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ORIGINAL ARTICLE

Increased SEC14L2 expression is associated with clinicopathological features and worse prognosis in oral squamous cell carcinoma

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Abstract

Abnormal expression of SEC14L2 has been implicated in many human cancers. However, the role of SEC14L2 in oral squamous cell carcinoma (OSCC) remains unclear. Therefore, this study aimed to evaluate the expression and prognostic roles of SEC14L2 in OSCC. OSCC tumors and adjacent non-tumors were collected from OSCC patients and used for *SEC14L2* mRNA expression by quantitative reverse transcription PCR (RT-qPCR). Additionally, the expression of *SEC14L2* was further analyzed using The Cancer Genome Atlas—Head Neck Squamous Cell Carcinoma (TCGA-HNSCC) dataset to identify its relationship with HNSCC clinical characteristics. The Kaplan–Meier plot was used to assess survival rates, and the Tumor Immune Estimation Resource (TIMER) database was used to examine the correlation between *SEC14L2* expression and tumor immune cell infiltration. In silico tools also looked at SEC14L2 involvement in cancer pathways through its protein network. The mRNA and protein levels of SEC14L2 are notably higher in both OSCC and HNSCC tissues compared to adjacent normal tissues. Upregulation of SEC14L2 was associated with advanced tumor stages, grades, metastasis, HPV-negative, and TP53 mutations in cancer patients. In addition, the high expression of *SEC14L2* was negatively correlated with the poor survival of cancer patients and the infiltration of diverse immune cells in cancer patients. According to the findings of this investigation, SEC14L2 is significantly elevated in OSCC/HNSCC patients and associated with a worse prognosis. More investigation and clinical studies are required to completely understand the therapeutic potential of SEC14L2 in HNSCC and convert these findings into better patient outcomes.

Keywords Health · OSCC · Mortality · Genetics · Prognostic indicator · Immune infiltration

Introduction

The prevalence of head and neck squamous cell carcinoma (HNSCC) worldwide underscores the critical need for comprehensive research in this area [1]. Among HNSCC cases, oral squamous cell carcinoma (OSCC) is the predominant form, originating in the oral cavity and accounting for approximately 70% of all instances. Factors, such as human papillomavirus infections and tobacco use, contribute to the risk of this disease [2]. With an annual toll of 300,000 lives and 650,000 reported cases, head and neck cancer poses a significant global health concern. Notably, in emerging nations like Sri Lanka and Southeast Asian countries like India, OSCC stands out as the most prevalent cancer [3, 4]. Despite advancements in the diagnosis and care of OSCC, patients continue to face a poor prognosis, primarily attributed to late-stage diagnoses and the lack of effective therapies [5–8]. Existing

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evidence underscores the link between the formation and progression of HNSCC and the altered expression of oncogenes and tumor suppressors [9–11]. However, the highly sensitive and specific nature of its biomarkers presents challenges in the personalized diagnosis and treatment of HNSCC [12–14]. Consequently, a compelling argument emerges for the imperative need to delve deeper into understanding and addressing the complexities of HNSCC for improved patient outcomes.

The 2015 TCGA consortium unveiled molecular insights into head and neck cancer, emphasizing alterations in tumor suppressor genes, WNT-β-catenin signaling, and epigenetics [15, 16]. Unique genetically HPV-positive head and neck tumors with a favorable prognosis were identified [17]. While 10% of HNSCC patients present with metastatic disease, the majority face locally progressive disease with a high risk of recurrence primary treatments include surgical removal, followed by adjuvant radiation, with or without platinum-based chemotherapy, or concurrent chemoradiation. However, multimodality treatment negatively impacts patient quality of life [18]. Overcoming challenges such as tumor immune resistance is essential for advancing the field, especially in improving responses to immunotherapies with limited current benefits [19, 20].

In recent years, various Sec14-like proteins have been discovered and extensively studied, with research revealing their critical role in human health [21]. Dysfunctional Sec14-like proteins are implicated in various diseases, including breast cancer, prostate cancer, ataxia, and syndromes marked by retinal degeneration [22, 23]. The SEC14L2 gene, responsible for producing a cytosolic protein, belongs to the lipid-binding protein family, which includes Sec14p, cellular retinol-binding protein, and alpha-tocopherol transfer protein. This gene encoded protein activates squalene monooxygenase, a downstream enzyme in cholesterol biosynthesis [24, 25].

Numerous studies over the past decade highlight alpha-tocopherol, the primary bioactive form of natural vitamin E, for its anticancer properties. With origins traced back to 1922, Vitamin E, especially alpha-tocopherol, exhibits essential antioxidant properties sourced from vegetables and nuts. Recognized for inhibiting oral carcinogenesis and managing oxidative stress, incorporating Vitamin E into oral health strategies offers a practical approach to boosting overall well-being [26, 27]. In this study, we conducted a comprehensive review of recent literature in SEC14L2 and utilized the Cancer Genome Atlas (TCGA) database, specifically focusing on mRNA and protein expression data across various genes in patient samples from malignancies, including HNSCC. Given the significant upregulation of SEC14L2 expression observed in cancer patients, our research aims to delve into the expression patterns and clinical significance of SEC14L2 in both OSCC and HNSCC.

Materials and methods

Patient recruitment and sample collection

For this investigation, we recruited a total of 40 patients diagnosed with oral squamous cell carcinoma (OSCC) to collect samples for validating the expression of *SEC14L2* mRNA. The recruitment took place at the Department of Oral Surgery, Saveetha Dental College and Hospitals in Chennai, India. The sample size determination was performed using G Power statistical software (version 3.1.9.6), considering parameters, such as effect size, error probability, and statistical power, as guided by a previous study [28]. During surgical procedures, tumor tissues from OSCC and adjacent non-tumor tissues were collected from the patients. The collected samples underwent histopathological analysis, verified by a pathologist. Patient-specific clinical data were compiled and presented in Table 1. It is important to note that this study only included patients with primary OSCC tumors, and individuals with other cancers, systemic or genetic illnesses, or recurrent cancer were excluded. Ethical considerations were paramount in this research, and the study strictly adhered to the principles outlined in the Declaration of Helsinki. Approval for the study protocol was obtained from the Institutional Human Ethical Committee (IHEC) at Saveetha University, with the reference number

Table 1 Clinical features of patients with oral squamous cell carcinoma

S. No	Variable	Category	No. of patients (%)
1	Gender	Male	32 (80)
		Female	8 (20)
2	Age	≤ 50 years	17 (42.5)
		≥ 51 years	23 (57.5)
3	Grade	Well differentiated	23 (57.5)
		Moderately differentiated	15 (37.5)
		Poorly differentiated	2 (5)
4	Site	Buccal	12 (30)
		Tongue	9 (22.5)
		Other (RMT, GBS, Maxilla, Mandible)	19 (47.5)
5	Stage	I	5 (12.5)
		II	8 (20)
		III	8 (20)
		IV	19 (47.5)
6	Laterality	Left	15 (37.5)
		Right	25 (62.5)
7	Lymph node metastasis	Yes	15 (37.5)
		No	25 (62.5)

RMT retromolar trigone, *GBS* gingivobuccal sulcus

IEC NO: SDC/FAC-12/19/003. Informed consent was duly obtained from each patient or their legal guardian and the tissues were promptly stored at −80 °C to preserve their integrity.

RNA extraction and RT-qPCR analysis

The TRIzol reagent (Thermo Fisher Scientific, MA, USA) was used to extract total RNA from the tumor and nearby normal tissues by the manufacturer's instructions. Nanodrop One (Thermo Scientific, USA) was used to evaluate the quantity and quality of RNA. Following the manufacturer's instructions, RNA was turned into cDNA using the Takara 1st strand cDNA synthesis kit (Takara, Tokyo, Japan). cDNA was employed as a template for the RT-qPCR analysis, and gene expression was examined. All protocols and standards followed by pervious literatures [29]. The following primer sequences were used for RT-qPCR analysis. The *SEC14L2* forward primer 5′-TGG AGC GGA TGT TGG TTT-3′ and reverse primer 5′-TTG GCA TGA ATG AAG CTG TAG G-3′; *GAPDH* forward primer 5′-TCC AAA ATC AAG TGG GGC GA-3′ and reverse primer 5′-TGA TGA CCC TTT TGG CTC CC-3′. A total of 20 µl of PCRs were made using the following ingredients: 2 µl of cDNA template, 50 mM forward and reverse primers, 10 µl of 2× SYBR, and DDH_2O. The Bio-Rad CFX Opus 96 (Bio-Rad, Hercules, CA, USA) was used for RT-qPCR, and the following procedure was provided by Bio-Rad. Denaturation at 95℃ for 3 min at the beginning, then 40 cycles of denaturation at 95 °C for 10 s and annealing at 58 °C for 30 s. *GAPDH* was considered a reference housekeeping gene. The mRNA quantitation was analyzed using the $2^{-\Delta\Delta Ct}$ method. Experiments were performed in triplicates.

Gene expression analysis by UALCAN database

Our analysis of the TCGA dataset highlights the predominant influence of OSCC within HNSCC, constituting approximately 70% of samples and notably affecting specific oral anatomical regions, including the tongue, lip, palate, gum, floor of the mouth, oropharynx, and other unspecified areas. Leveraging the TCGA-HNSC dataset, our study strategically explores SEC14L2 expression, offering a comprehensive analysis with robust correlations and insights specific to OSCC within the broader HNSC context. The TCGA-HNSCC dataset, consisting of 520 HNSCC and 44 normal tissues, facilitated the assessment of *SEC14L2* mRNA expression. Additionally, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) database, encompassing 108 HNSCC and 71 normal tissues, provided insights into SEC14L2 protein expression. Utilizing the UALCAN database, we further examined the correlation between *SEC14L2* expression and clinicopathological characteristics in HNSCC (http://ualcan.path.uab.edu) [30].

Survival analysis by Kaplan–Meier plotter

To analyze HNSCC patient survival, the Kaplan–Meier plot (https://kmplot.com) [31] uses gene expression data from TCGA cancer patients. In this study, Kaplan–Meier survival analysis was used to examine the predictive significance of SEC14L2 mRNA levels in patients with HNSCC.

Immunohistochemistry and tumor infiltration analysis

Immunohistochemistry (IHC), the most common technique for locating proteins in tissues, is used for both histopathological diagnosis and research. Antibodies are essential in modern pathology for identifying the presence and location of specific proteins in surgical specimens. Using the Protein-Atlas immunohistochemistry tool (https://www.proteinatlas.org/) [32], we examined if *SEC14L2* expression was present in HNSCC samples. TIMER2.0 (http://timer.cistrome.org) [33], which employs six cutting-edge algorithms to produce a more accurate estimation of immune infiltration levels, can be used with TCGA or user-provided tumor profiles. The relationship between *SEC14L2* expression and tumor immune cell infiltration was examined in our work using the TCGA-HNSC dataset in TIMER 2.0.

In silico functional analyses

The gene interaction network of *SEC14L2* was analyzed using GENEMANIA (http://genemania.org/) [34]. An online database called STRING was used to examine protein and protein interaction networks. STRING (https://stringdb.org/) [35] stands for Search Tool for the Retrieval of Interacting Genes/Proteins. Using the STRING database, interactions between SEC14L2 and oncogene proteins were examined. Another database used for functional enrichment analysis, network visualization, and gene annotation is Metascape (https://metascape.org/) [36]. This information can be used to determine the biological importance of gene sets or clusters, which aids in the interpretation of large-scale omics data. In Metascape, the data were prepared for the functional enrichment analysis of SEC14L2 using its network gene and proteins.

Statistical analysis

Student's *t*-test or one-way ANOVA was carried out as part of the statistical analysis using SPSS software version 25 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 9.4.0 (GraphPad Software Inc., San Diego, CA,

USA). $P < 0.05$ was chosen as the threshold for statistical significance.

Results

SEC14L2 mRNA and protein expression were significantly upregulated in OSCC and HNSCC tumors

In this comprehensive investigation, SEC14L2 expression was scrutinized across diverse tumor and normal samples, utilizing multiple databases to ensure robust and reliable results. Our findings revealed significant dysregulation of SEC14L2 expression in various cancer samples, as demonstrated in Fig. 1A, where statistical significance was achieved ($p < 0.05$). The UALCAN results, presented in Fig. 1B, further underscored the significance of SEC14L2 dysregulation, revealing a substantial increase in mRNA expression in HNSCC tissues compared to normal tissues ($p < 0.001$). This observation was validated through RT-qPCR, as depicted in Fig. 1C, where a highly significant difference in *SEC14L2* mRNA expression was confirmed ($p < 0.0001$), aligning with the UALCAN results. Moreover, the investigation extended to the examination of SEC14L2 expression in matched OSCC tumor tissues and adjacent normal tissues, as illustrated in Fig. 1D. The results unveiled a significant disparity in *SEC14L2* mRNA expression between these paired samples ($p < 0.001$), providing further evidence of its dysregulation in oral cancer. The protein-level analysis of SEC14L2 expression consistently corroborated these findings. Utilizing the UALCAN database, Fig. 1E demonstrated a significant overexpression of SEC14L2 protein in HNSCC tissues ($p < 0.001$). This was further validated through immunohistochemistry, as illustrated in Fig. 1F, reinforcing the robustness of our observations regarding SEC14L2 dysregulation in the context of HNSCC.

SEC14L2 expression was associated with clinicopathological features, prognosis, and tumor infiltration

In our investigation of the correlation between the clinicopathological features of HNSCC and SEC14L2 expression, the UALCAN database provided valuable results. Notably, elevated SEC14L2 expression exhibited associations with

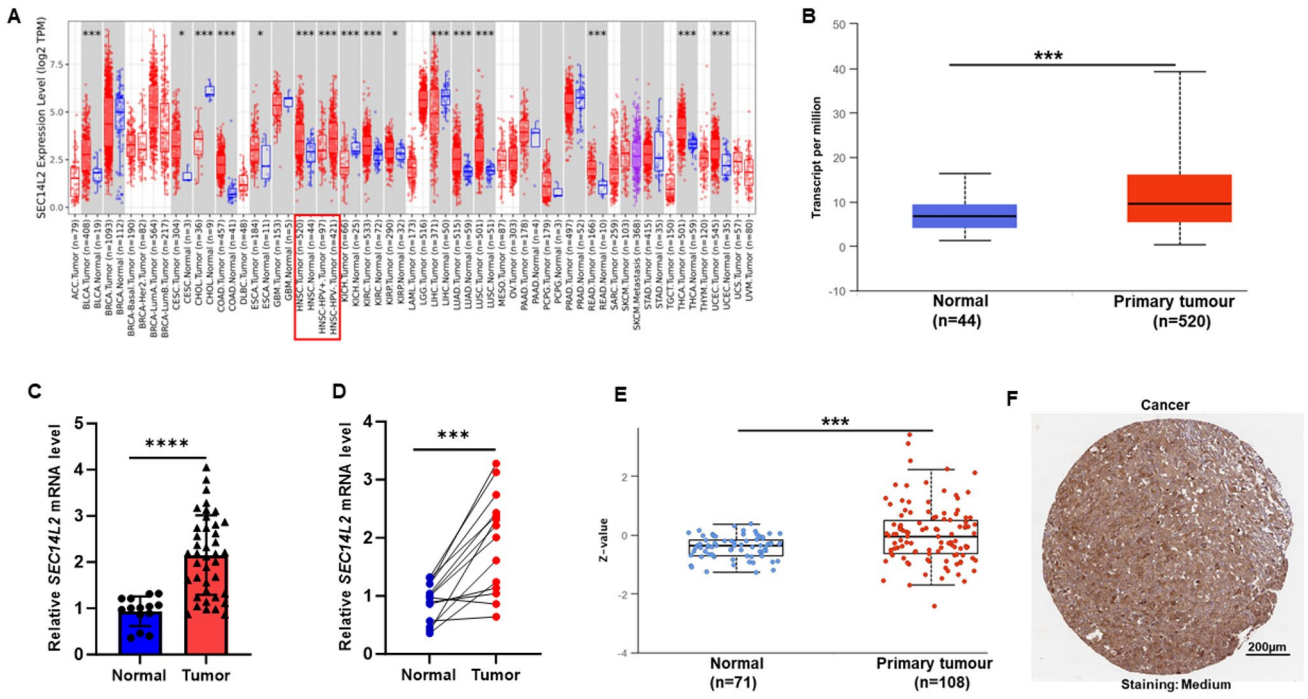

Fig. 1 SEC14L2 expression in cancer. The TIMER 2.0 database showed that *SEC14L2* mRNA is highly expressed in various cancers (**A**), particularly in HNSCC (**B**). RT-qPCR results are also similar to TCGA-HNSC dataset results, the *SEC14L2* mRNA level was significantly upregulated in OSCC tumor tissue (**C**) and the *SEC14L2* mRNA level significantly increased in matched OSCC tissues (**D**). SEC14L2 protein was significantly increased in HNSCC samples (**E**). The *X*-axis represents sample type and *Y*-axis indicates levels of SEC14L2 expression (**A**–**E**). TPM (transcripts per million) (**A**, **B**) and the fold change (**C**, **D**) were used to measure *SEC14L2* mRNA expression levels. The Z-score was used to assess SEC14L2 protein expression (**E**). **F** Immunohistochemistry staining also shows high *SEC14L2* expression in HNSCC tissue. The staining intensity is strong and quantity: >75% in cancer tissue. ****$p < 0.0001$, ***$p < 0.001$, *$p < 0.05$. Image Source: UALCAN (**A**, **B**, **E**), RT-qPCR analysis in OSCC samples (**C**, **D**), Protein-atlas (**F**)

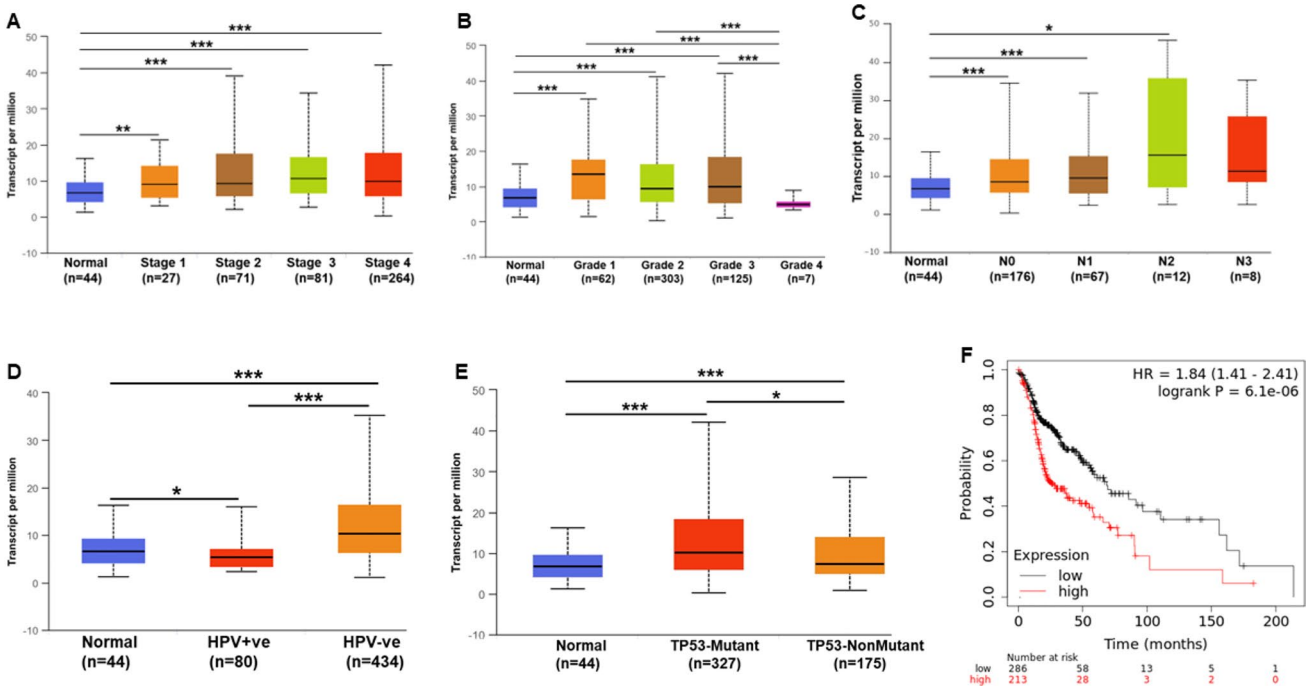

Fig. 2 Correlation of *SEC14L2* expression with HNSCC clinicopathological features. Box-plot represents the SEC14L2 mRNA expression significantly altered and correlated with the clinicopathological features of HNSCC including tumor stage (**A**), tumor grade (**B**), nodal metastasis (**C**), HPV status (**D**), and TP53 mutant status (**E**). The *X*-axis represents sample type and *Y*-axis indicates levels of SEC14L2 expression (**A**–**E**). The Kaplan–Meier plot indicates high SEC14L2 expression affects the overall survival rate (**F**) suggesting a worse prognosis in HNSCC patients. Image Source: UALCAN. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$

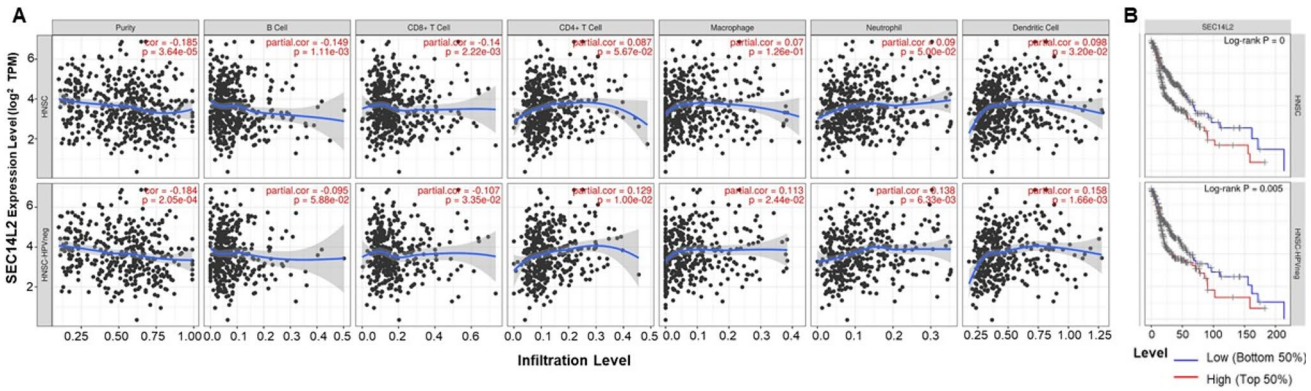

Fig. 3 Immune cell infiltration and *SEC14L2* expression in HNSCC tumor microenvironment. **A** The correlation plot suggests that SEC14L2 is significantly associated with tumor immune cell infiltration including B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (the *X*-axis represents immune cell infiltration level and the *Y*-axis indicates levels of SEC14L2 expression). **B** Kaplan–Meir plot indicates that the *SEC14L2* expression is associated with poor prognosis in HNSCC patients. Image Source: TIMER 2.0

crucial parameters, such as cancer stage, tumor grade, nodal metastasis, HPV status, and TP53 mutant status, as illustrated in Fig. 2A–E. Furthermore, Kaplan–Meier analysis demonstrated a significant impact of high SEC14L2 expression on the overall survival rate of HNSCC patients, indicative of a worse prognosis (Fig. 2F, $p < 0.001$). To delve into the influence of SEC14L2 on the immune microenvironment in HNSCC, we utilized the TIMER2.0 database. The results, presented in Fig. 3A, revealed a negative correlation between SEC14L2 expression and immune cell infiltration, specifically B cells, CD4+ T cells, macrophages, and dendritic cells. Additionally, high SEC14L2 expression was

associated with a poorer prognosis, as depicted in Fig. 3B. These findings underscore the potential role of SEC14L2 in shaping the immune landscape within HNSCC and its implications for patient outcomes.

Functional analysis revealed that SEC14L2 and its network are strongly associated with HNSCC

To better understand SEC14L2 interactions, we analyzed gene and protein data from GeneMANIA and STRING. The resulting network highlighted SEC14L2 primary connections with oncogenes and various proteins (Fig. 4A, B). Furthermore, our exploration extended to functional enrichment analysis using Metascape, shedding light on the pivotal role of SEC14L2 in processes crucial to cancer pathogenesis. The analysis indicated its involvement in key functions related to localization, metabolism, and cellular processes (Fig. 4C). These findings deepen our understanding of SEC14L2 potential impact on cancer development and emphasize its multifaceted role in cellular mechanisms.

Discussion

In this comprehensive study, we conducted a thorough investigation into the expression of SEC14L2 and its clinical implications in Head and Neck Squamous Cell Carcinoma (HNSCC), utilizing the TCGA-HNSC dataset and validating our findings in Oral Squamous Cell Carcinoma (OSCC) tumor samples.

The significance of SEC14L2 transcends the realm of HNSCC, as it has been identified as the alpha-tocopherol-associated protein (TAP), a crucial binding partner for alpha-tocopherol in various tissues. Alpha-tocopherol, the most common and bioactive form of natural vitamin E, has been shown to have anticancer characteristics during the past 10 years through a variety of studies. It is noteworthy that alpha-tocopherol-associated protein (TAP), also known as SEC14L2, has become an important binding partner for alpha-tocopherol in human serum as well as in important tissues like the liver, brain, and prostate [37]. It is clear that the lipid-binding protein SEC14L2 plays a vital role in supporting effective viral replication of clinical hepatitis C virus (HCV) isolates under cell culture conditions [25]. The potential of SEC14L2 as a biomarker or therapeutic

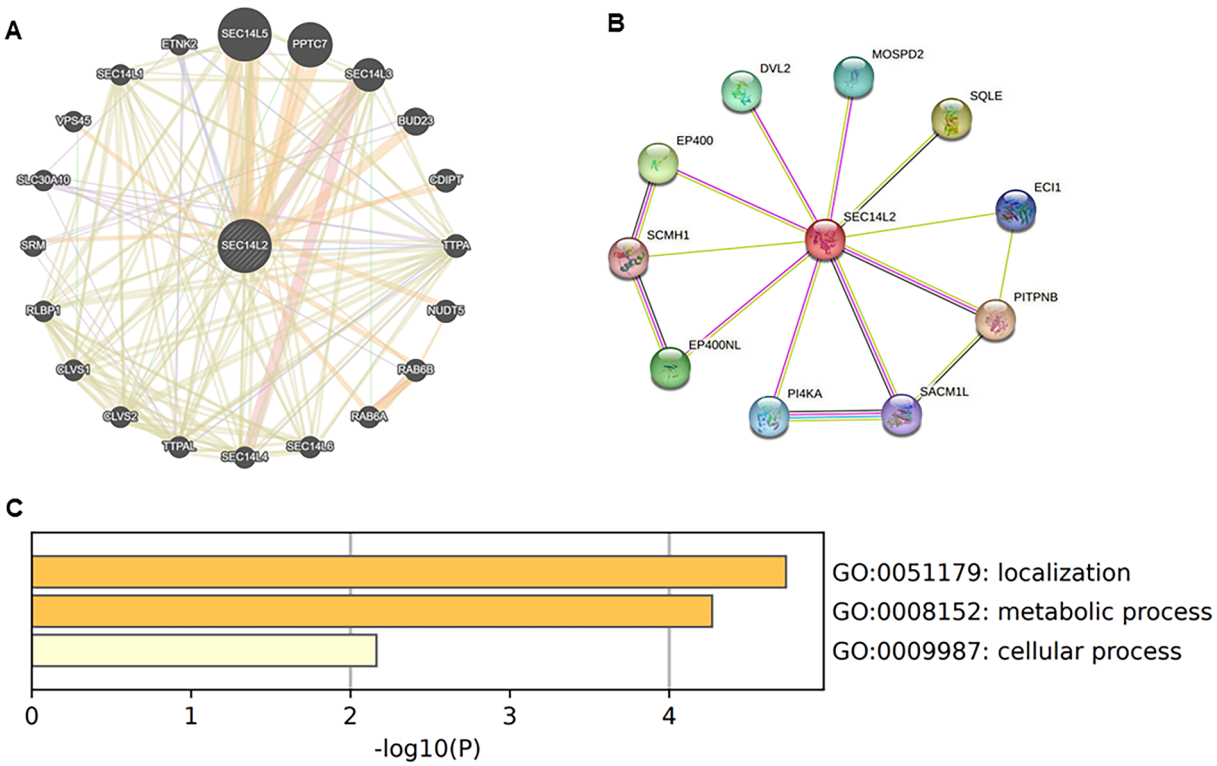

Fig. 4 SEC14L2 network and functional enrichment analysis. **A** Gene–gene interaction network was analyzed using the GeneMANIA database. **B** Analysis of the SEC14L2 protein in the STRING database shows the SEC14L2 protein and its partner protein interaction network. **C** The functional enrichment analysis of the SEC14L2 network is associated with localization, metabolic process, and cellular process. Image Source: GeneMANIA (**A**), STRING (**B**) and Metascape (**C**)

target for castration-resistant prostate cancer (CRPC) is highlighted by the significant correlation between reduced SEC14L2 expression and CRPC, as well as its alignment with increased prostate cancer aggressiveness and a poor prognosis. This connection further emphasizes the importance of SEC14L2 in the context of prostate cancer [38]. The impact of SEC14L2 extends beyond the boundaries of a single disease because it is closely related to other illnesses. SEC14L2 is particularly implicated in diseases like Plica Syndrome and ataxia with vitamin E insufficiency. These relationships highlight the multiple physiological significances of SEC14L2 and its potential function in several clinical situations. SEC14L2 acquires a role of larger clinical relevance by illuminating its contributions to a spectrum of illnesses, necessitating in-depth investigation for a clearer understanding of its implications in health and disease [39–42].

Our rigorous analysis uncovered a robust upregulation of SEC14L2 in both OSCC and HNSCC tumors, establishing the consistency of our observations across diverse samples. The noteworthy dysregulation of SEC14L2 was evident not only in HNSCC but also in various cancer samples, emphasizing its broad relevance in the context of cancer. Significantly, heightened *SEC14L2* expression demonstrated intricate associations with key clinicopathological features in HNSCC, including tumor stage, grade, nodal metastasis, HPV status, and TP53 mutant status. Kaplan–Meier analysis highlighted its clinical relevance, indicating a substantial impact on overall survival and pointing toward a worse prognosis for HNSCC patients exhibiting elevated *SEC14L2* expression. The observed negative correlation between *SEC14L2* and immune cell infiltration, coupled with its association with a poorer prognosis, suggests a potential role in shaping the immune landscape within HNSCC.

Furthermore, our functional analysis unveiled the intricate network of SEC14L2, emphasizing its strong associations with oncogenes and key cellular processes crucial to cancer pathogenesis. These findings provide in-depth insights into the multifaceted role of SEC14L2 in HNSCC, offering a comprehensive understanding of its potential implications for disease progression and patient outcomes.

Liu et al. found strong evidence supporting a correlation between reduced SEC14L2 expression and CRPC. This decrease in SEC14L2 expression was additionally associated with increased prostate cancer aggressiveness and a very bad prognosis. These findings highlight SEC14L2 intricate role in the etiology of CRPC and place it in a promising position for future biomarker or therapeutic targeting in the CRPC landscape. The findings of the study highlight SEC14L2 potential clinical relevance and its potential contribution to the development of customized therapies for CRPC patients [38]. A study conducted by Xi Wang showed TAP/Sec14L2 elevated expression levels in normal/benign breast, prostate, and liver tissues but substantially reduced expression in lung, colon, and kidney tissues. This study highlights tissue-specific differences in TAP/Sec14L2 expression, which may indicate that many organs have unique physiological functions [43]. Limited studies have investigated SEC14L2 expression in cancer, thereby impeding a comprehensive understanding of the gene's role. There is a need for further exploration of SEC14L2 in the context of cancer to enhance our comprehension.

Furthermore, the increased expression of SEC14L2 associated with HNSCC implies a potential adverse effect of vitamin E. Hence, conducting functional studies becomes imperative to unravel the upstream and downstream pathways of the SEC14L2 gene in HNSCC.

Our findings firmly establish SEC14L2 as a pivotal prognostic biomarker, demonstrating its potential to identify and classify disease states in their early stages. The association of SEC14L2 expression with tumor grades suggests its crucial role in the differentiation of HNSCC tumorigenesis, emphasizing its involvement in tumor invasion. Additionally, the correlation with HPV and TP53 mutant status further underscores SEC14L2 significant role in HNSCC pathogenesis. Furthermore, prognosis and tumor infiltration suggest its involvement in tumor microenvironment and worse prognosis.

However, it is crucial to acknowledge certain limitations in our study. The confirmation of elevated *SEC14L2* expression in OSCC tumor tissue was determined through RT-qPCR experiments in a limited number of samples, warranting further investigation in a larger cohort. Moreover, the outcomes derived from our bioinformatics analysis require validation through forthcoming biological experiments, encompassing both in vivo and in vitro methodologies. Despite these limitations, our results suggest that SEC14L2 holds promise as a novel biomarker in the diagnosis of OSCC, serving as a plausible prognostic predictor.

Conclusion

Our study highlights significant upregulation of *SEC14L2* mRNA and protein expression in HNSCC, particularly notable in OSCC. Utilizing data from the TCGA and analyzing OSCC patient samples, we establish associations between *SEC14L2* dysregulation and crucial clinicopathological features, including tumor stage, tumor grade, nodal metastasis, HPV status, and TP53 mutant status. High *SEC14L2* expression emerges as a prognostic indicator, correlating with a poorer overall survival rate in HNSCC patients. Functional analysis highlights the various associations of SEC14L2 with oncogenes and proteins that are crucial for cancer pathogenesis, positioning *SEC14L2* as a potential

prognostic biomarker and therapeutic target in head and neck cancers. Therefore, this requires further exploration and clinical research.

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Author contributions Jonah Justin David contributed to data acquisition, analysis, and interpretation, and drafted and critically revised the manuscript. Balachander Kannan, Chandra Pandi, Vijayashree Priyadharsini Jayaseelan, Jeevitha Manicka Vasagam, and Paramasivam Arumugam contributed to data acquisition and analysis, critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical statement This study was approved by the Institutional Ethical Committee of the Saveetha Dental College and Hospital. All participants signed an informed consent form.

Data availability The transcriptome data and related clinical information that support the findings of this study are available on the TCGA official website.

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