tobacco and alcohol consumption, and risk stratification connected with DNA repair gene polymorphism in OPMD. The information on SNP in DNA repair genes as 'Prognostic Biomarkers to screen high-risk individuals thwart adverse health consequences related to environmental exposures in cancer. Furthermore, this review will give indepth understanding over the susceptibility to oral cancer development, raising social awareness among people and prevention of alcohol dependence and tobacco-related diseases. Finding out how SNPs influence the wellbeing of a person and transforming to develop new medicines will undoubtedly allow treatment of the most common devastating disorders.

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Conflict of Interest

The authors declare no competing interest.

Ethical Statement

Ethical approval was not required for this review.

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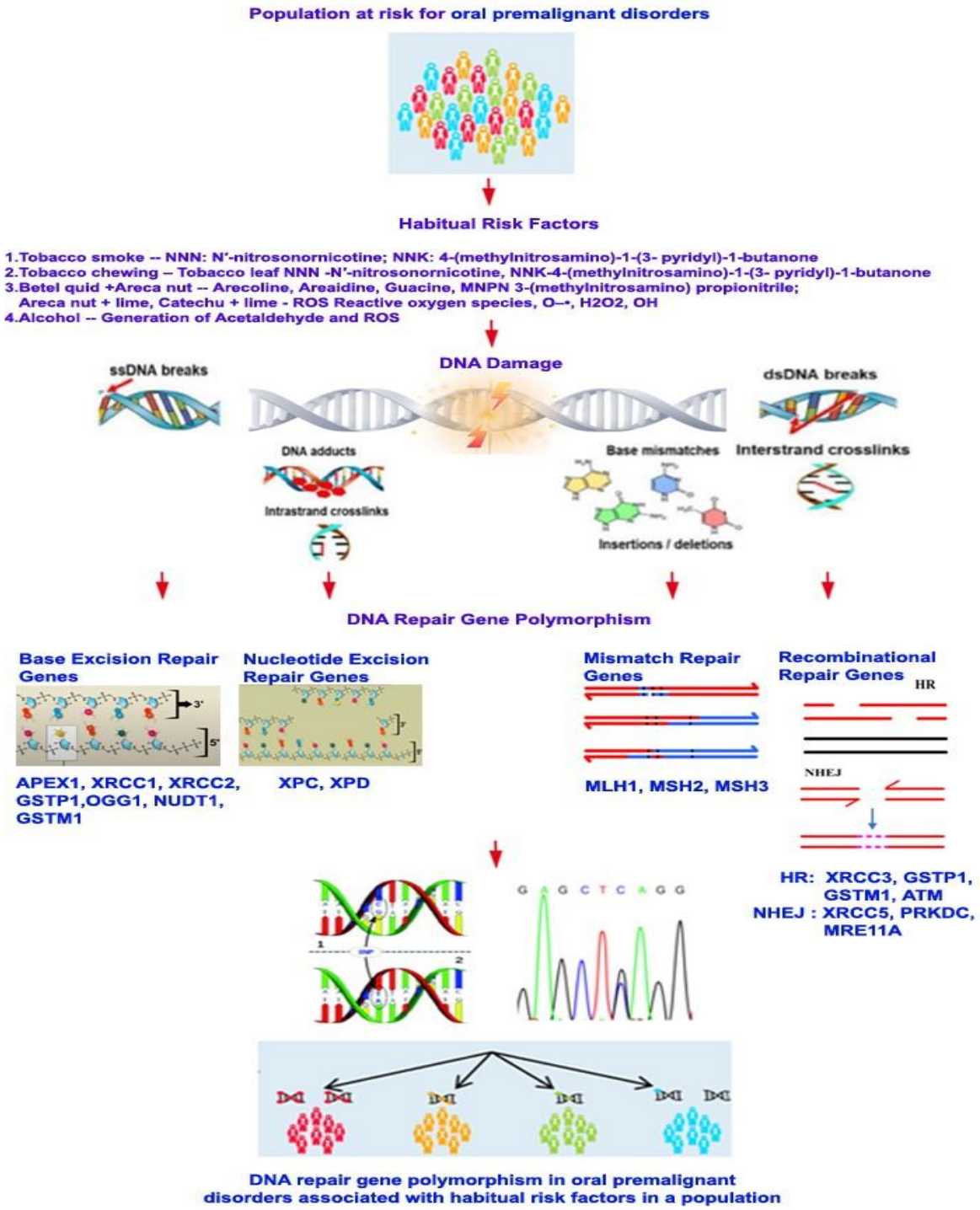

Figure 1. DNA repair gene polymorphism in Oral premalignant disorders associated with habitual risk factors.

Source/	Population	Gene/	SNP	Reference

Phenotype		**Function**	**(Major/Minor Alleles)**	
Tobacco/ oral leukoplakia	Indian	XRCC1 (BER)	Arg399Glu G/A	[50]
Tobacco/ OPMD	Pakistani	APEX1 (BER)	Ser129Arg (A/C), Val131Gly, 13T/G	[51]
Tobacco/ OPMD	Turkish	XRCC1 (BER)	Arg194Trp (G/A), Arg399Gln (A/A), (A/G), (G/G)	[52]
Tobacco/ OPMD	Chinese	XRCC1 (BER)	Arg194Trp (G/A), Arg280His (C/G,T), Arg399Gln (C/C), (C/T), (T/T)	[53]
Tobacco/ OPMD	Indian	XRCC1 (BER)	Arg399Gln (A/A), (A/G), (G/G)	[45]
Smoking/ OPMD	Indian	XRCC2 (BER)	Arg188His (C/G,T)	[45]
Smoking/ OPMD	Caucasian	XRCC1 (BER)	R399Q (T/A,C,G)	[46]
Tobacco/ OPMD	Indian	APEX1 (BER)	Asp148Glu (T/A,C,G)	[43]
Toabcco/ OPMD	Pakistani	APEX1 (BER)	Ser129Arg (A/C), Val-131Gly (G/A) 13T/G,	[51]
Tobacco and Alcohol/ Oral Leukoplakia		XRCC1 (BER)	399Gln (T/C)	[54]
Tobacco and A6lcohol/ OPMD	Japanese	OGG1 (BER)	rs2075747 (A/A, A/G, G/G) (Ser326Cys),	[55]

			rs1052133 (C/C, C/G, G/G) (Ser326Cys), rs2072668 (C/C, C/G, G/G) (Ser(326)Cys,), rs1801129 (A/G)	
Tobacco and Alcohol/ OPMD	Japanese	GSTP1 (BER and HRR)	rs947894 (A/A, A/G, G/G), rs762803 (A/A, A/C, C/C)	[55]
Tobacco and Alcohol/ OPMD	Japanese	NUDT1 (MTH1) (BER)	rs4866 (A/A, A/G), rs1062492 (C/T)	[55]
Tobacco/ OPMD	Caucasian	hOGG1 (BER)	Ser326Cys (A/T)	[56]
Alcohol/ OPMD	Europen Japanese, USA, Indian	GSTM1 (BER and HRR)	Null Genotype	[57]
Tobacco and Alcohol/ OPMD	Indian	GSTM1 (BER and HRR)	Null Genotype	[58]
Tobacco/ OPMD	Caucasian	XPC (NER)	A499V (C/A,G,T)	[46]
Tobacco/ OPMD	Caucasian	XPD (NER)	K751Q (c.2251A/C)	[46]
Tobacco/ OPMD	Indian	XPD (NER)	Asp312Asn (C/A,T)	[43]
OPMD	Caucasian	XPD (NER)	Lys751Gln (T/A,G)	[54]
Tobacco/ OPMD	Brazilian	MLH1 (MMR)	c.-93G/A	[59]
Tobacco / OPMD	Brazilian	MSH2 (MMR)	c.211 + 9C/G	[59]
Tobacco/ OPMD	Brazilian	MSH3 (MMR)	c.3133G/A	[59]
Tobacco/ OPMD	Indian	MLH1 (MMR)	-93 A/G	[60]

Tobacco/ OPMD	Caucasian	MLH1 (MMR)	c.-93G/A	[61]
Tobacco/ OPMD	Caucasian	MSH2 (MMR)	c.211 + 9C/G	[61]
Tobacco/ OPMD	Caucasian	MSH3 (MMR)	c.3133G/A	[61]
Tobacco/ OPMD	Indian	MSH3 (MMR)	rs12515548 (A/G)	[62]
Tobacco and Alcohol/ OPMD	Indian	*hMLH1* (MMR)	rs1800734 (-93G/A)	[58]
Tobacco/ OPMD	Pakistani	XRCC3 (HR)	Thr241Met (G/A)	[58]
Tobacco/ OPMD	Caucasian	XRCC3 (HR)	T241M (G/A)	[46]
Tobacco and Alcohol/ OPMD	Indian	*ATM* (HR)	rs189037 (G/G)	[58]
Tobacco and Alcohol/ OPMD	Indian	*XRCC3* (HR)	rs861539 (C/T) (Thr/Thr vs. Met/Thr)	[58]
Tobacco/ OPMD	Indian	MRE11A (Double-strand break repair -DSB)	rs12360870 (G/A)	[62]
Tobacco Exposure/ OPMD	Indian	XRCC5 (Recombinational Repair-NHEJ)	rs207943 (C/G)	[62]
Tobacco Exposure/ OPMD	Indian	PRKDC (NHEJ-DSB)	rs7003908 (A/C)	[62]

Table 1: DNA repair gene polymorphism in OPMD associated with habitual risk factors

Source/ Phenotype	**Population**	**Gene/ Function**	**SNP (Major/Minor Alleles)**	**Reference**

Tobacco and Alcohol/ OPMD	Japanese	GSTM2, (DNA damage)	rs655315 (A/G), rs428434 (C/G)	[55]
Alcohol/ OPMD	Japanese	GSTM3, (DNA damage)	rs1332018 (G/T)	[55]
Tobacco and Alcohol/ OPMD	Japanese	GSTT2, (DNA damage)	rs1622002 (C/T), rs2719 (G/T), rs2267047 (T/C), rs140186	[55]
Tobacco and Alcohol/ OPMD	Japanese	NQO1 (DNA damage)	rs1800566 (G/A)	[55]
Tobacco and Alcohol/ OPMD	Japanese	NAT1 (metabolism of tobacco carcinogens)	rs15561 (A/A), (A/C)	[55]
Tobacco and Alcohol/ OPMD	Japanese	NAT2 (metabolism of tobacco carcinogens)	rs1801280 (C/C), (C/T), rs1799929 (C/T), (T/T), rs1799930 (A/A), (A/G), (G/G), rs1495744	[55]
Tobacco and Alcohol/ OPMD	Japanese	ADH1A (Ethanol catabolism)	rs931635 (A/G), rs1229967 (G/C,T), rs1229970 (A/C), rs975833 (G/C), rs1618572 (C/G,T), rs2276332 (A/C)	[55]
Tobacco and Alcohol/ OPMD	Japanese	ADH1B (Ethanol catabolism)	rs17033 (T/C), rs1159918 (A/C) , rs1042026 (T/C)	[55]

Tobacco and Alcohol/ OPMD	Japanese	ADH1C (Ethanol catabolism)	rs1789924 (C/G,T), rs1693430 (C/A,T), rs2009181 (A/G), rs2298755 (C/A,G), rs3216150 (->A,AA)	[55]
Tobacco and Alcohol/ OPMD	Japanese	ALDH2 (Ethanol Metabolism)	rs671 (G/A), rs2238151 (T/C), rs2238152 (G/T), rs441 (T/C)	[55]
Drinking/ OPMD	Europe Japan, USA, India	ADH1B (Alcohol catabolism)	His48Arg (T/C,G)	[57]
Drinking/ OPMD	Europe Japan, USA, India	ADH1C (Alcohol catabolism)	I350V (T/A,C)	[57]

Table 2: Tobacco carcinogen and Ethanol metabolism gene polymorphism in OPMD associated with habitual risk factors