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Genes involved in metastasis in oral squamous cell carcinoma: A systematic review

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Abstract

Background and Aims: Oral squamous cell carcinoma is the most prevalent malignancy in the oral cavity, with a significant mortality rate. In oral squamous cell carcinoma patients, the survival rate could decrease because of delayed diagnosis. Thus, prevention, early diagnosis, and appropriate treatment can effectively increase the survival rate in patients. In this systematic review, we discussed the role of different genes in oral squamous cell carcinoma metastasis. Herein, we aimed to summarize clinical results, regarding the potential genes that promote oral squamous cell carcinoma metastasis.

Methods: This systematic review was carried out under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. An electronic search for all relevant articles published in English between January 2018 and April 2022 was performed using Scopus, PubMed, and Google Scholar search engines. All original studies published in English were included, and we excluded studies that were in a non-English language.

Results: A total of 4682 articles were found, of which 14 were relevant and detected significant genes in oral squamous cell carcinoma progression. These findings investigated the overexpression of interferon-induced proteins with tetratricopeptide repeats 1 and 3 (IFIT1, IFT3), high-mobility group A2 (HMGA2), transformed growth factor-beta-induced, lectin galactoside-binding soluble 3 binding protein (LGALS3BP), bromodomain containing 4, COP9 signaling complex 6, heterogeneous nuclear ribonucleoproteins A2B1 (HNRNPA2B1), 5′–3′ exoribonuclease 2 (XRN2), cystatin-A (CSTA), fibroblast growth factors 8 (FGF8), forkhead box P3, cadherin-3, also known as P-cadherin and Wnt family member 5A, ubiquitin-specific-processing protease 7, and retinoic acid receptor responder protein 2 genes lead to promote metastasis in oral squamous cell carcinoma. Overexpression of some genes (IFIT1, 3, LGALS3BP, HMGA2, HNRNPA2B1, XRN2, CSTA, and FGF8) was proven to be correlated with poor survival rates in oral squamous cell carcinoma patients.

Conclusion: Studies suggest that metastatic genes indicate a poor prognosis for oral squamous cell carcinoma patients. Detecting these metastatic genes in oral squamous cell carcinoma patients may be of predictive value and can also facilitate assessing oral squamous cell carcinoma development and its response to treatment.

KEYWORDS
metastasis, neoplasm metastasis, oral squamous cell carcinoma, systematic review

1 | INTRODUCTION

Oral cancer (OC) continues to be one of the most prevalent cancers of the head and neck region. Despite significant advancements in diagnostic procedures and treatment modalities, patient survival rates are still concerning.[1–5] Oral squamous cell carcinoma (OSCC) is reported to be the most frequently encountered malignancy in the oral cavity, accounting for over 90% of all OCs. The morbidity and mortality rates among young adults have been growing recently, with more than 140,000 individuals dying from this condition.[5–7] According to the International Classification of Diseases, 10th revision codes C00–C06, OC refers to any malignant neoplasm in the lip and oral cavity. In 2020, GLOBOCAN reported OC as the 16th most common cancer globally, with 377,713 incident cases and 177,757 deaths. In contrast, 65.8% of all new cases came from Asian nations.[8] In Asia, there have been tendencies toward increasing and decreasing OSCC incidence in Sri Lanka and Pakistan, respectively.[9] The epidemiological pattern of OSCC in Iran is comparable to other cancers and remarkably similar to that of Pakistan and India.[10]

Despite the recent progress in chemotherapy, radiotherapy, and traditional surgery, the 5-year survival rate of OSCC still hovers around 50%.[6] It has been proposed that OSCC development is etiologically related to alcohol consumption, tobacco use, Shammah, khat chewing, water pipe smoking, ethnicity, sexual behaviors, human papillomavirus infection, occupational activity, external agent exposure, dietary micronutrient deficiency.[4,11–16]

There are many factors that can contribute to the development of cancer and increase mortality rates in patients.[4,17,18] One of these influential factors is a gene mutation that can potentially lead to neoplastic changes in the oral cavity.[19] Multiple genetic and environmental factors trigger the inactivation of tumor suppressor genes and, or activation of oncogenes and, therefore, induce gene mutations.[20] The interplay between intrinsic tumor cell characteristics and the interaction between cancer cells and the tumor microenvironment induces cancer metastasis.[1] Poor therapeutic results and decreased patient survival are caused by the highly malignant phenotype of OSCC, which includes the existence of nodal and distant metastasis at the time of diagnosis.[21] The relatively low survival rate of OSCC-afflicted patients is mainly attributed to its high propensity for lymphatic metastasis.[17,22–24]

Metastasis is a stage of tumor development that includes a variety of processes, such as the development of cellular motility and invasion capabilities, the epithelial-to-mesenchymal transition (EMT), and angiogenesis. Therefore, several steps are required for cancer cells to spread from their original site to the metastatic one, as shown in the invasion-metastasis cascade.[25] A series of biological processes can initiate the invasion-metastasis cascade, which starts at the primary tumor site, invades the extracellular matrix of the surrounding tissue and then causes distant metastasis through the blood and lymph vessels.[26] Metastasis can be classified as regional and distant. When tumor cells from the initial location enter lymphatic pathways and spread to regional lymph nodes in the neck, generating a micrometastasis, this is known as regional metastasis, is a critical prognostic biomarker for oral and oropharyngeal carcinomas.[27,28] Diffusion of tumoral cells from the initial location to an anatomically distant place is defined as distant metastasis. Notably, up to 40% of OSCC patients may develop metastasis.[23,24] Furthermore, nonmetastatic patients can benefit from the local treatment of the original tumor, while neck lymph node dissection is typically required in cases with metastasis. The elucidation of the molecular mechanism involving epigenetic regulation in OSCC metastasis has long been awaited because it correlates well with a poor prognosis.[29,30] This approach is typically accompanied by an increased risk of perioperative complications, functional disorders, and maxillofacial abnormalities.[31,32]

In the management of OSCC, effective screening and therapy for metastatic individuals.[1,21] OSCC metastasis is characterized by two clinical features[23,33]; the first is that the rate of metastasis varies in different anatomical parts of the head and neck, and the second is that oral metastasis is typically observed as lymph node metastasis. Although the exact mechanisms of metastasis remain unknown, cell invasion and migration are integral to OSCC metastasis.[34,35] Multiple factors are engaged in the occurrence and development of metastasis. Under the simultaneous effects of various pathogenesis (including genetic and environmental factors), the DNA mutations in normal cells activate proto-oncogenes and disrupt the function of tumor suppressor genes, resulting in impaired cell growth and division.[36–40] Malignant and normal cells have different gene activity states, resulting in other protein syntheses, which ultimately lead to further cell functions.[41,42] Consequently, identifying tumor markers may offer a more accurate, rapid, practical, and affordable technique for the early prognostic and diagnostic advancement of malignancies to prevent metastasis and attenuate mortality rates.[43–47] Therefore, in this study, we aimed to identify the potential biomarkers to predict metastasis in OSCC.

2 | MATERIALS AND METHODS

The suggested reporting components for meta-analysis and systematic reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement were followed when conducting this systematic review.[48] "Which genes impact and promote OSCC metastasis?" was the main question.

2.1 | Study design

We conducted a systematic review of studies using various gene expressions as potential biomarkers for monitoring OSCC and predicting treatment response and metastasis. The analysis generated a list of genes that may be involved in metastasis.

2.2 | Study eligibility criteria

The following were the criteria for selection: studies conducted in vitro and in vivo, studies on patients diagnosed with OSCC, studies conducted on cell lines, and full-text articles available in the English language specifically aimed at identifying genes associated with the metastasis of OSCC. Exclusion criteria were as follows: patients with tumors except for OSCC, patients with recurrent OC, patients who have been treated, studies that were in a non-English language, and all articles other than original, letters to the editor, and reviews were excluded from the report.

2.3 | Search strategy and quality assessment

An electronic search for all relevant articles published in English between January 2018 and April 2022 was performed using the databases Scopus, PubMed, and Google Scholar. The key search terms used either alone or in combination were [("OSCC" OR "squamous cell carsinoma of head and neck"[MeSH Terms] AND "OSCC metastasis" OR "neoplasm metastasis"[MeSH Terms] AND "genes"[MeSH Terms]. The quality and methodology of the selected papers using the Newcastle Ottawa checklist. (Supplementary File, Figure [S1]).

2.4 | Screening and data selection

There were two stages to the selection process. After eliminating duplicates, the titles and abstracts of pertinent papers were first reviewed. This phase was managed by two independent reviewers (N. M., M. Z.). Disagreements between authors were resolved by an independent author (F. M.). The second stage of this evaluation was conducted by these two independent reviewers, who gathered pertinent data regarding the research features of each of these possibly relevant publications (N. M., M. Z.). The following data were extracted: author (s), publication year, study design, sample size, gene detection method, the name of the gene (s) identified, the impact of genes on OSCC metastasis, and the main outcome. This information is presented in Table 1. The data was collected in Microsoft Excel spreadsheet software and verified by the corresponding author.

3 | RESULTS

3.1 | Study selection and screening

The search across databases yielded 4682 entries in dentistry, medicine, and molecular biology. A total of 433 were found in PubMed, 1119 in Scopus, and 3130 in Google Scholar. After removing 420 duplicates via software and manually, 4262 unique records were left for screening. After screening by title, 1995 studies were included. The subsequent screening step by both title and abstract resulted in 23 studies being included. Full-text screening of the included studies resulted in 14 being selected for review.[1,4,6,17,37,44,49–58] A flowchart that depicts the screening process is displayed in Figure 1.

3.2 | Study characteristics

All studies included in this systematic review were original studies. All studies were published between 2018 and 2022. Studies were selected all around the world (Table 2). The studies included in this systematic review encompass a variety of samples. There were 12 original research articles focused on the use of cell lines and OSCC tissues, and 2 articles focused solely on OSCC tissues to identify genes involved in metastasis. These articles included 1217 OSCC patients, and there were 22 cell lines used; the most commonly used normal cell lines were NOK, HaCaT, Hs 680, Tg, and HOK. Squamous cell carcinoma cell lines, such as SAS, SCC4, SCC9, SCC15, SCC25, CAL27, CAL33, OSC-19, HOC313, Ca9-22, Tca8113, HN4, HN6, HN30, HSC-3, HSC-4, UM2, and KB were also frequently used. The studied genes were as follows: interferon-induced proteins with tetratricopeptide repeats 1 and 3 (IFIT1, IFIT3), high-mobility group A2 (HMGA2), transformed growth factor-beta-induced (TGFBI), lectin galactoside-binding soluble 3 binding protein (LGALS3BP), bromodomain containing 4 (BRD4), COP9 signaling complex 6 (CSN6), heterogeneous nuclear ribonucleoproteins A2B1 (HNRNPA2B1), 5′–3′ exoribonuclease 2 (XRN2), cystatin-A (CSTA), fibroblast growth factors 8 (FGF8), forkhead box P3 (FoxP3), cadherin-3, also known as P-cadherin (CDH3) and Wnt family member 5A (WNT5A), ubiquitin-specific-processing protease 7 (USP7), retinoic acid receptor responder protein 2 (Rarres2). All authors analyzed OSCC metastasis by studying genes by immunohistochemistry and, or Q-PCR and, or Western blot analysis.

TABLE 1 Main characteristics of the included studies.

Authors (years)	In vivo	In vitro	Number of OSCC patients	Methods for studying gene expression	Genes	Main outcomes
Pidugu et al.[17] (2018)	Xenograft nude mice, Human tissue	SAS cells and SCC25	215	Q-PCR and Western blot analysis (in vitro), Q-PCR and histopathological staining (in vivo)	IFIT1, IFIT3	High expression of IFIT1 or IFIT3 is associated with lymphovascular invasion, advanced T-stage, lymph node metastasis, perineural nerve invasion, extranodal extension, and poor overall survival.
Wang et al.[4] (2019)	BALB/C nude mice	HSC-3	52	Q-PCR and Western blot analysis (In vitro), Q-PCR and histopathological staining (in vivo)	TGFBI	High expression of TGFBI is associated with the T classification, advanced clinical stage, and poor prognosis of OSCC. Knockout of TGFBI inhibited cell proliferation, enhanced cell migration, invasion, metastasis, and suppressed tumor growth.
Zhang et al.[6] (2019)	Human tissue	SCC4, CAL27, HSC-3 and HaCaT	92	RT-PCR and western blot analysis (in vitro), immunohistochemical staining (in vivo)	LGALS3BP	Overexpression of LGALS3BP mediated metastasis and can regulate OSCC migration and proliferation via PI3K/AKT pathway. Levels expression of LGALS3BP associated with advanced T stages, more recurrence, and less overall survival.
Yamamoto et al.[44] (2019)	BALB/nude mice, Human tissue	HOC313, SAS, OSC-19, and HaCaT	36	Q-PCR and Immunoblotting (in vitro), chromatin immunoprecipitation (ChIP), ChIP-qPCR (in vivo)	BRD4	High expression of BRD4 associated with lymph node metastasis.
Sakata et al.[1] (2019)	Human tissue	Ca9-22 and SAS	110	Immunohistochemistry, Q-PCR, and western blot analysis (in vitro), Q-PCR and immunohistochemistry (in vivo)	HMGA2	High expression of HMGA2 is associated with lymph node metastasis, N-stage, distant metastasis, survival rates, and poor prognosis. Increased EMT, EGF-A, VEGF-C, FGF-2, Slug, and Vimentin and decreased E-cadherin.
Gao et al.[37] (2020)	Human tissue	CAL27, Tca8113, and Hs 680. Tg	36	qRT-PCR and Western blot analysis	CSN6	Overexpression of CSN6 is associated with distant lymph node metastasis and poor prognosis. It can promote OSCC malignant progression by TIMP-2.
Zhu et al.[49] (2021)	Haman tissue	CAL27 and SCC4	38	Immunohistochemistry, Q-PCR, and western blot analysis (in vitro), Q-PCR and immunohistochemistry (in vivo)	HNRNPA2B1	Overexpression of HNRNPA2B1 related to lymph node metastasis, migration, proliferation, invasion, survival rate, clinical stage, and T classification of OSCC by targeting EMT. Knockdown of HNRNPA2B1 inhibited their migration, proliferation, and invasion and increased the level of E-cadherin and N-cadherin.

TABLE 1 (Continued)

Authors (years)	In vivo	In vitro	Number of OSCC patients	Methods for studying gene expression	Genes	Main outcomes
Liu et al.[50] (2021)	Human tissue	SCC15, SCC25, CAL27, Tca8113, and HOK	77	qRT-PCR (in vitro), immunohistochemistry staining and western blot analysis (in vivo)	XRN2	High expression of XRN2 is associated with lymph node metastasis, tumor differentiation, pathological clinical stage, and poor survival. Downregulation of XRN2 increased apoptosis and expression of E-cadherin, and it could inhibit cell proliferation, migration, and invasion, and reduce the expression of Vimentin.
Wang et al.[51] (2021)	Haman tissue	HN4, HN6, HN30, CAL27, and CAL33	231	qRT-PCR (in vitro), immunohistochemistry staining, Western blot analysis, and qRT-PCR (in vivo)	CSTA	Low expression of CSTA related to nodal metastasis, high tumor grade, and poor survival. Overexpression of CTSA inhibited OSCC cell migration, invasion, and proliferation.
Hao et al.[52] (2021)	Mice, Human tissue	NOK, HSC-4, HSC-3, CAL27, and UM2	30	Immunofluorescence staining, qRT-PCR, and Western blot analysis (in vitro), immunohistochemistry staining (in vivo)	FGF8	Expression of FGF8 induced poor survival rate of OSCC patients and promoted OSCC cell invasion, migration, and tumor metastasis via EMT, E-cadherin, and decreased Vimentin, and Snail.
Hayashi et al.[53] (2021)	Human tissue	–	106	immunohistochemical staining	FoxP3 + Tregs	FoxP3 expression has an impact on nodal metastasis.
Khan et al.[54] (2021)	Human tissue	–	60	Immunohistochemistry staining	WNT5A, CDH3	Overexpression of WNT5A and P-cadherin is associated with lymph node metastasis, tumor stage, and invasion.
Yang et al.[55] (2021)	Human tissue	HSC3, HSC4, KB	92	Western blot analysis (In vitro), Immunohistochemistry staining (in vivo)	USP7	High expression of USP7 associated with lymph node metastasis, proliferation, migration, and histological differentiation, activates the Akt/ERK pathway, invasion-related factors MMP2, MMP9, and VEGF, and inhibits apoptosis.
Hu et al.[56] (2022)	Human tissue	Cal27, SCC9, and SCC15	74	ELISA, qRT-PCR, and Western blot analysis (in vitro), immunohistochemistry staining (in vivo)	RARRES2	Overexpression of chemerin is related to poor clinical outcomes and is involved in OSCC progression and metastasis.

Abbreviations: Akt, protein kinase B; BRD4, bromodomain containing 4; CDH3, cadherin-3; CSN6, COP9 signaling complex 6; CSTA, cystatin-A; ELISA, enzyme-linked immunosorbent assay; EMT, epithelial–mesenchymal transition; ERK, extracellular-regulated kinase; FGF8, fibroblast growth factors 8; FoxP3, forkhead box P3; HMGA2, high-mobility group A2; HNRNPA2B1, heterogeneous nuclear ribonucleoproteins A2B1; IFIT1, IFIT3, interferon-induced proteins with tetratricopeptide repeats 1 and 3; LGALS3BP, lectin galactoside-binding soluble 3 binding protein; MMP-2, matrix metalloproteinase-2; OSCC, oral squamous cell carcinoma; PI3K, phosphoinositide 3-kinase; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RARRES 2, retinoic acid receptor responder protein 2; TGFBI, transformed growth factor-beta-induced; USP7, ubiquitin-specific-processing protease 7; VEGF, vascular endothelial growth factor; WNT5A, Wnt family member 5A; XRN2, 5′–3′ exoribonuclease 2.

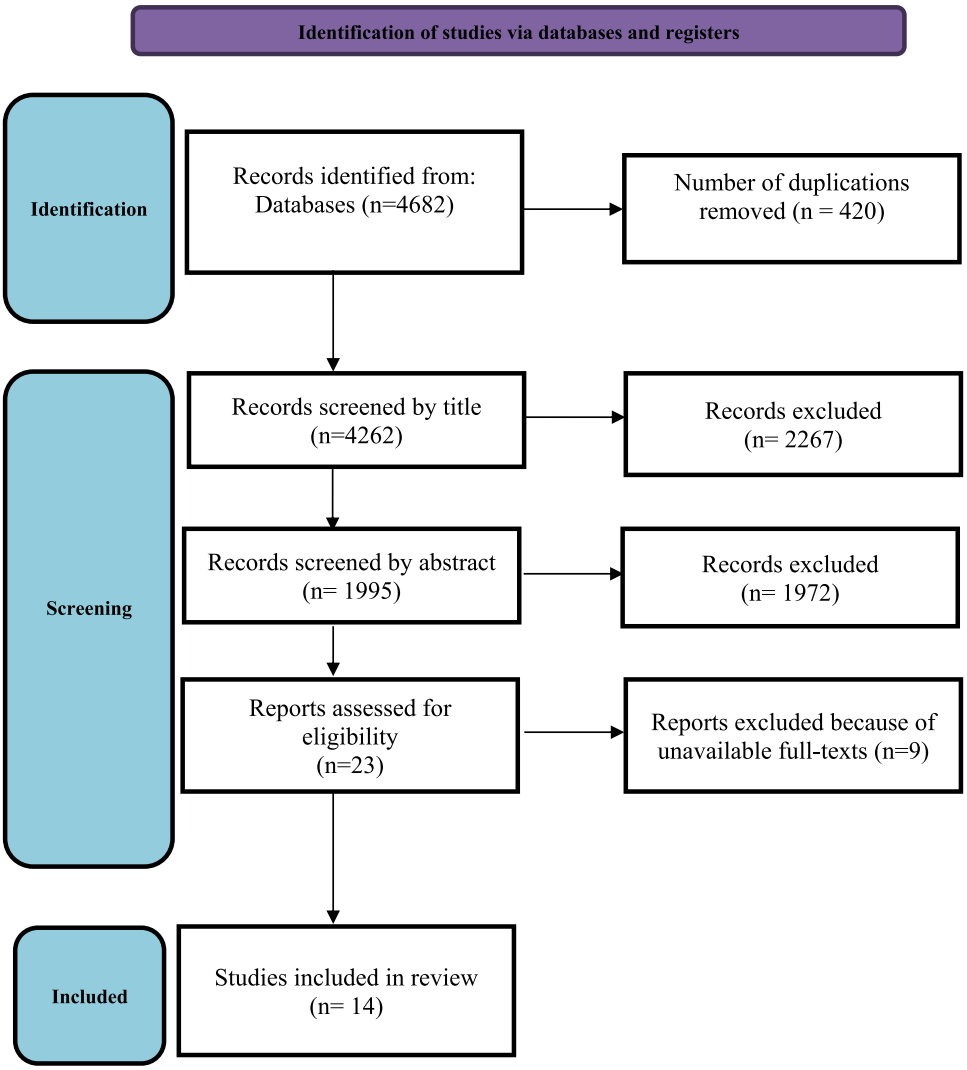

FIGURE 1 Preferred Reporting of Systematic Reviews and Meta-Analyses flow diagram related to bibliographic searching and study selection.

4 | DISCUSSION

The present systematic review of 14 studies assessed the relationship between genes and metastasis in patients with OSCC. Importantly, we show that the expression of some genes is significantly correlated with OSCC metastasis. We hypothesized that there would likely be aberrations in some gene expression involved in metastasis and poor prognosis in OSCC patients. We conducted a comprehensive assessment of the published data on OSCC to provide a complete overview of the potential use of diverse gene expression as biomarkers for monitoring OSCC, predicting metastasis, and treatment response. To the best of our knowledge, this is the first systematic review demonstrating the involvement of genes in OSCC metastasis. We investigated the genes associated with OSCC metastasis, which include IFIT1 and IFT3, HMGA2, TGFBI, LGALS3BP, BRD4, CSN6, HNRNPA2B1, XRN2, CSTA, FGF8, FoxP3, CDH3 and WNT5A, USP7, and Rarres2. These genes exhibit a various range of biological functions (Table 3).

Several studies have reported that overexpression of certain genes can lead to metastasis in OSCC patients, including studies by Pidugu et al.[17] Pidugu reports that elevated expression of IFIT1 or IFIT3 increases tumor growth and regional and distant metastatic activity both in vitro and in vivo. Yamamoto et al.[44] demonstrated that BRD4 cell line levels were elevated in OSCC patients and frequently related to metastasis through the epigenetics regulation of the MMP2 gene. Sakata et al.[1] demonstrated how HMGA2 affects clinical outcomes and controls angiogenesis-related genes in OSCC. Data from Sakata suggest that elevated HMGA2 expression may also be a novel potential biomarker for OSCC that may be used to predict distant metastases and prognosis. Gao et al.[37] and Yang et al.[55] discovered that CSN6 and USP7 were noticeably increased in OSCC tissues and cell lines, which is noticeably significant to the incidence of lymph node or distant metastases and poor prognosis of OSCC patients. They also confirmed that CSN6 may accelerate the malignant development of OSCC by controlling TIMP-2. Zhu et al.[49] showed that HNRNPA2B1 may have the potential to promote proliferation,

TABLE 2 General data of identified studies.

Author and year of publication	Journal	Center/hospital	Country	Number of patients	Data collection
Pidugu et al.[17] (2018)	*Oncogene*	MacKay Memorial Hospital in Taipei, Taiwan	Taiwan	215	2018
Wang et al.[4] (2019)	*Journal of Cancer*	First People's Hospital of Yunnan Province, Yunnan, China	China	52	2008–2017
Zhang et al.[6] (2019)	*Cellular Signalling*	Nanjing Stomatological Hospital, Medical School of Nanjing University	China	92	2008–2014
Yamamoto et al.[44] (2019)	*British Journal of Cancer*	Kumamoto University Hospital, Kumamoto, Japan	Japan	36	2012–2015
Sakata et al.[1] (2019)	*International Journal of Molecular Sciences*	Kumamoto University Hospital	Japan	110	2003–2013
Gao et al.[37] (2020)	*European Review for Medical and Pharmacological Sciences*	Gansu Provincial Hospital	China	36	NA
Zhu et al.[49] (2021)	*Frontiers in Oncology*	The Department of Oral and Maxillofacial Surgery at the Second Xiangya Hospital	China	36	2011–2013
Liu et al.[50] (2021)	*Pathology—Research and Practice*	Department of Oral and Maxillofacial Surgery, the Affiliated Hospital of Qingdao University	China	77	NA
Wang et al.[51] (2021)	*Archives of Oral Biology*	NA	China	231	NA
Hau et al.[52] (2021)	*International Jourrnal of Oal Science*	Department of Oral and Maxillofacial Surgery, Hospital of Stomatology, Sichuan University.	China	30	NA
Hayashi et al.[53] (2021)	*Clinical and Experimental Dental Research*	Aichi Medical University Graduate School of Medicine Oral and Maxillofacial Surgery	Japan	106	1992–2009
Khan et al.[54] (2021)	*Clinical Oral Investigations*	Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India	India	60	2013
Yang et al.[55] (2021)	*Genetics and Molecular Biology*	Department of Pathology in the Affiliated Hospital for Guilin Medical University	China	92	2010–2017
Hu et al.[56] (2022)	*Frontiers in Oncology*	Affiliated Hospital of Qingdao University	China	74	2005–2010

Abbreviation: NA, not available.

TABLE 3 Description of the genes selected in the study.

Gene symbol	Gene name	Gene function and biological process in cancer
IFIT1 and IFIT3	Tetratricopeptide repeats 1 and 3	Contributes to cancer progression, and regulation of EGFR signaling, also it can be a prognosis biomarker of OSCC. Over expression inhibits metastasis and low expression induces cell migration by activating atypical PKC signaling.[17,59,60]
TGFBI	Transformed growth factor-beta-induced	Overexpression of TGFBI promotes OSCC, and it is a key hub gene in a protein–protein interaction network.[4,61]
LGALS3BP	Lectin galactoside-binding soluble 3-binding protein (also known as 90K or Mac-2BP)	Contributes to cancer progression, and malignant tumors. Over expression of LGALS3BP facilitated metastasis by increasing the adhesiveness of cancer cells and inhibiting monocyte-derived fibrocyte differentiation.[6]
BRD4	Bromodomain containing 4	Involved in carcinogenesis, cell proliferation, progression, and lymph node metastasis.[44]
HMGA2	High-mobility group A2	Involved in cell growth and metastatic potential in tumor cells.[1]
CSN6	COP9 signaling complex 6	Involved in the occurrence and development of tumors. Over expressed in a variety of malignant tumors such as breast cancer, ovarian cancer, and colon cancer, also it can be a prognosis biomarker of OSCC.[37]
HNRNPA2B1	Heterogeneous nuclear ribonucleoproteins A2B1	Involved in various tumors, promotes the progression of esophageal cancer by ACLY and ACC1.[37,49,62]
XRN2	5′–3′ exoribonuclease 2	Involved in some tumors, it can be a prognostic biomarker in a variety of cancers, including lung cancer, hepatocellular carcinoma, acute myeloid leukemia, and OSCC.[50,63]
CSTA	Cystatin-A	CSTA inhibits a variety of proteinases such as papain and cathepsins B, H, and L. The level of CSTA expression is associated with high tumor grade, nodal metastasis, cell migration, invasion, cell proliferation, and poor survival.[51]
FGF8	Fibroblast growth factors 8	Expression disorder of FGF8 can lead to angiogenesis, wound repairing, homeostasis, cell differentiation, and cell migration.[52,64]
FoxP3 + Tregs	Forkhead box P3	Involved in the immunosuppressive function, development, differentiation of T-regs, and master regulator of development and functional activity.[53]
CDH3, WNT5A	P-cadherin, hWnt family member 5A	P-cadherin is involved in cellular motility, proliferative activity, and apoptosis. WNT5A protein regulates the promotion or suppression of cancer progression.[54,65]
USP7	Ubiquitin-specific-processing protease 7	Involved expression of various tumor-related genes, such as p53 and Ki-67, promotes the proliferation, and knockdown of USP7 increases p53 expression and inhibits cancer cell proliferation.[55,66]
RARRES2	Retinoic acid receptor responder protein 2	It is upregulated in neuroblastoma, esophageal squamous cell carcinoma, and OSCC.[56,67]

Abbreviations: EGFR, estimated glomerular filtration rate; OSCC, oral squamous cell carcinoma; PKC, protein kinase C.

migration, and invasion of OSCC by targeting EMT via the LINE-1/TGF-b1/Smad2/Slug signaling pathway and provide insight into the critical roles of HNRNPA2B1 in OSCC. Liu et al.[50] reported that the malignant phenotype of OSCC was notably suppressed with the downregulation of XRN2 and found that the downregulation of XRN2 inhibited cell proliferation, migration, and invasion while promoting apoptosis of OSCC cells. According to Wang et al.,[51] CSTA is a promising biomarker and therapeutic target with prognostic implications in OSCC patients. The tumor differentiation and lymphatic metastasis of OSCC may be significantly influenced by CSTA.

Other studies showed that FGF8, TGFBI, and Rarres2 genes are overexpressed in OSCC, which can prevent OSCC metastasis by inhibiting them.[4,52,56] Hayashi et al.[53] showed that OSCC patients with tumor-infiltrating FoxP3+ T cells have a poor prognosis and nodal metastases.

The overexpression of the above genes in OSCC-invaded tissue of patients with lymph node metastasis suggests that overexpression of these genes may increase the risk of malignancy.[68,69] Although distant metastasis occurs in about 10% of OSCC patients, this pathological process causes a poor prognosis and a significantly extended recovery.[70] According to the investigated studies, the HMGA2 and CSN6 genes promote the distant metastasis of OSCC.[1,37] Additionally, IFIR1,3, LGALS3BP, HMGA2, HNRNPA2B1, XRN2, CSTA, and FGF8.[1,6,17,49–52] stated a significant correlation between poor survival rates in OSCC patients or cell lines.

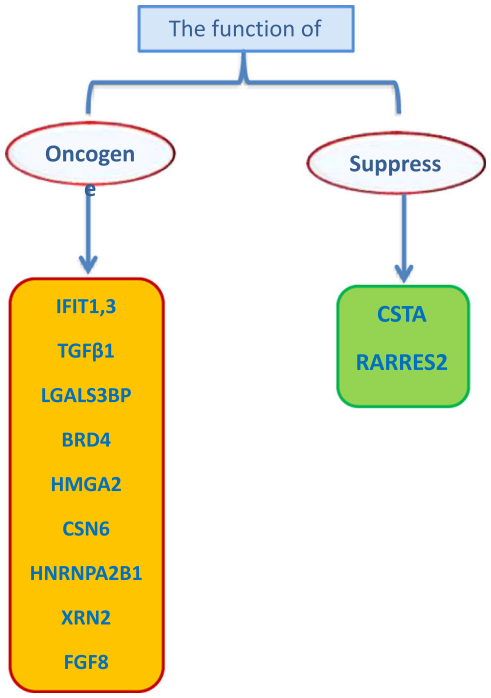

FIGURE 2 The role of genes as oncogene or tumor suppressors in oral squamous cell carcinoma. BRD4, bromodomain containing 4; CSN6, COP9 signaling complex 6; CSTA, cystatin-A; FGF8, fibroblast growth factors 8; HMGA2, high-mobility group A2; HNRNPA2B1, heterogeneous nuclear ribonucleoproteins A2B1; IFIT1, 3, interferon-induced proteins with tetratricopeptide repeats 1 and 3; LGALS3BP, lectin galactoside-binding soluble 3 binding protein; RARRES 2, retinoic acid receptor responder protein 2; TGFβI, transformed growth factor-β-induced; XRN2, 5′–3′ exoribonuclease 2.

Several genes have been associated with aberrant cell migration, invasion, metastasis, and resistance to immunotherapy and chemotherapy.[71–75] In delayed diagnosis, metastasis is occasionally a sequela of OC, contributing to its low survival rates and poor outcomes. In the context of OC, lymph node metastasis, and its underpinning mechanisms have always been an area of particular interest. Genes can serve as suppressors or oncogenes in metastasis and regulate OSCC progression through different epigenetic and genetic mechanisms at transcription, translation, and even post-transcriptional levels[76–80] (Figures 2 and 3). One of these pathways is EMT, which can be induced by genes involved in metastasis. During this process, epithelial cells lose their polarity and intercellular adhesion and acquire migratory and invasive characteristics.[81] Furthermore, the expression levels of some markers in this process decreased (E-cadherin and Claudin1), while others increased (β-catenin, snail, and vimentin).[82–85] Studies have shown that HMGA2, HNRNPA2B1, XRN2, CSTA, and FGF8 regulate the metastasis of OSCC by inducing or inhibiting the EMT process. Thus, this suggests that invasion, cellular survival, and angiogenesis mediated by the genes mentioned above may be involved in the process of metastasis, and detecting these genes can serve as a potential method for early prediction of metastasis.

5 | CONCLUSION

In cancer patients, metastasis is the major cause of mortality. OSCC metastasis is widespread because of late diagnosis, resulting in a poor survival rate. According to the results of this study, we can conclude

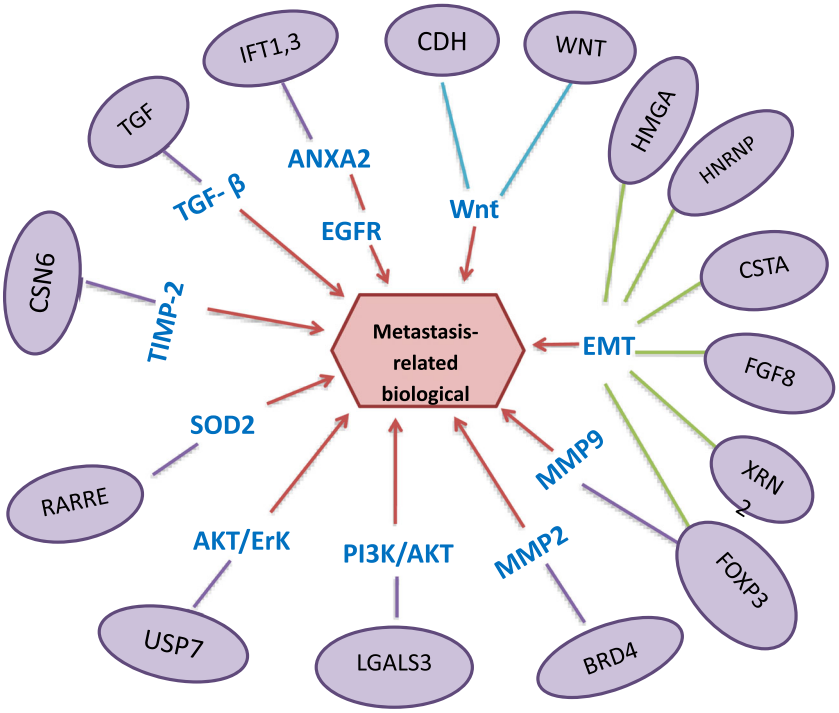

FIGURE 3 Genes involved in OSCC metastasis and related biological processes. AKT, protein kinase B; BRD4, bromodomain containing 4; CDH3, cadherin; CSN6, COP9 signaling complex 6; CSTA, cystatin-A; EGFR, estimated glomerular filtration rate; EMT, epithelial–mesenchymal transition; ERK, extracellular-regulated kinase; FGF8, fibroblast growth factors 8; HMGA, high-mobility group A2; HNRNP, heterogeneous nuclear ribonucleoproteins; IFIT1, 3, interferon-induced proteins with tetratricopeptide repeats 1 and 3; LGALS3BP, lectin galactoside-binding soluble 3 binding protein; MMP-2, matrix metalloproteinase-2; OSCC, oral squamous cell carcinoma; PI3K, phosphoinositide 3-kinase; RARRES 2, retinoic acid receptor responder protein 2; SOD2, superoxide dismutase 2; TGF, transformed growth factor; USP7, ubiquitin-specific-processing protease 7; XRN, 5′–3′ exoribonuclease.

that genes involved in metastasis are IFIT1 & IFT3, HMGA2, TGFBI, LGALS3BP, BRD4, CSN6, HNRNPA2B1, XRN2, CSTA, FGF8, FoxP3, CDH3 and WNT5A, USP7, and Rarres2. That high expression of the above genes, excluding FoxP3 and LGALS3BP, related to metastasis that confirms overexpression of the genes above might contribute to malignant potential. Identifying the genes mentioned above could be very helpful for improving the prognosis of patients suffering from OSCC. Studies show that OSCC patients with metastatic genes have a poor prognosis. Furthermore, we believe that further studies are necessary to compare the results of the genes already studied and investigate new genes involved in OSCC metastasis.

AUTHOR CONTRIBUTIONS

Nooshin Mohtasham: Conceptualization; investigation; methodology. **Marzieh Zarepoor**: Data curation; formal analysis; investigation. **Zahra Shooshtari**: Validation; writing—original draft. **Kiana Kamyab Hesari**: writing—review and editing. **Farnaz Mohajertehran**: Conceptualization; data curation; formal analysis; methodology; project administration; resources; validation. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Dr. Farnaz Mohajertehran and Dr. Nooshin Mohtashsm, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Dr. Farnaz Mohajertehran and Dr. Nooshin Mohtasham. Dr. Farnaz Mohajertehran had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Farnaz Mohajertehran affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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