Abstract. Squamous cell carcinoma (SCC) is the most common epithelial malignancy in the oral cavity. SCCs and their variants constitute over 90% of oral malignancies, and the disease is associated with poor prognosis. OSCC is a complex malignancy where environmental factors, virus infections, and genetic alterations most likely interact, and thus give rise to the malignant condition. Herein, we review the available literature regarding high-risk factors such as alcohol and tobacco usage; discuss the roles of human papillomaviruses (HPV), the Epstein-Barr virus, and the human herpes simplex virus (HSV); and evaluate several candidate genes associated with the condition: p53, p16INK4 and p21WAF1/CIPI, survivin, B-cell lymphoma-2 (BCL-2), keratins, Fibroblast growth factor 3 (FGF3), FGF4, FGF19, Oral cancer overexpressed gene 1 (ORAOV1), and Cyclin D1 (CCND1).

Oral cancer is usually defined as a neoplastic disorder in the oral cavity, which includes the following areas: lip, buccal mucosa, lower and upper alveolar ridges, retromolar gingiva, oropharynx, floor of the mouth, hard palate, and the anterior two thirds of the tongue (1).

Squamous cell carcinoma (SCC) is by far the most common epithelial malignancy in the oral cavity. SCCs and their variants constitute over 90% of oral malignancies. Over 90% of OSCCs arise from pre-existing potentially malignant lesions (2). Although some primary tumours can be treated, many patients will develop secondary primary tumours, suggesting multifocal tumour development. Two major aetiological factors in SCC of the oral cavity are social habits of tobacco use and alcohol consumption (3, 4).

Four groups of genes are involved in the multiple genetic events of malignant cell transformation: oncogenes, tumour-suppressor genes, DNA repair genes, and DNA sequences that control apoptosis. The normal function of the p53 tumour-suppressor gene, located on the short arm of chromosome 17, is that of the guardian of genome (5). Damage to DNA is associated with nuclear accumulation of the p53 protein, presumably inducing growth arrest for repair or induction of apoptotic cell death (6). Mutation in the p53 gene is frequently found in human cancer, and in 40-50% causes of SCC of the head and neck (7). These mutations most likely result from carcinogen-induced DNA damage (8). Elevated p53 expression has been reported in patients with head and neck SCC and a history of heavy smoking (9) and heavy alcohol use (10).

Both epidemiological and molecular data suggest that certain types of human papillomaviruses (HPV), as well as some members of the Herpesviridae family, such as Epstein-Barr virus (11) and human herpes simplex virus (HSV), have an oncogenic capability (12-17).

Tobacco Smoking

It has been known for decades that smoking is one of the strongest risk factors for oral cancer. Epidemiological investigations have shown that heavy tobacco smoking is a major risk factor for the development of oral cancer (7, 18-23). Tobacco smoke condensate contains substances that act as both initiators and promoters of carcinogenesis. The risk of cancer development from smoking remains significant up to approximately five years after quitting, but beyond that time, the risk decreases (1). Recent studies from India and China have also confirmed this knowledge (24, 25). In pipe smokers, the risk for lip cancer development is slightly elevated (26).

Alcohol

Studying the isolated effect of the use of alcohol in humans has several problems. Not only are heavy drinkers frequently heavy smokers (27), but the accuracy of the self-reported use of
alcohol is poor, partly because social acceptance of alcohol abuse is lower than the one for tobacco use (28). Nevertheless, the correlation between the use of alcohol and the development of oral cancer has been confirmed (11, 18, 29), and heavy use of alcohol, especially in combination with heavy tobacco use (30), might be a major risk factor for cancer development in the oral cavity (7, 29, 31, 32). Animal studies have shown that ethanol promotes 4-NQO-induced oral carcinogenesis. The relative risk from smoking and alcohol, each taken independently, is nearly identical, but taken together, their effects may be synergistic for oral cancer development (27), with a nearly sevenfold increase of risk (23). The effect of alcohol-containing mouthwashes has been studied with regard to oral cancer development, and studies have shown that the use of alcohol-based mouth rinses increase the risk of oral cancer (33, 34).

**Smokeless Tobacco**

The International Agency for Research on Cancer (IARC) concluded that “there is sufficient evidence that the use of smokeless tobacco (ST) can cause oral cancer in humans and that chewing tobacco may increase the risk for oral cancer development” (35). ST products contain a large array of carcinogens, although the number found is actually smaller than in cigarette smoke (35).

There are two main types of ST: chewing tobacco and snuff. Worldwide, various names are used to denote ST products: plug, gutkha, khwam, khaini, iq’milk, zarda, naswar, nax, chimo, toombak, shamma, gudhaku, gul, mishri, maras, and moist snus. Approximately 150 million people use ST worldwide (35).

Benz(a)pyrene and other polycyclic aromatic carcinogens are the most important carcinogenic agents in the cigarette smoke; in unburnt tobacco, however, tobacco-specific nitrosamines (TSNAs) are the strongest carcinogens (36). The metabolites of nitrosamines, particularly nitrosornicotine (NNN) and 4-(methyl(nitrosamino)-1-(3-pyridyl)-1-butane (NNK), are found locally in the saliva of ST users and in their body fluids. These agents are known to cause toxic effects, particularly cancer (36) and other cellular and DNA changes, at the local placement sites, and indirectly and systemically. Epidemiological evidence of a significantly increased risk of oral cancer in ST users was recently reviewed (35). Even ST products that are claimed to be low in nitrosamines, are likely to raise the risk of oral cancer among users by up to 30% (37).

**Snuff.** Among the high-income countries, Sweden has the highest per capita consumption of smokeless tobacco, predominantly in the form of oral moist snuff. Swedish snuff (snus) contains lower levels of some harmful substances, for example, nitrosamines, than do many brands available in North America and some low-income countries (38). In a Swedish study, Hirsch et al., reported 16 oral cancer cases among Swedish snuff dippers: The mean age of the patients at the time of diagnosis was 72.9 years and the mean time of snuff use prior to cancer diagnosis was 42.9 years (39). Their cancers developed at exactly the location where the snuff was placed, mostly on the upper vestibulum, and all were pathologically confirmed as SCCs (39). Zatterstrom et al. (40) described a case of well-differentiated oral carcinoma in a 90-year-old Swedish man who had been a habitual snuff-dipper for 70 years. In a population-based prospective study, Roosaar et al. provided suggestive evidence that snus-related risks cannot be lightly ignored, evidence inconsistent with claims that the use of Scandinavian moist snus is without demonstrable risk (41, 42). In a study of the interactive effect of Swedish snuff and Sudanese toombak on human oral cells, Costea et al. demonstrated that toombak has greater potential to induce abnormal development of normal mucosa than does Swedish snuff (43). In a population-based case–control study in southern Sweden, Rosenquist et al. (44) demonstrated that both tobacco smoking and alcohol consumption are risk factors for oral and oropharyngeal SCC, and that using Swedish moist snuff had no effect on the risk.

**Betel quid.** Betel quid/areca nut use has long been common in South and Southeast Asia and the Asia Pacific region and is still common among migrant communities in Africa, Europe, and North America. Areca nut (usually incorporated into betel quid) is the fourth most common psychoactive substance in the world, after caffeine, alcohol, and nicotine, being used by several hundred million people. It is now well-accepted that the use of areca nut causes oral submucous fibrosis (OSMF) (45). According to IARC, there is evidence of the carcinogenic risk of chewing betel quid with or without tobacco (35). When betel is chewed, it produces mild psychoactive and cholinergic effects, and its use is associated with pre-malignant oral leukoplakia, OSMF, and SCC (46).

**Toomboak.** In Sudan, ST is usually used in a form of oral dipping tobacco, locally called toomboak, which was introduced over 400 years ago (47). Toomboak is not chewed but dipped and retained between the gums and the lips, cheeks, or floor of the mouth, and sucked slowly for approximately 10-15 minutes (48). Toomboak differs from the types of snuff used in Scandinavia and the USA in terms of tobacco species, fermentation, aging, manufacturing methods, pH, moisture, and nitrosamine content (48). The factors of toomboak are believed to have significant adverse health consequences, particularly in terms of addiction and oral cancer development, are its pH (range 8-11) and high levels of tobacco-specific nitrosamines (48) (TSNAs), particularly NNN and NNK, are found in the saliva and body fluids of toomboak dippers (48-50). Compared with snuff from Sweden and the USA, toomboak contains 100-fold higher levels of TSNAs (37).
Toombak dippers develop a clinically and histologically characteristic lesion at the site of dipping. Researchers have demonstrated that the use of toombak plays a significant role in the aetiology of oral SCC, the TSNAs present in toombak possibly acting as principal carcinogens (47, 51, 52).

**Viruses**

The impact of viruses regarding oral SCC has been studied since the beginning of the 20th century, when Ellerman and Bang, and Rous isolated an infective agent which later was shown to be a virus that had the ability to induce tumours in chickens (53, 54). During the 1930s, Richard Shope was able to transfer a papillomavirus, by using cell-free medium, to rabbits (55). Groupe et al. showed in various studies that leukaemia and sarcoma could be induced in mice through an infectious virus (56). Another major step was achieved when two research groups successfully transformed cells which were infected with Rous sarcoma virus, into mice (56, 57). It was thereby possible to identify specific viral oncogenes that could transform normal cells into cancer cells.

**HPV.** Human papillomavirus (HPV) was identified as a causal agent of cervical cancer by zur Hausen and colleagues in 1983 (58). The association of HPV with oral cavity and oropharyngeal cancer was first reported by Loning et al. (59) and de Villiers et al. (60) in 1985 (61). HPV types detected were classified into (i) non-oncogenic (low-risk, such as HPV6, 11, 26) and (ii) oncogenic (high-risk, such as HPV16, 18, 31) categories, according to the World Health Organization's International Agency for Research on Cancer (62). The molecular mechanism of viral oncogenesis of HPV has been established. After viral infection, disruption occurs most frequently in an E2-open reading frame of the HPV genome (integration), and the break of E2 allows for the dysregulation of the E6/E7 oncoprotein. The viral protein, E6, promotes the degradation of p53, and E7 inactivates the retinoblastoma protein (pRb), which leads to cell cycle dysregulation and eventually to malignant transformation (63). HPV 16 and 18 seem to be the most important viruses responsible for tumourigenesis and can be found in pre-malignant and malignant lesions of the oral cavity in up to 80% of cases (64). HPV is a risk factor for head and neck cancer, of which approximately 25% are infected with HPV (65). In the past, oral cancers were mainly encountered in the elderly, whereas today the rise in oral cancer mortality is among the largest recorded for any common neoplasm. Therefore, effective and reproducible detection of HPV status is a necessity (66), utilizing methods such as HPV DNA detection using polymerase chain reaction (PCR) (67) or in situ hybridization; detection of HPV E6 or E7 mRNA using reverse transcriptase PCR; and immunohistochemical analysis of p16 overexpression (68).

**EBV (HHV-4).** The Epstein-Barr virus (EBV) was the first human virus to be assigned oncogenic potential. In 1968, EBV was demonstrated to be the major aetiological agent of infectious mononucleosis (69). Since then, EBV has been implicated in a wide variety of malignant and benign tumours, as well as in classic infectious diseases (70). EBV infects approximately 90% of the world’s adult population asymptptomatically and is associated with hairy leukoplaenia (HL), epithelial cancer such as Burkitt’s lymphoma, immunoblastic lymphoma, nasopharyngeal cancer (71), and oral squamous cell carcinoma, as well as some benign and potentially malignant oral lesions and diseases, including oral lichen planus, gingivitis, and periodontitis. After primary infection, EBV establishes a latent infection in a small proportion of B-lymphocytes and oronasopharyngeal and salivary gland epithelial cells. The virus periodically replicates in the oropharynx or in the salivary gland epithelium, and is then shed in the saliva (72).

EBV infects almost everyone in developing countries and 80-95% of adults in developed countries. In the USA, about 50% of all 5-year-old children, and nearly 95% of adults, harbour EBV. In Japan, EBV DNA was detected in 90% of throat washings from healthy adults (21-57 years old) and in 38% of saliva from healthy children (0-6 years old) (70). The prevalence of EBV in oral samples varies widely between studies. Southeast Asian studies found a high prevalence of EBV and suggested an aetiological role of EBV in OSCC (73). Through immunohistochemical detection of LMP-1, the EBV antigen was associated with transforming cell activity in an Egyptian population (74). By contrast, North American studies, as well as West and North European studies, regularly report lower prevalence of EBV, suggesting that the aetiological role of EBV in oral SCC may be questionable (72).

**HSV-1.** In 1962, Schneeweis identified two serotypes (75), which was subsequently confirmed by Nahmias and Dowdle in 1968 (76). Herpes simplex virus type-1 (HSV-1) is found predominantly in oropharyngeal infections, and HSV-2 has a strong predilection for anogenital sites. Both types of viruses cause a large range of clinical symptoms (77). HSV-1 is a cytotoxic virus that readily infects and destroys human cells, including cancer cells. Infections with HSV are frequent in the general population and occur normally during early adolescence, manifesting as herpetic gingivostomatitis or pass asymptomatically. After primary infection, the virus travels along the axons of sensory nerve fibres that innervate the affected area, to the trigeminal ganglion, where it stays in a latent form. When the balance between the virus and the host is disturbed, fast replication and reactivation occurs (78). Various conditions or stimuli can influence the loss of balance and viral reactivation. The reactivation of latent HSV is generally associated with the appearance of vesicles on the lips, but it can also be characterized by the release of viruses...
in the saliva without any symptoms or objective changes (79). Lately, a revived interest in the potential use of replicating, or conditionally replicating, viruses for the treatment of cancer has occurred. Oral cancer is under investigation for susceptibility to herpes viruses and adenoviruses, in both animal models and clinical trials (77). Larsson et al. demonstrated that HSV-1 and snuff interact during the development of malignant lesions (80), and Hirsch et al. demonstrated an increased incidence of malignant tumours in rats exposed to snuff and HSV/snuff compared to control animals (81). HSV-1 infection has been suggested as a risk factor in the development of human malignancies, and some studies have shown association between the herpes virus and head and neck carcinomas (78). Associations between HSV and head and neck carcinomas in humans have been inconsistent, and a few investigations have examined potential interactions of herpes viruses with risk factors of oral cancer such as tobacco, alcohol, and high-risk HPV types (78, 82-86).

Candidate Genes

In the 1970s Varmus et al. suggested that oncogenes were present not only in viruses, but also in all cells within the human genome, leading to the hypothesis that human genetic mutations may increase susceptibility of cancer development with/without viral infections (87). During the late 1930s, chromosomal breaks were reported by McClintock, (88, 89) who showed that a repaired chromosome could contain extra gene copies (copy number variation, CNV) (88, 89). The chromosome breakage occurs at common fragile sites (CFSs), which contain key genes that seem to be highly conserved between species (90). It has since been shown that CNVs play important roles in the pathogenesis of different diseases and phenotypes (91-95) and may increase susceptibility for viral integration (96). Huang et al. showed that cell populations within a cell line derived from OSCC tissue displayed CNV and complex rearrangements, displaying the complexity of the genetic origin of OSCC development (97). The results were subsequently supported by Jin et al. and Reshmi et al. (98, 99). It is known that CNV increases genomic instability, which may lead to altered expression of specific genes (91, 100-104).

p53. p53 is a tumour-suppressor gene located on the short arm (p) of chromosome 17 (105). It is involved in cell-cycle control, apoptosis, and DNA repair, and participates in the process of carcinogenesis (106). Loss of p53 function can occur through gene mutation, deletion, or inactivation (107). Mutation of the p53 tumour-suppressor gene may represent the most common genetic change in human cancer (108). Prostate (109), ovarian (110), brain (111), breast (112) and gastric cancer (113), and SCC of the head and neck (114) have been reported to be associated with p53 mutations. Some studies have reported associations between smoking and alcohol use and the frequency of p53 mutations and p53 overexpression (115), (116). Studies have shown a higher frequency of p53 gene mutations in (toombak) snuff-associated oral SCC obtained from Sudan compared to Sudanese non-users (117), and a significantly lower frequency of p53 protein expression in OSCCs from toombak dippers compared to those from non-dippers in Sudan and Scandinavia (118). An immunohistochemical study also showed overexpression of the p53 protein and Ki-67 in snuff-induced lesions (119).

\(p16^{INK4A}\) and \(p21^{WAF1/CIP1}\). Cell-cycle regulatory genes include \(p16^{INK4A}\) and \(p21^{WAF1/CIP1}\), which code for cyclin-dependent kinase inhibitor proteins essential for cellular growth, differentiation, and apoptosis (120), and cyclin regulatory subunits, inducing G1 arrest (121). \(p16^{INK4A}\) is thought to act as a tumour suppressor, as inactivation or deletion is observable in various types of malignancies (122). The cyclin-dependent kinase inhibitor \(p21^{WAF1/CIP1}\) encoded by the \(WAF1/CIP1\) gene, plays an important role in the regulation of the G1-S transition of the cell-cycle. The \(p21^{WAF1/CIP1}\) protein functions as a main downstream effector of p53 protein. In response to DNA damage, wild-type p53 accumulates and binds to the promoter region of the \(WAF1/CIP1\) gene, thus inducing \(p21^{WAF1/CIP1}\) expression. The expression of functional \(p21^{WAF1/CIP1}\) inhibits the activity of the cyclin/cyclin-dependent kinase complex to promote cell-cycle progression (120). \(p21^{WAF1/CIP1}\) expression can also be induced by p53-independent pathways such as the effects of genotoxic drugs and growth factors (121). \(p21^{WAF1/CIP1}\) overexpression has been reported to be associated with poorer prognosis in bladder (123), ovarian (124), breast (125), and oesophageal carcinoma (126), as well as oral SCC (127).

Survivin. One study has shown that Survivin belongs to the group of inhibitor of apoptosis (IAP) family proteins (128). Overexpression of some IAP family members has been noted in carcinomas, suggesting that IAP-mediated inhibition of apoptosis may contribute to tumourigenesis (129). Among the IAP proteins, interest recently has been a shown for Survivin, which encodes for a multifunctional protein that suppresses apoptosis by association with caspases and Second Mitochondria-derived Activator of Caspases (SMAC)/Direct IAP Binding Protein with Low pi (DIABLO) and regulates mitosis by interacting with other chromosomal passenger proteins such as Inner Centromere Protein (INCENP) and aurora-B (130). The association of some IAP family members, especially Survivin, with human oral SCC has been extensively reported (131). Studies have shown a higher Survivin expression level in both primary oral SCC
and pre-malignant lesions compared to normal oral tissues (132), as well as increased Survivin expression in specimens obtained from toombak-user OSCC samples when compared to toombak-user control samples (133). The mechanisms of IAP overexpression in cancer are largely unknown. Amplification of the Survivin locus on chromosome 17 and DNA demethylation of its promoter region has been suggested as a possible mechanism of surviving up-regulation in some types of cancer (134).

**BCL-2.** The B-cell lymphoma 2 (BCL-2) gene belongs to a family of oncogenes and is implicated in cancer development through inhibiting apoptosis (135). A previous study has shown that BCL-2 is significantly decreased in the periphery of well-differentiated and moderately-differentiated oral SCC tumour islands and in poorly-differentiated oral SCC compared to normal oral epithelium (136). A study has shown that BCL-2 mRNA and protein were progressively lost with increasing degree of dysplasia (137). Others have reported sporadic (138) lack of BCL-2 expression (139). The expression of BCL-2 during experimental oral carcinogenesis differs, depending on the anatomical site. BCL-2 expression was shown to be lower for dysplasia of the tongue compared to similar lesions of the buccal region (140). Jalouli et al. showed a decrease in BCL-2 expression in samples obtained from toombak-user oral SCCs compared to toombak-user control samples (133).

**Keratins.** Cytokeratins (CKs) are intermediate filament genes expressed in specific cell types, such as muscle and glia cells (141), and are essential for cell shape, motility, and structural integrity (142). Changes in some keratins have been documented in several studies. Loss of CK13 has been observed in tongue SCC, which is related to the invasive and metastatic ability of cancer cell lines (143, 144). A decrease in the expression of CKs has been observed in cytokeratin-2E, 2P, 6A-F, 7, 13, 14, 15, 17, 18, and 19 in normal tissue, and their expression is almost absent in cancer cell populations, which may reflect the loss of differentiation in tumour cells (144). Other studies have reported down-regulated expression of CK13 in oral SCC (145, 146), as well as a decrease of CK13 expression associated with an increase in the grade of malignancy in a transitional cell carcinoma (147). Jalouli et al. showed that CK13 and CK1 were down-regulated in oral SCC samples from toombak users and non-toombak users compared to control samples (133). Lack of CK13 expression has been observed in the majority of invasive carcinoma cells (148).

The **11q13.3 region.** Ambatipudi et al. performed an extensive literature survey regarding suggested genes associated with oral cancer (149). They identified a total of n=277 genes, out of which n=39 genes were reported several times, and n=28 showed evidence of CNV or altered expression patterns. Among the 28 genes, several were located within the 11q13.3 region. Genes mapped to the 11q13.3 region include fibroblast growth factors (FGF) 3, 4, and 19; oral cancer overexpressed 1 (ORAOV1); and cyclin D1 (CCND1). Previous studies have shown evolutionary conservation of the FGF3, FGF4, FGF19, ORAOV1, and CCND1 regarding the order of genes between several species, such as human, dog, mouse, and zebra fish (92, 150-152). Alternative symbols and the biological processes, in which the FGFs and CCND1 are involved, are presented in Table I. Multiple reports regarding co-amplification and/or overexpression concerning either one or several of the genes associated with oral SCC are available (97, 98, 100, 101, 153-161). The region has also been associated with the dorsal hair ridge of Ridgeback dogs (92, 152), as well as with several types of carcinoma, other than OSCC, such as those of the oesophagus, breast, pancreas, liver, bladder and ovary, and Kaposi’s sarcoma (99, 151, 162, 163).

**FGFs.** In 1986, Casey et al. mapped the FGF3 gene by combining in situ and somatic cell hybridization. The gene is 9456 bp in size and has two known transcripts (164). The gene’s genomic coordinates are 69,624,992-69,633,792. FGF4 was mapped by in situ hybridization in 1988 (165) and it was found that FGF3 and FGF4 were co-amplified in human melanoma. The genomic coordinates of FGF4 are 69, 587, 796-69, 590, 170; it consists of 2374 bp and contains three exons. FGF19 has one known transcript, 6, which is 1 kb in size, with the genomic coordinates 69, 513, 005-69, 519, 105, and was identified in 1999 (166). The three FGFs contain three exons and play important roles during early development.

**ORAOV1.** In 2002, Huang et al. identified a gene, denoted tumour that amplified and overexpressed sequence 1 (TAOS1) in oral SCC obtained from cultured human cell lines (97). These results were supported by Xia et al. (93), who suggested that TAOS1 amplification may occur during early oral carcinogenesis. The TAOS1 gene, which was renamed ORAOV1, consists of five exons and is located on chromosome 11q13.3 with the genomic coordinates 69, 480, 330-69, 490, 164. There are nine known transcripts that lead to protein products, and expression has been identified in a wide range of tissues. A spliced variant of ORAOV1 was identified and denoted as ORAOV1-A (157). The transcript lacked exon 3 and the alternative splicing caused a coding frame-shift, resulting in the introduction of a new stop codon in exon 4 (in-frame), leading to a shortened open reading frame. To identify various functions of ORAOV1, Jiang et al. (156) utilized cultured cell lines derived from human tongue SCC to perform knockout studies, with a small-interfering RNA (siRNA) approach. The in vivo results demonstrated
Table I. Overview of candidate gene, their alternative names and a presentation of their known involvement in biological processes.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Alternative names</th>
<th>Known biological process-involvement</th>
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<tbody>
<tr>
<td><strong>FGF3</strong></td>
<td>• Fibroblast growth factor 3</td>
<td>• Morphogenesis; anatomical structure, tail and semicircular canal</td>
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<td></td>
<td>• FGF-3</td>
<td>• Cell differentiation</td>
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<td></td>
<td>• Oncogene INT2</td>
<td>• Cell-cell signalling</td>
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<td></td>
<td>• Proto-oncogene Int-2</td>
<td>• Fibroblast growth factor and insulin receptor signalling pathway</td>
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<td></td>
<td>• INT-2 proto-oncogene protein</td>
<td>• Multicellular organismal and thymus development</td>
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<td></td>
<td>• Heparin-binding growth factor 3</td>
<td>• Development</td>
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<td></td>
<td>• Murine mammary tumor virus integration site 2, mouse</td>
<td>• Organ induction and otic vesicle formation</td>
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<tr>
<td></td>
<td>• V-INT2 murine mammary tumor virus integration site oncogene homolog</td>
<td>• Signal transduction</td>
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<td></td>
<td>• Fibroblast growth factor 3 (murine mammary tumor virus integration site (v-int-2) oncogene homolog)</td>
<td>• Positive regulation of cell division</td>
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<td>• Negative regulation of cardiac muscle tissue</td>
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<td><strong>FGF4</strong></td>
<td>• Fibroblast growth factor 4</td>
<td>• Mesenchymal cell proliferation</td>
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<td>• FGF-4</td>
<td>• Multicellular organismal development</td>
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<td>• HSTF-1</td>
<td>• Odontogenesis of dentin-containing tooth</td>
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<td>• Oncogene HST</td>
<td>• Signal transduction</td>
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<td>• Kaposi sarcoma oncogene</td>
<td>• Stem cell maintenance</td>
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<td></td>
<td>• Transforming protein KS3</td>
<td>• Positive regulation of cell division, ERK1 and ERK2 cascade, gene expression, cell proliferation and transcription from RNA polymerase II promoter</td>
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<td>• Heparin-binding growth factor 4</td>
<td>• Negative regulation of apoptotic process</td>
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<td>• Heparin secretory-transforming protein 1</td>
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<td>• Fibroblast growth factor 4 splice isoform</td>
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<td>• Human stomach cancer, transforming factor from FGF-related oncogene</td>
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<td><strong>FGF19</strong></td>
<td>• Fibroblast growth factor 19</td>
<td>• Fibroblast growth factor receptor and insulin signalling pathway</td>
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<td></td>
<td>• FGF-19</td>
<td>• Nervous system and heart development</td>
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<td>• Neural crest cell migration</td>
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<td>• Positive regulation of JNK, ERK1 and ERK2 cascade, gene expression, cell proliferation and glucose import</td>
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<td>• Negative regulation of bile acid biosynthetic process</td>
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<td>• Oral cancer-overexpressed protein 1-A</td>
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<td>• Tumor-amplified and overexpressed sequence 1</td>
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<td><strong>CCND1</strong></td>
<td>• G1/S-specific cyclin-D1</td>
<td>• G1 phase of mitotic cell cycle</td>
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<td>• BCL-1 oncogene</td>
<td>• Leydig cell differentiation</td>
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<td>• PRAD1 oncogene</td>
<td>• S phase of mitotic cell cycle</td>
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<td>• B-cell CLL/lymphoma 1</td>
<td>• Canonical Wnt receptor signaling pathway</td>
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<td>• B-cell lymphoma 1 protein</td>
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<td>• Lactation</td>
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<td>• Mammary gland alveolus and liver development</td>
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<td>• Mitotic cell cycle</td>
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<td>• Mitotic cell cycle G1/S transition DNA damage checkpoint</td>
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<td>• Organ regeneration</td>
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<td>• Re-entry into mitotic cell cycle</td>
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<td>• Regulation of phosphorylation and catalytic activity</td>
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<td></td>
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<td>• Positive regulation of cell proliferation, cyclin-dependent protein kinase activity, protein phosphorylation and mammary gland epithelial cells</td>
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<td>• Negative regulation of epithelial cell differentiation and Wnt receptor signalling pathway</td>
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increased tumour necrosis due to induction of the S-phase cell-cycle arrest (G2-phase inhibition and increase of apoptosis). In an attempt to further evaluate ORAOV1 functions, utilizing a cell line of different origin and xenografts, the research group performed additional knockout studies for which human HeLa cells derived from cervical cancer were used. It was shown that in vivo ORAOV1 loss of function in cervical cancer correlates with ORAOV1 loss of function in tongue SCC. In addition, ORAOV1 silencing was shown to increase p53 expression levels. Furthermore, HeLa cell xenografts displayed reduction/necrosis in tumour volume (158).

CCND1. In 1992, CCND1 was assigned to 11q13 by somatic cell hybrid studies and fluorescence in situ hybridization (167). The genomic coordinates are 69, 455, 872–69, 469, 241. It consists of five exons, is ~13.3 kb in size, and seven splice variants are known. The gene has a positive regulation of cyclin-dependent kinases 4 and 6, which leads to inactivation of the Rb (retinoblastoma, a cell-cycle regulator) protein, promoting progression from the G1 to S phase (161).

Conclusion

Oral SCC development is a complex and not fully understood process, which involves environmental factors such as tobacco, alcohol, viral infections and genetic susceptibility. More research is needed for better understanding of the underlying mechanisms regarding oral cancer development. It is important to sample fresh tissues samples in prospective studies, as well as to analyze formalin-fixed, paraffin-embedded tissues from the pathological archives in the search for answers.

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References


