Revisión/Review

Polimorfismos genéticos en desórdenes potencialmente malignos, una revision sistematica

Single nucleotid polymorphism associated to oral potentially malignant disorders: a systematic review

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Resumen

Los desórdenes orales potencialmente malignos (DOPM), generalmente, pueden ser predecesores del desarrollo del cáncer oral. El mayor desafío es poder predecir, mediante los SNP presentes en los individuos con lesiones, el progreso hacia un carcinoma oral…pueden progresar hacia un carcinoma oral según los polimorfismos de un solo nucleótido (SNP) presentes en los individuos con estas lesiones. Los meta-análisis de estudios sobre asociaciones genéticas son claves para establecer los componentes genéticos de las enfermedades complejas que permitan avanzar en estrategias terapéuticas y diagnóstico clínico temprano.
Objetivo: Identificar la asociación entre las variantes polimórficas (SNPs) de genes relacionados con el cancer oral presentes en lesiones potencialmente malignas estudiados recientemente, y el desarrollo en ellas de malignidad. Métodos: según delineamientos PRISMA, y las bases electrónicas utilizadas fueron: PubMed, Scopus, CancerLit y Cochrane. Se seleccionaron 27 estudios que reunieron los criterios de inclusión/exclusión entre enero de 2004 y diciembre de 2015. Se extrajeron datos de los SNPs bialélicos, odds ratios y IC 95%; para valorar fuerza de asociación entre cada variante genética y presencia de DOPM. La heterogeneidad fue analizada por la prueba Q y cuantificada por pruebas Tau2 y el estadístico I2. Se utilizó el paquete meta R software 2.15.3. Resultados: Los 27 estudios sumaron un total de 2915 casos y 4715 controles. Los siguientes polimorfismos se observaron asociados a leucoplasia oral: CYPA1 (m1/m2), XDP (Gln/Gln), GSTM1 (null), and P53 (intron6). Los polimorfismos asociados con lesiones de liquen plano fueron: CIITA (rs6498122), TNFR2 (+587), TNFα (-308), and P53 codon72. Los polimorfismos asociados a fibrosis submucosa fueron MICA, NAT2 Lys268Arg, NAT2 Gly286Glu, XRCC3 Thr241Met, COX2 -765; G>C, FAS 1377, G>A y FAS 670, A>G. Conclusiones: Los genotipos fueron heterocigotas u homocigotos para la variante polimórfica. Los SNP de los genes mencionados se asocian a riesgo de cáncer de cabeza y cuello, por lo cual la presencia de estos SNP podría ser indicativos de mayor riesgo de desarrollo de cáncer.

PALABRAS CLAVES: revisión sistemática – desordenes potencialmente malignos -cáncer oral-polimorfismos.

Abstract

Objective. To identify the association between polymorphic variants (SNPs) of genes related to oral cancer present in potentially malignant lesions studied recently, and the development of malignancies. Study Design. A systematic review was conducted of literature in PubMed, CancerLit and Cochrane from January 2004 through June 2015. Results. Individual participant data of 2915 cases and 4715 controls from 27 genetic studies were analyzed. The following polymorphisms have significant associations with Oral Leukoplakia: CYPA1 (m1/m2), XDP (Gln/Gln), GSTM1 (null), and P53 (intron 6). Polymorphisms that showed an association with Oral Lichen Planus were: CIITA (rs6498122), TNFR2 (+587), TNFα (-308), and P53 codon 72. Polymorphisms associated with Oral Submucous Fibrosis were: A6 of the MICA gene, NAT2 Lys268Arg, NAT2 Gly286Glu, XRCC3 Thr241Met, COX2 -765; G>C, FAS 1377, G>A and FAS 670, A>G. All the risk genotypes were heterozygous or homozygous for the polymorphic variants.Conclusions. Patients with Oral Potentially Malignant Disorders in which genotypes as CYP1A1 m1/m2, XDP Gln/Gln, GSTM1 null, P53 intron 6, CIITA rs6498122, TNFR2 +587, TNFα -308 y P53 codon72, FAS 1377, FAS 670, MICA A6, NAT2 rs1208, XRCC3 rs861539, COX2 -765 seem to have greater risk of develop oral cancer.

KEY WORDS: systematic review, oral potentially malignant disorders, risk, poylimorphism

Introduction

Oral Potentially Malignant Disorders (OPMD), in general, may be predecessors for the development of oral cancer. They are described as a family of morphological changes in which the potential for malignant transformation may be increased[1]. A lack of prevention or of early intervention on this pathologies means that the patients affected have physical deformations or mutilations, with a negative impact on their quality of life[2]. The greatest challenge is to predict which cellular and molecular features of OPMD will be able to progress to oral cancer, based on the important concept that cancer progression is an evolutionary process which results from accumulation of genetic and epigenetic variations in somatic cells[3]. Systematic review is one of the mechanisms for assessing the total effect of a polymorphism and/or gene and is accepted as the key method to establish the genetic components of complex diseases. It also enables stronger and more generalized conclusions for identifying some models of risk markers that predict risks of oral cáncer and/or tumor progression, in order to improve prevention, early detection (mainly in patients with OPMD) and treatment[4-7].

In a previous work about the association of single nucleotide polymorphisms (SNP) in head and neck cancer, we showed that people considered at risk of developing head and neck carcinomas have an increase of gene polymorphism expression related to inflammation, carcinogenic metabolism, the stabilization and repair of the cellular genome, regulation of proliferation and/or apoptosis[8]. The main question is if SNPs associated with oral cancer are present in patients with OPMD. So, the aims of this work were: To identify the association between polymorphic variants (SNPs) of genes related to oral cancer present in potentially malignant lesions studied recently, and the development of malignancies

Material and methods

Search strategy and selection criteria

This study was made using the PRISMA preferred reporting items for systematic reviews and meta-analysis guidelines. We conducted a systematic review of case-control studies from the PubMed, Medline, Cochrane, and Cancer Lit data bases between January 2004 and January 2015. Language is not restricted. The search strategy included the following keywords (variably combined): "Gene Expression Regulation, Neoplastic", leukoplakia and lichen ("Gene Expression Regulation, Neoplastic"[Mesh]) AND "Leukoplakia, Oral"[Mesh]) AND ("Mouth Mucosa/growth and development"[Mesh] OR "Mouth Mucosa/immunology"[Mesh] OR "Mouth Mucosa/pathogenicity"[Mesh] OR "Mouth Mucosa/pathology"[Mesh]) ("Cell Transformation, Neoplastic"[Mesh]) AND "Hyperplasia"[Mesh]) AND "Precancerous Conditions"[Mesh], oral cavity and oral potentially malignant disorders AND polymorphism.

Data extraction

Data was collected of adult patients of both genders with diagnoses of oral leukoplakia (OL), oral submucous fibrosis (OSF), or oral lichen planus (OLP), according to the criteria of ICD-10C00-C14 WHO or another specific source, in whom genetic polymorphisms were identified. At first, abstracts and titles of all the identified papers obtained by the electronic search were evaluated. All studies which met the inclusión criteria were assessed (full papers) in order to establish their validity and for subsequent data extraction.

Inclusion /exclusion criteria

Original papers that report the presence/absence of mutation and/or polymorphism by conventional PCR (polymerase chain reaction) using primers for allele-specific sequences or for specific restriction enzymes, Odds Ratios (OR). It was adjusted for alcohol and tobacco, with 95% Confidence Intervals (CIs).

Original papers that did not report PCR genotyping and studies of patients with systemic diseases or with syndromes, pregnancy or with indication of long-term medication were excluded.

Study Quality Assessment

The case-control study guidelines of the Scottish Intercollegiate Guidelines Network and MOOSE were followed. Three members of the team (AB, AMZ, JLB) evaluated complete articles independently and double-

blinded, to establish their quality. The papers were encoded and delivered independently to each reviewer. Disagreements were resolved by reiteration, discussion and consensus with the participation of a third member[9].
All studies were adjusted for gender, tobacco, and alcohol. Clinical trials, chromosomal alterations or in vitro cell culture studies were not included. ORs and 95% CIs were estimated between presence/absence of OPMD in each genotype[10].

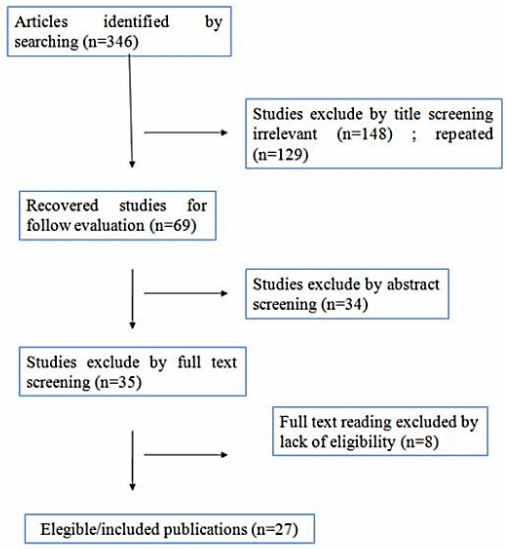

Figure 1: Flow chart for the selection of included articles.

Results

General aspects of studies and population
Twenty-seven original reports were retrieved from 346 potential reports that addressed the issue of DNA gene / polymorphisms and OPMD risk (Fig. 1): OL-16 studies[11-25], OLP-9 studies[26-34], OSF-4 studies[35-38].
The overall assessment of the quality of the studies was high, 25 from 27 (92.6%). It should be noted that 18 (66.7%) of the studies were made in Asian countries (China, Thailand, India, Taiwan, Japan), 3 (11.1%) in North America (USA), 4 (14.8%) in South America (Brazil), 1 (3.7%) in Eastern Europe (Serbia), and 1 (3.7%) in North Africa (Egypt) (Tables 1 to 3).
The total number was 2915 cases (2054 OL, 601 OLP, and 260 OSF) and 4715 controls (Tables 1 and 3).
The average age range was between 16 and 85 years, and was similar in both cases and controls. Other aspects that were also studied are not included in this paper because they are not homogeneous.
53 polymorphisms/genes were analyzed (Tables 2 and 3) related to cell cycle regulation/apoptosis, carcinogenic metabolism, inflammatory processes, progression and DNA repair pathways.
All the risk genotypes were heterozygous or homozygous for the polymorphic variants. OL was seen to be significantly associated with the following genes/polymorphisms: CYPA1 (m1/m2), XDP (Gln/Gln), GSTM1 (null), and P53 (intron 6) (Table2). In patients with OLP, the polymorphisms associated were TNFR2 (+587), TNFα (-308, rs1800629), and P53 codon 72 (Table 2).
The polymorphisms related to patients with OSF were: MICA gene A6, NAT2 Lys268Arg (rs1208), NAT2 Gly286Glu (rs1799931), XRCC3 Thr241Met (rs861539), COX2 -765; G>C, FAS 1377, G>A and FAS 670, A>G (Table 3).

Discussion

Cancer prevention is one of the best public health strategies, since it is a low-cost method with high effectiveness over time. Early detection enables intervention at early stages of the disease, when there is still high potential to achieve a cure. However, applying medical genomics generates inequality for the access of lower socioeconomic sectors to the new technology, and health systems need to use information and communication to build a critical and political awareness to favor all the population and improve its quality of life. The identification of a biomarker profile of oral cancer risk would help to recognize when an OPMD lesion becomes malignant [39-41].
The OPMDs selected in this systematic review were OL, OSF and OLP because it is known that they have a malignant

transformation rate: OL 2-12% [42,43] ; OSF 7–14% [44], and OLP between 0.4 and 5% [45, 46].

Study characteristics

The majority of studies reviewed are from Asia and America, with fewer from Europe and Africa. However, comparing the prevalence of OPMD is not very feasible, as it seems to vary with race, geographical region and the individual genetic load of each person, and these confounders have not been included in all the studies. Oral health conditions may be influenced by a series of factors such as socioeconomic stratum, cultural features and educational level, which differ between and within countries.

Different social positions, medical conditions, work and financial and personal situations impact general and oral health, and this is most noticeable in less-favored communities in developing countries[47].

Oral leukoplakia

XPD polymorphism was seen to be associated with OL in one of the studies included in this work [16]. This poymorphism is recognized as an excision repair cross-complementing group 2 (ERCC2) genes, which encodes the XPD protein, an ATP-dependent helicase within the multi-subunit transcription repair factor complex.

The polymorphisms, Lys751Gln (A35931C, rs13181 or rs1052559) at codon 751 in exon 23 of gene XPD, may lead to a reduction in helicase activity and DNA repair capacity and may be important in the carcinogenesis and progression of head and neck cancers (Farnebo et al., 2015; Zhou et al., 2014).

SNP P53 intron 6 was related to OL. One of the well-studied intronic polymorphisms of P53 is intron 6 (rs17880604), which is not within splice site consensus sequences or enhancers. It is known that intronic mutations and polymorphisms can occur within regulatory sequences such as promoters, enhancers, silencers and regulatory miRNA, or modify gene expression by altering RNA splicing[48]. Furthermore Mitra et al[22]. suggest that p53 haplotype 1-2-2 (comprising the absence of 16 bp duplication allele at intron 3, Arg at codon 72, and the presence of NciI at intro 6) is a better indicator of tobacco habit and dose-associated leukoplakia and oral cáncer risk.

Table 1 shows the relationship among CYP1A1 and GSTM1 and OL; these genes are associated with metabolic processes of carcinogens such as tobacco. It is widely known that smoking tobacco is a risk factor both for oral cancer and for some OPMDs, and that it is related to the intensity and duration of this habit over time[41]. GSTM1 plays a critical role in the detoxification and elimination of electrophilic carcinogens by their conjugation with glutathione. Deletion of these genes has been suggested as a risk factor for certain cancers, including colorectal, pancreatic and esophageal cancer[49]. The CYP1A1 gene codes for a phase I enzyme (aryl hydrocarbon hydroxylase) which activates tobacco procarcinogens like polyaromatic hydrocarbons and aromatic amines into their carcinogenic forms. Certain variant genotypes of the CYP1A1 gene which one cause enhanced enzymatic activity appear to play a role in susceptibility to adduct formation and presumably cancer risk[43].

Oral Lichen Planus

In this work, the polymorphisms of the CIITA gene (rs6498122) were associated with OLP 28. The CIITA gene, located on chromosome 16p13, is a transcriptional coactivator that regulates γ-interferon-activated transcription of Major Histocompatibility Complex (MHC) class I and II genes and its deficiency or aberrant expression is linked to the Type II bare lymphocyte syndrome and to cancer[50].

The polymorphisms of the genes TNF-α (multifunctional proinflammatory cytokine produced by macrophages) and TNFR2 have been observed related to this pathology[51]. It has been known for some years that cancer propagates without control through transformed cells, which must be recognized by the immune system before they become a tumor [52]. In very many cases, however, the transformed cells evade the immune defenses. Authors such as Piva et al., 2013 have observed that the presence of inflammatory infiltrates, with overexpression of NFKB and TNF-α, in epithelial dysplasias, favors the transformation and invasion processes, generating a link between inflammation and cancer. Other studies of oral squamous cell carcinoma have reported that TNF-alpha-

308 G/A may be related to a risk of OPMD [53].

Studies in colon cancer cells have demonstrated that IL-6- and TNFα- induced TNFR2 expression is mediated primarily by STAT3, and provide evidence that TNFR2 may contribute to the tumor-promoting roles of STAT3[54].

Yanatatseneeji et al., 2010[37] showed that codon 72 was related to OPDM. Clinical and in vitro data suggest that the p53 codon 72 variant may serve as a risk factor for many different types of cancers and may play a role in the modulation of certain environmental risk factors. The most frequent p53 polymorphism is the codon 72 polymorphism on exon 4, which has been reported to modify the risks of many types of cancers, such as esophagus, stomach, ovary, cervix, bladder, and lung cancer. The transcribed proteins for the polymorphisms have been shown to be different, structurally by electrophoretic mobility assay and functionally in vitro, with the p53 (Pro\Pro) variant protein being a stronger inducer of transcription and showing slower kinetics in inducing apoptosis than the p53 (Arg) genotype, and with the p53 (Arg) type also suppressing transformation of primary cells to a greater degree than the p53 (Pro) type[55]. However, our own recent study in relation to SNP and risk head and neck cancer reported no significant association with TP53[8]. At the level of epidemiological studies in various cancers, the association of this polymorphism with cancer is controversial and there is scant literature on this in relation to oral cancer [56].

Oral Submucous Fibrosis

The polymorphism of MICA-A6, encoded alleles of the major histocompatibility complex class I chain-related genes, are associated with presence of OSF. In the literature, an association has been observed between the MICA STR polymorphism and risk of oral cancer, obtaining different results according to the study population [57]. In addition; OSF has been associated with genes related to inflammatory processes such as COX-2 765G>C rs20417 in patients with a diagnosis of OSF[26]. The COX-2 gene is recognized as a prostanoid derivative with activity in cardiovascular disease and cancer, as well as in relation to smoking. Exposure to cigarette smoke has been seen to induce the expression of COX-2 and thus provoke disequilibrium in its derivatives, among which is an increase of PGE2. The latter has a proinflammatory effect and has been seen to contribute to carcinogénesis and tumor progression[52].

Table 3 shows that NAT1 and NAT2 are associated with OSF. These enzymes are important for the metabolism of tobacco carcinogens. Due to polymorphisms, improper activities of these enzymes may lead to the formation of DNA adducts that may modulate the risk of tobacco-related oral potentially malignant disorders and cancer. NAT2 is a Phase II enzyme expressed primarily in the liver and its substrates are commonly found in the environment, e.g., heterocyclic and aromatic amines in cigarette smoke, diesel exhaust and roasted meat. Studies of the role of N-acetyltransferases (NAT) in prostate cancer (PCa) susceptibility in men in Latin American countries showed that the presence of the NAT2G857A genotype increased the risk of PCa more than 3 times and suggested that the investigation of germline polymorphisms of NAT2 gene may be useful in the assessment of Latin American patients at risk of PCa [58].

In the other hand, XRCC3 Thr241Met (rs861539) has been associated with the presence of OSF. It is known that DNA is constantly damaged by oxygen free radicals originating in the metabolism (endogenous) or by chemical or physical mutagens (exogenous), which activate different DNA repair pathways [59]. DNA double-strand break repair mechanisms involve two main pathways: homologous recombination (HR) and non-homologous end joining (NHEJ).

In the HR process, genetic deletions and rearrangements of genes XRCC2, XRCC3, and RAD51 have been observed. The cellular processes of DNA repair in carcinogenesis are important because they stabilize the genome by reducing mutations provoked by carcinogens[60].

Fas and its ligand (FasL) genes were related to OSF[24]. These genes play an important role in apoptosis and carcinogenesis; such as breast cancer, gastric cancer, and esophageal cancer, in particular in Asian populations[61].

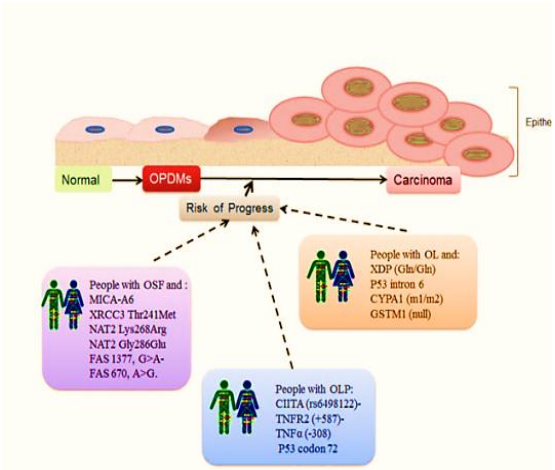

Figure 2: Schematic drawing of genetic polymorphic variants in the development of oral cancer from different Oral potentially malignant disorders *Ref:. OL: oral leukoplakia; OLP: oral lichen planus; OSF: oral submucous fibrosis.*

Conclusion

The results of this study allow to propose that patients with Oral Potentially Malignant Disorders in whith genotypes as CYP1A1 m1/m2, XDP Gln/Gln, GSTM1 null, P53 intron 6, CIITA rs6498122, TNFR2 +587, TNFα -308 y P53 codon72, FAS 1377, FAS 670, MICA A6, NAT2 rs1208, XRCC3 rs861539, COX2 -765 seem to have greater risk of develop oral cancer.

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Table 1.Characteristics of Studies; CC: case-control study.**AF**: absolute frequency; **RF**: relative frequency.

Type of lesion	*Authors*	*Origin*	*Gene(s)*	*Design*	*Cases (place)*	*Controls (place)*	*Gender AF (RF)*		*Age (years) Average±SD[a] or Median[b] and range[c]*	
							Cases	*Control*	*Cases*	*Control*
Oral Leukoplakia	Tanic´ et al., 2009 (8)	Serbia	**P53** (exons 5-9)	CC paired	32 Clinic of Maxillofacial Surgery, School of Dentistry, University of Belgrade	32 Clinic of Maxillofacial Surgery, School of Dentistry, University of Belgrade	NR	NR	NR	NR
	Majumder et al., 2007 (9)	India	**XRCC1** (codon 194, Arg>Trp) (codon 280, Arg> His) (codon 399, Arg>Gln) **XPD** (A > C 156, Arg>Arg) **NAT2**	Cross sectional	224 R. Ahmed Dental College and Hospital at Kolkata, India	389 R. Ahmed Dental College and Hospital at Kolkata, India	Male 196 (87%) Female 28 (13%)	Male 302 (78%) Female 87 (22%)	47±10.3[a] 25–75[c]	49 ±11.9[a] 25–80[c]
	Shukla et al., 2012 (10)	India	**GSTM1** **CYP1A1**	Cross sectional	57 Institute of Dental Sciences KLE University, KLE's Prabhakar Kore Hospital & Medical Research Centre, Belgaum Cancer Hospital and Padmashree Dr. R.B. Patil Cancer Hospital Hubli	72	Male 48 (84.2%) Female 9 (15.8%)	Male 57 (79.2%) Female 15 (20.8%)	44.1±16.24[a]	50.38±16.26[a]
	Pu et al., 2009 (11)	USA	**COX-2** (-765, G > C, rs20417) (exon 10, +837, T > C, rs5275) (exon 10, -90, C > T, rs689470)	CC paired	147 University of Texas M. D. Anderson Cancer Center	147 Kelsey-Seybold Clinic at Houston			57.48± 13.61[a]	59.10 ± 11.04 [a]
	Duarte et al., 2006 (12)	Brazil	**GSTM1**	CC paired	52 Dental Clinics of the School of Dentistry	52 Dental Clinics of the School of Dentistry	Male 31 (59.6%) Female 21 (40.4%)	Male 31 (59.6%) Female 21 (40.4%)	47.9[a] 25–87[c]	48.6[a] 29–81[c]
	Duarte et al., 2006 (13)	Brazil	**GSTT1**	CC paired	52 Dental Clinics of	52 Dental Clinics of	Male 31	Male 31	47.9[a]	48.6[a]

				the School of Dentistry	the School of Dentistry	(59.6%) Female 21 (40.4%)	(59.6%) Female 21 (40.4%)	25–87[c]	29–81[c]
Mahimkar et al., 2010 (14)	India	**CYP1A1**(MspI) **GSTM1** **GSTT1** **GST P1** (Ile105Val) **XRCCI** (Arg194Trp and Arg399Gln) **XPD** (Lys751Gln and Asp312Asn) **hOGG1** (Ser326Cys)	Cross sectional	66	101	Male 60 (91%) Female 6 (9)	Male 99 (98.0%) Female 2 (2%)	39 ± 13[a] 40[b] 17–68[c]	37±11.5[a] 36.5[b] 18-77[c]
Mondal et al., 2013 (15)	India	**LIG4** **MRE11A** **PRKDC** **NBN** **RAD50** **XRCC5** **XRCC6** **MSH6** **MSH3**	Cross sectional	253 R. Ahemed Dental College and Hospital, Kolkata	535 R. Ahemed Dental College and Hospital, Kolkata	Male 213 (84.2%) Female 39 (15.4%)	Male 379 (70.8%) Female 156 (29.2%)	46[b] 20–75[c]	48[b] 22–85[c]
Duarte et al., 2008 (16)	Brazil	**GSTM1** **GSTT1** **GSTP1** (105Ile/Val) **CYP1A1**(462Ile/Val) **CYP2E1** (-1019 RsaIand-1259 PstI)	CC paired	80 Dental Clinics of the School of Dentistry at Universidade Federal de Minas Gerais	80 Dental Clinics of the School of Dentistry at Universidade Federal de Minas Gerais	Male 47 (58.8%) Female 33 (41.2%)	Male 47 (58.8%) Female 33 (41.2%)	47.3[a] 45.5[b]	47.8[a] 47.0[b]
Majumder et al., 2012 (17)	India	**NAT1** (445, G > A, rs4987076) (559, C > T, rs4986782) (1088, T > A, rs1057126) (1095, C > A, rs15561) **NAT2** (341, T > C, rs1801280) (481, C > T, rs1799929) (590, G > A, rs1799930) (803, A > G, rs1208) (857, G > A, rs1799931)	Cross sectional	224 R. Ahmed Dental College and Hospital at Kolkata, India	389 R. Ahmed Dental College and Hospital at Kolkata, India	NR	NR	> 25	> 25
Datta et al., 2007 (18)	India	Mitochondrial Polymorphisms GSTP1	Cross sectional	224 R. Ahmed Dental College and Hospital at Kolkata, India	389 R. Ahmed Dental College and Hospital at Kolkata, India	Male 196 (87%) Female	Male 302 (78%) Female	47 ± 10.8[a]	50.4 ± 11.5[a]

							28 (13%)	87 (22%)	
	Mitra et al., 2005 (19)	India	**P53 (**rs1042522)	Cross sectional	197 R. Ahmed Dental College and Hospital at Kolkata, India	348 R. Ahmed Dental College and Hospital at Kolkata, India	Male 170 (86%) Female 24 (14%)	Male 265 (76%) Female 81 (24%)	
	Ye et al., 2008 (20)	USA	**P53 (rs1042522)** **P21** **P27** **CDK4** **CDK6** **CCND1** **STK15**	CC paired	147 University of Texas M. D. Anderson Cancer Center in Houston, Texas	147 University of Texas M. D.Anderson Cancer Center in Houston, Texas	Male 82 (55.8%) Female 65 (44.2%)	Male 82 (55.8%) Female 65 (44.2%)	57.5 ±13.6[a]	59.1 ±11.0[a]
	Wang et al., 2010 (21)	Taiwan	**FAS (-1377, G > A and -670, A > G)** **FAS-L (-844, C > T)**	Cross sectional	70 Department of Oral and Maxillofacial Surgery and Pathology, Kaohsiung Medical University Hospital in Southern-Taiwan	280 Department of Oral and Maxillofacial Surgery and Pathology, Kaohsiung Medical University Hospital in Southern-Taiwan	Male 65 (92.9%) Female 5 (7.1%)	Male 133 (47.5%) Female 147 (52.5%)	49.81 ± 10.22[a]	52.08 ± 10.21[a]
	Lin et al., 2008 (22)	Taiwan	**COX-2** (-765, G > C) **P53** (codon 72, rs1042522)	Cross sectional	84 Department of Oral and Maxillofacial Surgery and Pathology, Kaohsiung Medical University Hospital in Southern-Taiwan	333 Department of Oral and Maxillofacial Surgery and Pathology, Kaohsiung Medical University Hospital in Southern-Taiwan	Male 75 (89.35%) Female 9 (10.7%)	Male 188 (56.5%) Female 145 (43.5%)	50.9 ± 10.4[a]	50.6 ± 11.0[a]
	Yang et al. 2008 (23)	USA	**ATM D1853N** **NBS1 E185Q** **BRCA2 N372H** **XRCC3 T241M** **RAG1 K820R**	CC paired	147 The University of Texas M. D. Anderson Cancer Center	147 Kelsey-Seybold Clinic at Houston	Male 82 (55.8%) Female	Male 82 (55.8%) Female	57.5 ±13.6[a]	59.1 ±11.0[a]

			LIG4 T91I) **XRCC3A17893G XRCC4** **IV7-1** **KU80** **XRCC2**					65 (44.2%)	65 (44.2%)	
Oral Lichen	Barkokebas et al., 2011 (24)	Brazil	Mannose-binding lectin gene (**MBL-2**)	CC paired	45 (Oral Medicine unit of Universidade Federal de Minas Gerais, Brazil and Oral Medicine unit of Universidade Federal de Pernambuco)	45 (Oral Medicine unit of Universidade Federal de Minas Gerais, Brazil and Oral Medicine unit of Universidade Federal de Pernambuco)	Male 17 (37.8%) Female 28 (62.2%)	Male 17 (37.8%) Female 28 (62.2%)	45[b] 18—67[c]	45[b] 19–65[c]
	Wu et al., 2013 (25)	China	**CIITA** (rs11074938, rs6498126, rs6498131, rs8063850, rs7189406, rs6498124, rs8048002, rs8043545, rs12932187, rs11647384, rs4774, rs4781011, rs6498122, rs11074939, and rs11074934)	CC	42	86	Male 15 (35.7%) Female 27 (64.3%)	Male 37 (43%) Female 49 (57%)	46.4±14.8[a] 18–79[c]	43.7±8.82[a] 24–71[c]
	Dan et al., 2010 (26)	China	**IL-8** (−251 A/T, rs4073) (+781 C/T, rs2227306)	Cross sectional	109	101	Male 76 (69.7%) Female 33 (30.3%)	Male 72 (71.3%) Female 29 (28.7%)	43.9[a] 16–71[c]	43.5[a] 18–69[c]
	Fujita et al., 2009 (27)	Japan	**FcgRIIA** (131) **FcgRIIB** (775) **FcgRIIIB**(NA) **FcaRI**(324 and 56) **IL-1a** (+4845) **IL-1b** (-31) **IL-1ra** (+2018) **IL-2** (-330) **IL-6** (-572) **IL-10** (1087) **TNFR2** (+587) **TGF-b1** (-509)	Cross sectional	32 (Oral and Maxillofacial Surgery Clinic, Niigata University Medical and Dental Hospital)	99 (Oral and Maxillofacial Surgery Clinic, Niigata University Medical and Dental Hospital)	Male 5 (15.6%) Female 27 (84.4%)	Male 50 (50.5%) Female 49 (49.5%)	59.1[a] 36–83[c]	24.7[a] 28–35[c]

		MMP-1 (-1607)							
Kimkong et al., 2011 (28)	Thailand	**TNF-α** (863, rs1800630) (308, rs1800629) (238, rs361525)	Retrospective	75	154	Male 13 (17.3%) Female 62 (82.7%)	Male 97 (63%) Female 57 (37%)	49.87 ±14.99[a]	30.9 ± 10.6[a]
Chauhan et al., 2013 (29)	India	**TNFα**-308 (rs1800629) **IL-1β**+3954 (rs143634) **IL-6** -597 (rs1800797)	Cross sectional	50 (Dental College, Trivandrum)	51 (Dental College, Trivandrum)	Male 11 (22%) Female 39 (78%)	NR	<40: 12 (24%) 40–50:19 (38%) >50: 19(38%)	NR
Bai et al., 2009 (30)	China	**TNF-α** (-308) **IL-10** (-1082) **IL-10** (-819) **IL-10** (-592)	Cross sectional	151	143	Male 65 (43.0%) Female 86 (57.0%)	Male 64 (44.8%) Female 79 (55.2%)	45[a] 16-75[c]	45.8[a] 16-72[c]
Abdel Hay et al., 2012 (31)	Egypt	**COX-2** (765, G > C)	CC paired	50 (Department of Dermatology, Faculty of Medicine and the Department of Oral Medicine, Diagnosis and Periodontology, Faculty of Oral and Dental Medicine, Cairo University)	50 (Department of Dermatology, Faculty of Medicine and the Department of Oral Medicine, Diagnosis and Periodontology, Faculty of Oral and Dental Medicine, Cairo University)	Male 14 (28%) Female 36 (72%)	Male 10 (20%) Female 40 (80%)	44.24 ± 10.14[a] 44-67[c]	41 ± 11.62[a] 18-62[c]
Yanatatsaneeji et al., 2010 (32)	Thailand	**P53** (codon72, rs1042522)	Cross sectional	97 Faculty of Dentistry, Mahidol University	94	Male 18 (18.6) Female 79 (81.4)	Male 55 (58.5) Female 39 (41.5)	36.2[a]	33.6[a]

Table 2. Polymorphisms studied. OR: odds ratio. [a]Reference category. **NR**: not reported. **NE**: not estimated. **Bold:** OR-CI95% significant. **WW: homozygous wild-type genotype; WM: heterozygous genotype; MM: homozygous variant genotype

Type of Lesion	Author	Country	Gene(s)	Polymorphism(s)	Genotype /Allele	OR	CI95%	Cases	Controls
Oral Leukoplakia	Tanic´ et al., 2009 (8)	Serbia	**P53**	Exon 5			NR	1	0
				Exon 6				8	0
				Exon 7				3	0
				Exon 8				3	0
				Exon 9				0	0
	Majumder et al., 2007 (9)	India	**XRCC1**	194, Arg>Trp	Arg/Arg[a]			177 (79%)	317 (82%)
					Arg/Trp	0.9	0.9–1.1	43 (19%)	62 (16%)
					Trp/Trp	0.9	0.8–1.2	4 (2%)	8 (2%)
				280, Arg> His	Arg/Arg[a]			160 (73%)	297 (77%)
					Arg/His	1.0	0.9–1.0	58 (26%)	87 (22%)
					His/His	1.0	0.9–1.0	2 (1%)	3 (1%)
				399, Arg>Gln	Arg/Arg[a]			100 (45%)	170 (44%)
					Arg/Gln	0.8	0.6–1.3	95 (42%)	179 (47%)
					Gln/Gln	0.9	0.9–1.0	29 (13%)	36 (9%)
			XPD	156, Arg>Arg	CC[a]			73 (33%)	124 (32%)
					AC	0.9	0.8–1.1	103 (46%)	191 (49%)
					AA	0.9	0.9–1.1	44 (21%)	73 (19%)
				312	Asp/Asp[a]			117 (52%)	205 (53%)
					Asp/Asn	0.9	0.9–1.1	89 (40%)	146 (38%)
					Asn/Asn	0.9	0.7–1.2	18 (8%)	36 (9%)
				751	Lys/Lys[a]			105 (47%)	190 (49%)
					Gln/Lys	0.9	0.9–1.1	98 (44%)	158 (41%)
					Gln/Gln	0.9	0.9–1.1	21(9%)	40 (10%)
	Shukla et al., 2013 (10)	India	**GSTM1**	Null	Present[a]			60 (69%)	114 (80.9%)

		CYP1A1		Null	1.9	0.65-5.52	27 (31%)	27 (19.1%)
				m1/m1[a]			57 (63.3%)	72 (48%)
				m1/m2	0.37	0.13-1.04	21 (23.3%)	72 (48%)
				m2/m2	2.53	0.4-15.30	12 (13.3%)	6 (4%)
Pu et al., 2009 (11)	USA	**COX-2**	−765, G > C, rs20417	WW*[a]	0.7	0.41−1.20	97 (72.4%)	90 (62.5%)
				WM+MM**			37 (27.4%)	54 (37.5%)
			Exon 10, +837, T > C, rs5275	**WW [a]**	**0.48**	**0.28-0.80**	**70 (51.5%)**	**50 (34.5%)**
				WM+MM			**66 (48.5%)**	**95 (65.5%)**
			Exon 10, −90, C > T, rs68479	WW [a]	0.43	0.14-1.33	131 (96.3%)	132 (91.3%)
				WM+MM			5 (3.7%)	13 (8.7%)
Duarte et al., 2006 (12)	Brazil	**GSTM1**	Null	0/0[a]	2.57	1.16–5.69	30 (57.7%)	18 (34.6%)
				+/0 or +/+			22 (42.3%)	34 (65.4%)
Duarte et al., 2006 (13)	Brazil	**GSTT1**	Null	0/0[a]	2.45	1.23-4.91	35 (48.6%)	20 (27.8%)
				+/0 or +/+			37 (51.4%)	52 (72.2%)
Mahimkar et al.,		**CYP1A1**	MspI	m1/m1[a]			22 (37.9%)	30 (52.6%)

			m1/m2	**2.39**	**1.10-5.17**	**35 (60.3%)**	**20 (35.1%)**
			m2/m2	0.19	0.03-1.34	1 (1.7%)	7 (12.3%)
	GSTM1	Null	Not null[a]			43 (72.9%)	33 (63.5%)
			Null	0.64	0.29-1.44	16 (27.1%)	19 (36.5%)
	GSTT1	Null	Not null[a]			31 (93.9%)	44 (100%)
			Null		NE	2 (6.1%)	0 (0%)
	GSTP1	Ile105Val	Ile/Ile[a]			23 (46.9%)	25 (48.1%)
			Ile/Val	0.88	0.40–1.96	22 (44.9%)	27 (51.9%)
			Val/Val		NE	4 (8.2%)	0 (0%)
	XRCCI	Arg194Trp	Arg/Arg[a]			43 (74.1)	44 (77.2%)
			Arg/Trp	1.18	0.51–2.74	15 (25.9)	13 (22.8%)
			Trp/Trp		NE	0 (0%)	0 (0%)
		Arg399Gln	Arg/Arg[a]			24 (40.7%)	25 (43.9%)
			Arg/Gln	1.17	0.54–2.56	27 (45.8%)	24 (42.1%)
			Gln/Gln	1.04	0.35–3.14	8 (13.6%)	8 (14%)
	XPD	Lys751 Gln	Lys/Lys[a]			26 (45.6%)	29 (53.7%)
			Lys/Gln	0.97	0.44–2.15	20 (35.1%)	23 (42.6%)
			Gln/Gln	**5.58**	**1.23–24.53**	**10 (17.5%)**	**2 (3.7%)**
		Asp312Asn	Asp/Asp[a]			23 (57.5%)	23 (51.1%)

				Asp/Asn	0.62	0.25–1.51	13 (32.5%)	21 (46.7%)
				Asn/Asn	4	0.54–28.25	4 (10%)	1 (2.2%)
		hOGG1	Ser326Cys	Ser/Ser[a]			24 (40%)	21 (37.5%)
				Ser/Cys	0.73	0.33–1.6	25 (41.7%)	30 (53.6%)
				Cys/cys	1.75	0.53–5.7	10 (16.7%)	5 (8.9%)
Mondal et al., 2013 (15)	India	**MRE11A**	rs12360870	G	2.264	1.702–3.013		
				A			(27.9%)	
		PRKDC	**rs7003908**	A	**0.162**	**0.062–0.427**		
				C			(**8.8%**)	
		XRCC5	rs207943	C				
				G				
		MSH3	rs12515548	A				
				G				
Duarte et al., 2008 (16)	Brazil	**GSTM1**	Null	+/– or +/+[a]	**2.10**	**1.07-4.14**	38 (47.5%)	53 (66.2%)
				-/-			**42** (**52.5**%)	**27** (**33.8**%)
		GSTT1	Null	+/– or +/+[a]	2.07	0.97-4.42	49 (61.2%)	62 (77.5%)
				-/-			31 (38.8%)	18 (22.5%)
		GSTP1	105, Ile/Val	AA[a]			30 (37.5%)	34 (42.5%)
				AG	1.61	0.79-3.26	45 (56.2%)	39 (48.7%)
				GG	1.04	0.27-3.93	5 (6.3%)	7 (8.8%)
		CYP1A1	462, Ile/Val	AA[a]			12 (15.0%)	13 (16.2%)
				AG	1.34	0.53-3.37	66 (82.5%)	67 (83.8%)
				GG	NE	NE	2 (2.5%)	0 (0%)
		CYP2E1	-1019, Rsal	+/+[a]			76 (95.0%)	69 (86.2%)
				+/-	0.31	0.07-1.37	4 (5.0%)	11 (13.8%)
			-1259, PstI	-/-[a]			75 (93.8%)	72 (90.0%)
				+/-	0.89	0.19-4.13	5 (6.2%)	8 (10%)
Majumder et al., 2012 (17)	India	**NAT1**	445, G > A, rs4987076	G/G (Ile/Ile)[a]			215 (96%)	368 (95%)
				G/A (Ile/Val)	0.8	0.3-1.8	9 (4%)	21 (5%)
				A/A (Val/Val)			0 (0%)	0 (0%)
			559, C > T, rs4986782	G/G (Gln/Gln)[a]			224 (73%)	388 (99%)
				G/A (Gln/Arg)		NE	0 (0%)	1 (1%)

				A/A (Arg/Arg)		NE	0 (0%)	0 (0%)
			1088, T > A, rs1057126	T/T[a]			102 (48%)	171 (47%)
				T/A	0.9	0.6-1.3	78 (37%)	146 (40%)
				A/A	1.0	0.8-1.3	32 (15%)	51 (13%)
			1095, C > A, rs15561	C/C[a]			98 (44%)	167 (43%)
				C/A	0.9	0.8-1.1	88 (39%)	164 (42%)
				A/A	0.9	0.9-1.1	37 (17%)	57 (15%)
Datta et al., 2007 (18)	India	**mt**	12308np	G[a]			50 (22%)	71 (18%)
				A	0.79	0.53- 1.18	173 (78%)	312 (82%)
			10398np	A[a]			89 (40%)	144 (38%)
				G	1.10	0.79-1.55	134 (60%)	239 (62%)
Mitra el al., 2005 (19)	India	**P53**	Intron 3	**1/1[a]**	**0.5**	**0.4–0.8**	**150 (78.5%)**	**226 (66.1%)**
				2/2+ 1/2			**41 (21.5%)**	**116 (33.9%)**
			Intron 6	**2/2[a]**	**1.6**	**1.1–2.3**	**132 (69.8%)**	**212 (61.6%)**
				1/1 + 1/2			**57 (30.2%)**	**132 (38.4%)**
			Codon 72, rs1042522	1/1 + 1/2[a]	0.7	0.5–1.1	124 (64.9%)	257 (75.2%)
				2/2			67 (35.1%)	85 (24.8%)
Ye et al., 2008 (20)	USA	**P53**	Intron 3	No insert			76 (68.5%)	103 (70.1%)
				1 insert	1.17	0.65-2.11	33 (29.7%)	41 (27.9%)
				2 insert	1.15	0.16-8.48	2 (1.80%)	3 (2.0%)
			Intron 6	GG			73 (71.6%)	104 (71.2%)
				GA	1.04	0.56-1.91	27 (26.4%)	40 (27.4%)
				AA	2.18	0.27-17.68	2 (2.0%)	2 (1.4%)
			Codon 72, rs1042522	GG			62 (56.4%)	68 (49.6%)
				GC	0.83	0.47-1.46	42 (38.2%)	53 (38.7%)
				CC	0.47	0.15-1.44	6 (5.4%)	16 (11.7%)
		P21	3’ UTR	CC			116 (84.7%)	121 (84.6%)
				CT	0.92	0.44-1.91	19 (13.9%)	21 (14.7%)
				TT	2.36	0.16-35.96	2 (1.5%)	1 (0.7%)
		P27	5’ UTR	CC			65 (52.9%)	82 (56.6%)
				CT	0.99	0.57-1.71	48 (39.0%)	55 (37.9%)
				TT	1.45	0.48-4.36	10 (8.1%)	8 (5.5%)
		CDK4	3’ UTR	AA			64 (47.1%)	73 (51.1%)
				AC	1.29	0.76-2.19	64 (47.1%)	56 (39.2%)
				CC	0.64	0.24-1.72	8 (5.9%)	14 (9.8%)
		CDK6	3’ UTR	CC			86 (66.7%)	81 (57.0%)
				CT	0.64	0.37-1.13	35 (27.1%)	55 (38.7%)
				TT	1.62	0.50-5.17	8 (6.2%)	6 (4.2%)
		CCND1	P241P	GG			37 (25.7%)	56 (38.1%)

				AG	1.58	0.89-2.83	70 (48.6%)	69 (46.9%)
				AA	2.75	1.33-5.71	37 (25.7%)	22 (15.0%)
		STK15	F31I	TT			78 (57.4%)	88 (61.1%)
				TA	1.08	0.64-1.83	49 (36.0%)	53 (36.8%)
				AA	2.49	0.59-10.46	9 (6.6%)	3 (2.1%)
Wang et al., 2010 (21)	Taiwan	**FAS**	1377, G > A	GG[a]			25 (29.8%)	115 (34.5%)
				GA	0.83	0.47–1.46	42 (50.0%)	165 (49.6%)
				AA	0.90	0.44–1.85	17 (20.2%)	53 (15.9%)
			670, A > G	AA[a]			25 (29.8%)	106 (31.8%)
				AG	0.93	0.52–1.63	41 (48.8%)	180 (54.1%)
				GG	0.90	0.45–1.83	18 (21.4%)	47 (14.1%)
		FAS-L	-844, C > T	TT			7 (8.3%)	28 (8.4%)
				CT	1.16	0.41–2.97	42 (50.0%)	123 (36.9%)
				CC	1.88	0.66–4.88	35 (41.7%)	182 (54.7%)
Lin et al., 2008 (22)	Taiwan	**COX-2**	-765, G > C	G/G[a]			65 (92.9%)	107 (38.2%)
				G/C + C/C	6.73	2.84–19.87	5 (7.1%)	173 (61.8%)
		P53	Codon 72, rs1042522	Arg72Arg[a]			18 (25.7%)	72 (25.7%)
				Arg72Pro	0.68	0.35–1.26	42 (60.0%)	152 (54.3%)
				Pro72Pro	0.84	0.35–2.12	10 (14.3%)	56 (20.0%)
Yang et al., 2008 (23)	USA	**ATM**	D1853N, rs1801516	GG[a]			102 (74.5%)	114 78.6
				GA	1.40	0.74–2.62	30 (21.9%)	28 (19.3%)
				AA	2.85	0.62–13.11	5 (3.6%)	3 (1%)
		NBS1	E185Q, rs1805794	CC[a]			67 (48.9%)	67 (46.5%)
				CG	1.06	0.62–1.81	59 (43.1%)	59 (40.9%)
				GG	0.54	0.22–1.30	11 (8.0%)	18 (12.5%)
		BRCA2	N372H, rs144848	TT[a]			70 (51.1%)	76 (53.1%)
				TG	1.01	0.59–1.72	59 (43.1%)	54 (37.8%)
				GG	0.64	0.23–1.80	8 (5.8%)	13 (9.1%)
		XRCC2	C41657T, rs718282	CC[a]			119 (87.5%)	131 (92.3%)
				CT	1.59	0.67–3.77	16 (11.8%)	11 (7.7%)
				TT		NE	1 (0.7%)	0 (0%)
		XRCC3	T241M**,** rs861539	CC[a]			63 (42.9%)	66 (44.9%)
				CT	1.15	0.68–1.95	63 (42.9%)	65 (44.2%)
				TT	1.41	0.64–3.11	21 (14.3%)	16 (10.9%)
		XRCC3	**A17893G, rs1799796**	AA[a]			63 (46.3%)	54 (37.5%)
				AG	0.85	0.49–1.48	66 (48.5%)	63 (43.8%)
				GG	**0.18**	**0.07–0.47**	**7** (**5.1**%)	**27** (**18.8**%)
		RAG1	K820R, rs2227973	AA[a]			107 (78.1%)	116 (80.0%)
				AG	1.13	0.59–2.14	28 (20.4%)	25 (17.2%)

			XRCC4	IV7-1, G > A, rs1805377	GG	0.47	0.08–2.82	2 (1.5%)	4 (2.8%)
					GG[a]			98 (72.1%)	109 (74.7%)
					GA	1.13	0.61–2.06	32 (23.7%)	31 (21.2%)
			KU80	Exon 21, +466, A > G, rs1051685	AA	0.61	0.14–2.64	5 (3.7%)	6 (4.1%)
					AA[a]			106 (74.6%)	108 (76.1%)
					AG	1.13	0.62–2.09	31 (21.8%)	31 (21.8%)
			LIG4	T911, rs1805388	GG	0.87	0.19–4.12	5 (3.5%)	3 (2.1%)
					CC[a]			93 (68.4%)	93 (64.1%)
					CT	0.74	0.43–1.29	40 (29.4%)	49 (33.8%)
					TT	1.34	0.23–7.69	3 (2.2%)	3 (2.1%)
Oral Lichen	Barkokebas et al., 2011 (24)	Brazil	**MBL-2**		A/A[a]	1.254	0.72–1.85	25 (55.6%)	24 (53.3%)
					A/0			19 (42.2%)	16 (35.5%)
					0/0			1 (2.2%)	5 (11.2%)
	Wu et al., 2013 (25)	China	**CIITA**	rs11074938	A[a]	0.737	0.437–1.243	40 (47.6%)	95 (55.2%)
					G			44 (52.4%)	77 (44.8%)
				rs6498126	C[a]	1.135	0.648–1.988	58 (69.0%)	114 (66.3%)
					G			26 (31.0%)	58 (33.7%)
				rs6498131	T[a]	1.516	0.809–2.843	21 (25.0%)	31 (18.0%)
					C			63 (75.0%)	141 (82.0%)
				rs8063850	A[a]	1.802	0.745–4.358	10 (11.9%)	12 (7.0%)
					T			74 (88.1%)	160 (93.0%)
				rs7189406	A[a]	1.002	0.594–1.690	44 (52.4%)	90 (52.3%)
					G			40 (47.6%)	82 (47.7%)
				rs6498124	T[a]	1.235	0.726–2.099	36 (42.9%)	65 (37.8%)
					G			48 (57.1%)	107 (62.2%)
				rs8048002	T[a]	1.515	0.772–2.973	70 (83.3%)	132 (76.7%)
					C			14 (16.7%)	40 (23.3%)
				rs8043545	C[a]	0.957	0.567–1.616	45 (53.6%)	94 (54.7%)
					G			39 (46.4%)	78 (45.3%)
				rs12932187	C[a]	0.893	0.520–1.532	52 (61.9%)	111 (64.5%)
					G			32 (38.1%)	61 (35.5%)
				rs11647384	A[a]	0.908	0.538–1.531	39 (46.4%)	84 (48.8%)
					G			45 (53.6%)	88 (51.2%)
				rs4774	**C[a]**	**0.418**	**0.198–0.882**	**10 (11.9%)**	**42 (24.4%)**
					G			**74 (88.1%)**	**130 (75.6%)**
				rs4781011	T[a]	0.796	0.333–1.902	75 (89.3%)	157 (91.3%)
					G			9 (10.7%)	15 (8.7%)
				rs6498122	**A[a]**	**2.099**	**0.989–4.452**	**74 (88.1%)**	**134 (77.9%)**
					G			**10 (11.9%)**	**38 (22.1%)**

			rs11074939	A[a]	1.097	0.608–1.977	23 (27.4%)	44 (25.6%)
				G			61 (72.6%)	128 (74.4%)
			rs11074934	T[a]	0.94	0.534–1.657	58 (69.0%)	121 (70.3%)
				C			26 (31.0%)	51 (29.7%)
Dan et al., 2010 (26)	China	**IL-8**	−251, A/T	AA[a]	0.208	0.050–0.862	13 (11.9%)	18 (17.8%)
				AT	(relative to		55 (50.5%)	51 (50.5%)
				TT	control)		41(37.6%)	32 (31.7%)
			+781, C/T	CC	NR	NR	40 (36.7%)	38 (37.6%)
				CT			59 (54.1%)	46 (45.5%)
				TT			10 (9.2%)	17 (16.8%)
Fujita et al., 2009 (27)	Japan	**FcγRIIA**	131	A[a]	1.45	0.68-3.10	54 (84.4%)	156 (78.8%)
				G			10 (15.6%)	42 (21.2%)
		FcγRIIB	775	T[a]	1.09	0.54-2.18	51 (79.7%)	155 (78.3%)
				C			13 (20.3%)	43 (21.7%)
		FcγRIIIB	NA	NA1[a]	1.61	0.91-2.84	33 (51.6 %)	125 (63.1%)
				NA2			31 (48.4 %)	73 (36.9%)
		FcαRI	324	G[a]	1.01	0.54-1.89	46 (71.9 %)	142 (71.7%)
				A			18 (28.1%)	56 (28.3%)
			56	T[a]	1.52	0.86-2.68	35 (54.7%)	128 (64.6%)
				C			29 (45.3%)	70 (35.4%)
		IL-1α	+4845	G[a]	5.54	0.72-42.62	63 (98.4%)	182 (91.9%)
				T			1 (1.6%)	16 (8.1%)
		IL-1β	-31	T[a]	1.05	0.60-1.86	33 (51.6%)	105 (53.0%)
				C			31 (48.4%)	93 (47.0%)
		IL-1ra	+2018	T[a]	1.32	0.42-4.10	60 (93.8%)	182 (91.9 %)
				C			4 (6.3%)	16 (8.1%)
		IL-2	-330	T[a]	1.09	0.60-1.97	42 (65.6%)	126 (63.6%)
				G			22 (34.4 %)	72 (36.4%)
		IL-6	-572	C[a]	1.06	0.53-2.12	51 (79.7%)	156 (78.8%)
				G			13 (20.3%)	42 (21.2%)
		IL-10	-1087	A[a]	1.17	0.30-4.54	61 (95.3%)	190 (96.0 %)
				G			3 (4.7%)	8 (4.0%)
		TNFR2	**+587**	**T[a]**	**2.17**	**0.99-4.77**	**52 (81.3%)**	**179 (90.4%)**
				G			**12 (18.8%)**	**19 (9.6%)**
		TGF-β1	-509	C[a]	1.16	0.66-2.04	35 (54.7%)	101 (51.0%)
				T			29 (45.3%)	97 (49.0%)

		MMP-1	-1607	1G[a]	1.25	0.70-2.23	26 (40.6%)	70 (35.4%)
				2G			38 (59.4%)	128 (64.6%)
	Kimkong et al., 2011(28)	Thailand	**TNF-α**	-863 (rs1800630)	AA	NR	NR	5 (6.67%)	6 (3.90%)
					AC			8 (10.67%)	35 (22.72%)
					CC			62 (82.66%)	113 (73.38%)
				-308 (rs1800629)	**AA[a]**	**10.93** AA compared with AG+ GG genotype (total OLP vs healthy control)	**1.21–251.9**	**5 (6.67%)**	**1 (0.65%)**
					AG			**7 (9.33%)**	**28 (18.18%)**
					GG			**63 (84%)**	**125 (81.17%)**
				-238 (rs361525)	AA			0 (0%)	0 (0%)
					AG	NR	NR	8 (10.67%)	11 (7.14%)
					GG			67 (89.33%)	143 (92.86%)
	Chauhan et al., 2013 (29)	India	**TNFα**	**-308 (rs1800629)**	G[a]			88 (88.0%)	101 (99.1%)
					A	**13.77**	**1.755-108.1**	**12 (12.0%)**	**1 (0.9%)**
			IL-1β	+3954 (rs143634)	C			79 (79.0%)	87 (85.3%)
			IL-6	-597 (rs1800797)	T	0.648	0.3127-1.345	21 (21.0%)	15 (14.7%)
					G			80 (80.0%)	77 (77.5%)
					A	1.30	0.667-2.53	20 (20.0%)	25 (24.5%)
	Bai et al.,2009 (30)	China	**TNF-α**	**-308**	**GG[a]**	**2.268**	**1.084–4.744**	**63 (77.8%)**	**127 (88.8%)**
					GA+AA			**18 (22.2%)**	**16 (11.2%)**
			IL-10	-1082	GG[a]	NR	NR	0 (0%)	3 (2.1%)
					GA+AA			70 (100%)	140 (97.9%)
			IL-10	-819	CC[a]	NR	NR	23 (15.2%)	28 (19.6%)
					CT+TT			128 (84.8%)	115 (80.4%)
			IL-10	-592	CC[a]	NR	NR	23 (15.2%)	28 (19.6%)
					CA+AA			128 (84.8%)	115 (80.4%)
	Abdel Hay et al., 2012 (31)	Egypt	**COX-2**	-765, G > C	GG[a]			30 (60%)	30 (60%)
					GC	1.102	0.464–2.615	14 (28%)	15 (30%)
					CC	0.815	0.232–2.865	6 (12%)	5 (10%)
	Yanatatsaneeji et al., 2010 (32)	Thailand	**P53**	**Codon 72 (rs1042522)**	**GG[a]**	3.17	1.58-7.25	**16 (16.49%)**	**27 (28.72%)**
					GC[a]			**36 (37.11%)**	**47 (50.00%)**
					CC			**45 (46.39%)**	**20 (21.28%)**

Table 3. Oral Submucous Fibrosis**.**Polymorphisms studied. OR: odds ratio. *Reference category. **NR**: not reported. **Bold:** OR-CI95% significant association. Age (years) Average ± SD[a] or Median[b]and range[c]

Author	Country (Place)	Gene	Polymorphism	Genotype /Allele	OR	CI95%	Cases n (%)	Controls n (%)	Other data
Liu et al., 2004 (33)	Taiwan	**MICA**	Intron 4 Exon 5	A4		NR	18 (23%)	107 (31%)	*Cases*, n=80 Male=79 (98.75%) Female= 1 (1.25%) Age=39.47±7.7[a]; 21-67[c] *Controls*, n=351 Male=185 (52.71%) Female=166 (47.29%) Age=42.1±10.7[a]; 22-71[c]
				A5		NR	44 (55%)	174 (50%)	
				A5.1		NR	36 (45%)	127 (36%)	
				A6	**3.48**	**1.8-6.71**	**18 (23%)**	**25 (8%)**	
				A9		NR	22 (28%)	32 (18%)	
Mukherjee et al., 2012 (34)	India	**NAT2**	481,C > T (rs1799929)	C*			94 (60.2%)	135 (68.8%)	
				T	1.46	0.94–2.26	62 (39.8%)	61 (31.1%)	
			Arg197Gln (rs1799930)	G*			152 (90.4 %)	178 (89.89%)	
				A	0.94	0.47–1.85	16 (9.6%)	20 (10.1%)	*Cases*, n=88 Male=48 (54.55%) Female=40 (45.45%)
			Lys268Arg (rs1208)	**A***			**90 (57.7%)**	**154 (77%)**	
				G	**2.45**	**1.55–3.87**	**66 (42.3%)**	**46 (22%)**	
			Gly286 Glu (rs1799931)	**G***			**92 (64.8%)**	**165 (84.18%)**	*Controls*, n=100 Male=61 (61.0%) Female=39 (39.0%)
				A	**2.89**	**1.73–4.83**	**50 (33.2%)**	**31 (15.8%)**	
		XRCC1	Arg194Trp (rs25487)	C*			142 (88.7%)	159 (80.3%)	Age= split as <38 and >38
				T	0.52	0.28–0.94	18 (12.3%)	39 (20.7%)	
			Arg 399 >Gln (rs 1799782)	G*			102 (59.3%)	127 (64.8%)	
				A	1.26	0.83–1.92	70 (40.7%)	69 (35.2%)	
		XRCC3	**Thr 241Met (rs861539)**	**C***			**125 (75.3%)**	**170 (86.7%)**	
				T	**2.15**	**1.25–3.77**	**41 (24.7%)**	**26 (13.3%)**	
Lin et al., 2008 (22)	Taiwan	**COX-2**	**-765, G > C**	**G/G***			**32 (82.05%)**	**107 (38.2%)**	*Cases*, n=39 Age= 43.10 ± 9.38* Male=39 (100.0%) Female=0 (0%) *Controls*, n=280 Age=52.08 ± 10.21[a] Male=133 (47.5%) Female=147 (52.5%)
				G/C + C/C	**3.20**	**1.32–8.94**	**7 (17.94%)**	**173 (61.8%)**	
		P53	Codon 72, rs1042522	Arg72Arg*			12 (30.77%)	72 (25.7%)	
				Arg72Pro	0.87	0.38–1.96	20 (51.28%)	152 (54.3%)	
				Pro72Pro	0.79	0.28–2.40	7 (17.94%)	56 (20.0%)	
Wang et al., 2010 (21)	Taiwan	**FAS**	**1377, G > A**	GG*			26 (49.1%)	115 (34.5%)	*Cases*, n=53 Age= 46.2 ± 10.2* Male=53 (100.0%) Female=0 (0%)
				GA	1.54	0.81–2.93	25 (47.2%)	165 (49.6%)	
				AA	**8.15**	**2.26–52.43**	**2 (3.8%)**	**53 (15.9%)**	
			670, A > G	AA*			27 (50.9%)	106 (31.8%)	
				AG	**1.92**	**1.01–3.72**	**22 (41.5%)**	**180 (54.1%)**	

	FAS-L	-844, C > T	**GG**	**4.42**	**1.59–15.80**	**4 (7.6%)**	**47 (14.1%)**	*Controls*, n=333 Age=50.6 ± 11.0* Male=188 (56.5%) Female=145 (43.5%)
			TT*			3 (5.7%)	28 (8.4%)	
			CT	0.62	0.13–2.11	29 (54.7%)	123 (36.9%)	
			CC	1.20	0.26–4.15	21 (39.6%)	182 (54.7%)	