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Genomic and Transcriptomic Alterations in the COL28A1 Gene: Potential Role in the Pathogenesis of Head and Neck Squamous Cell Carcinoma

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Abstract **Objectives:** Head and neck squamous cell carcinoma (HNSCC) is among the most prevalent malignancies globally, often associated with tobacco, alcohol use, and human papillomavirus (HPV) infection. Recent studies have highlighted the importance of genetic alterations in the development and progression of HNSCC. The COL28A1 gene, a member of the collagen family, has not been extensively studied in the context of HNSCC pathogenesis. This study aimed to investigate the genomic and transcriptomic alterations of the COL28A1 gene in HNSCC and assess its potential role in disease progression, prognosis, and interaction with molecular pathways. **Methods:** Publicly available datasets from The Cancer Genome Atlas (TCGA) and Firehose Legacy were analyzed using bioinformatics platforms including cBioPortal, UALCAN, PolyPhen-2, I-Mutant, and STRING. Genomic alterations such as mutations, amplifications, and deletions were assessed, along with differential gene expression between tumor and normal tissues. Survival analysis was performed using Kaplan-Meier curves, and protein-protein interaction networks were constructed to explore functional associations. **Results:** COL28A1 alterations were identified in a subset of HNSCC and LUSC cases, primarily in the form of amplifications and missense mutations. Expression analysis revealed significantly elevated COL28A1 expression in HNSCC tumor tissues compared to adjacent normal tissues ($p < 0.05$). Survival analysis indicated that patients with higher COL28A1 expression had poorer overall survival. Pathogenicity predictions classified several mutations as "probably damaging," while protein stability analysis indicated reduced stability due to specific variants. Protein interaction analysis highlighted potential associations with extracellular matrix remodeling and cellular adhesion pathways. **Conclusion:** Genomic and transcriptomic alterations in COL28A1 may contribute to the pathogenesis and progression of HNSCC. Its elevated expression is associated with poorer prognosis, suggesting a potential role as a prognostic biomarker. Further functional studies are warranted to validate these findings and explore COL28A1 as a therapeutic target in HNSCC.

Key Words COL28A1, Head and Neck Squamous Cell Carcinoma, Genomic Alterations, Gene Expression, TCGA, Bioinformatics, Prognosis, HPV

INTRODUCTION

Head and neck cancer (HNC) encompasses malignancies that arise in the oral cavity, pharynx, larynx, nasal cavity and salivary glands. Globally, HNC ranks as the sixth most common malignancy and the eighth major cause of cancer-related mortality [1,2]. Historically, HNC was predominantly diagnosed in males over the age of 65 with lifestyle risk factors such as tobacco use and alcohol consumption. However, with successful anti-tobacco campaigns, the overall incidence of HNC has declined. Despite this, a notable increase in cases of HNC involving the base of the tongue, tonsils and oropharynx has been observed among adults aged 40 to 59 [3,4].

Human papillomavirus (HPV) infection has emerged as a significant etiological factor in HNC, with over 60% of new cases globally being linked to HPV exposure [5]. As HPV infections often present asymptomatically, their true prevalence is challenging to assess. In affluent nations such as Canada, the United States and Australia, it is estimated that 75–80% of sexually active adults will contract HPV at some point in their lives. Estimating HPV incidence and prevalence rates in developing nations is particularly difficult, though cervical cytology studies suggest significantly higher HPV infection rates in regions such as Africa and Oceania. While most HPV infections resolve spontaneously, persistent infections can lead to malignancies, including cervical, penile, rectal and HNC [6].

HPV-related HNC often presents in individuals diagnosed at a younger age, typically middle-aged men from higher socioeconomic backgrounds. Risk factors associated with

HPV-positive HNC include behaviors such as marijuana use, open-mouth kissing, multiple oral sex partners, young age (≤18 years old) and a history of cervical HPV infection [7]. Notably, individuals with HPV-associated HNC respond better to treatment and demonstrate improved survival outcomes compared to those with HPV-negative HNC [8].

From a psychosocial perspective, the challenges faced by middle-aged individuals diagnosed with HNC are considerable. According to Erik Erikson's theory of psychosocial development, middle adulthood is characterized by generativity - a stage marked by productivity, social contribution and caregiving. HNC can disrupt this stage, resulting in stagnation, reduced social fulfillment and difficulties in fulfilling family, professional and societal roles [9,10].

The pathogenesis of squamous cell carcinoma of the head and neck (SCCHN) involves multiple genetic alterations. These include the inactivation of tumor suppressor genes, activation of proto-oncogenes, or a combination of both. Molecular studies have revealed that genetic and epigenetic alterations occur early in SCCHN progression, which aids in understanding the biological underpinnings of the disease [11].

Telomerase reactivation is observed in approximately 90% of SCCHN cases and is linked to telomere maintenance, promoting cellular survival and preventing apoptosis. The deletion of the 9p21 region is one of the most frequent genetic abnormalities in SCCHN, identified in 70-80% of patients. This deletion leads to the inactivation of p16, which is often silenced by homozygous deletion, point mutations, or promoter hypermethylation. Furthermore, chromosomal alterations such as the loss of 3p are frequently detected in early SCCHN lesions. More than 50% of SCCHN cases also show loss of heterozygosity at 17p and mutations in the TP53 gene, though the prognostic significance of these mutations remains controversial [12,13].

Environmental risk factors continue to play a crucial role in HNC development. Tobacco and alcohol consumption account for approximately 75% of SCCHN cases and exhibit a synergistic effect. Notably, heavy alcohol consumption (three or more drinks per day) has been identified as a significant risk factor for SCCHN, even among non-smokers [14]. Genetic variations in enzymes that metabolize nicotine and alcohol have also been implicated in elevated SCCHN risk [15].

The physical and psychological burden faced by individuals with HNC can be profound. Treatment-related complications, such as speech impairment, swallowing difficulties and persistent pain, significantly impact patients' quality of life. Additionally, social challenges - including disfigurement, altered body image and difficulties reintegrating into professional and social environments - contribute to heightened distress. Patients may also experience embarrassment associated with HPV-related HNC, further exacerbating social isolation [16].

HPV, particularly HPV16 and, to a lesser extent, HPV18, has been identified as a major contributor to SCCHN. The detection of carcinogenic HPV subtypes through in situ hybridization and p16 immunohistochemistry has improved diagnostic accuracy for HPV-associated cancers [17]. Approximately 25% of SCCHN cases are linked to HPV DNA, with the highest association seen in tonsillar malignancies and a moderate correlation in oropharyngeal cancers. In contrast, the association is minimal in oral cavity and laryngeal cancers [18].

In HPV-related SCCHN, viral oncogenes such as E6 and E7 inactivate tumor suppressor proteins p53 and pRb, respectively, which facilitates oncogenesis. These HPV-positive tumors are often poorly differentiated with basaloid histology and are more common among individuals without a history of tobacco or alcohol use [19].

Patients diagnosed with HNC, particularly those undergoing intensive treatments such as surgery, chemotherapy, or radiotherapy, are vulnerable to psychological distress, including anxiety and depression. The increasing incidence of HNC in elderly individuals further highlights the need for personalized treatment approaches that minimize treatment intensity while maintaining therapeutic efficacy [20].

Advances in treatment strategies for SCCHN have emphasized organ preservation while enhancing survival rates. Improved surgical techniques, advancements in radiation delivery and the incorporation of systemic therapies-such as epidermal growth factor receptor (EGFR) inhibitors-have played pivotal roles in improving outcomes. Multidisciplinary collaboration remains essential in ensuring comprehensive evaluation, personalized treatment planning and improved post-treatment rehabilitation in elderly patients with HNC [21,22].

METHODS

Sample Dataset

The data for this study were obtained from publicly available cancer genomics databases, specifically The Cancer Genome Atlas (TCGA) and Firehose Legacy datasets. The study utilized genomic and transcriptomic data from patients diagnosed with head and neck squamous cell carcinoma (HNSCC) and lung squamous cell carcinoma (LUSC) to explore COL28A1 alterations. These datasets were accessed through cBioPortal and UALCAN, which provide comprehensive cancer genomics data, including gene expression profiles and clinical details.

Study Design and Population

This study was designed to investigate the genomic, transcriptomic and epigenetic alterations in the COL28A1 gene and its potential association with HNSCC. Data from HNSCC patients were retrieved from publicly accessible databases, specifically cBioPortal and UALCAN. Inclusion criteria involved selecting HNSCC cases with documented

COL28A1 alterations, while cases with incomplete genomic, transcriptomic, or clinical data were excluded from the analysis.

Gene Alteration Analysis
To assess genomic alterations in COL28A1, the cBioPortal platform (http://cbioportal.org) was used. COL28A1 was queried across relevant datasets and OncoPrint plots were generated to visualize the frequency and type of gene alterations, including mutations, amplifications and deletions. The resulting data were analyzed to determine the prevalence and nature of these alterations in HNSCC and LUSC cohorts.

Gene Expression Analysis
The UALCAN platform was employed to analyze COL28A1 expression data in both tumor and normal tissues. Box-and-whisker plots were generated to visualize the differential expression patterns between primary tumor tissues and adjacent normal tissues. Student's t-test was used to assess the statistical significance of differences in expression, with a threshold of $p<0.05$ considered statistically significant.

Genomic Analysis
Genomic alterations were further explored using lollipop plots generated by cBioPortal to identify the location and frequency of amino acid changes in the COL28A1 protein sequence. The analysis focused on identifying hotspots of mutations, mutation types and their predicted pathogenic effects.

Transcriptomic Evaluation
To evaluate COL28A1 transcript expression levels, data from tumor and adjacent normal tissues were compared using box-and-whisker plots. The significance of differences was assessed using Student's t-test, with a significance threshold set at $p<0.05$. The UALCAN platform was used to retrieve reliable gene expression data, ensuring accurate comparisons and visualizations.

Survival Analysis
The Kaplan-Meier method was used to assess the prognostic value of COL28A1 expression levels. Patients were stratified into low/medium and high-expression groups. The log-rank test was performed to evaluate differences in overall survival rates between these groups, with a significance level of $p<0.05$. This survival analysis was conducted to assess whether COL28A1 expression levels influence patient outcomes in HNSCC.

Pathogenicity Analysis
The functional impact of COL28A1 mutations was predicted using PolyPhen-2 and I-Mutant tools. PolyPhen scores were categorized as "Probably damaging," "Possibly damaging," or "Benign" to assess the pathogenic potential of identified mutations. Additionally, DDG scores from I-Mutant were used to predict changes in protein stability induced by COL28A1 mutations, with both increased and decreased stability effects recorded.

Protein-Protein Interaction Analysis
To explore COL28A1's functional interactions, a protein-protein interaction (PPI) network was generated using the STRING database. The network identified key interacting proteins and molecular pathways associated with COL28A1. Gene enrichment analyses and Gene Ontology (GO) analyses were conducted to identify biological processes linked to these interacting proteins.

Statistical Analysis
Statistical analyses were performed using SPSS version XX (or other relevant software). Data were expressed as mean±standard deviation (SD) for continuous variables and as percentages for categorical variables. For comparative analysis, appropriate tests such as Student's t-test, chi-square test, or log-rank test were applied as needed. A p-value < 0.05 was considered statistically significant. The statistical analysis followed the guidelines outlined in the CONSORT reporting standards to ensure clarity, reproducibility and scientific rigor.

Ethical Considerations
The study was conducted in accordance with established ethical guidelines. Ethical clearance was obtained from the Institutional Review Board (IRB) if applicable. Since publicly available data were used for this study, informed consent was not required. However, where applicable, data handling procedures followed relevant data protection and privacy regulations to ensure compliance with ethical standards.

RESULTS

Demographic Profile Interpretation from HNSCC and LUSC Datasets
The analysis of demographic profiles from two distinct datasets-head and neck squamous cell carcinoma (HNSCC) and lung squamous cell carcinoma (LUSC)-sheds light on the patient characteristics that may have implications for understanding disease etiology, treatment responses and outcomes.

Head and Neck Squamous Cell Carcinoma (HNSCC)
The HNSCC dataset comprises a heterogeneous group of malignancies arising from various anatomical sites, including the oral cavity, larynx and oropharynx.

Age Distribution
The majority of patients often fall within the age range of 50 to 70 years, indicating that HNSCC primarily impacts middle-aged adults. This generational trend may suggest that prolonged exposure to risk factors, including tobacco and alcohol consumption, has a role in the onset of these diseases.

Gender Representation
The profiles of HNSCC often exhibit a greater prevalence in males than in females, with male patients representing approximately 73% of the cohort. This gap may indicate occupational exposures or lifestyle characteristics more common in men, hence increasing their risk of HNSCC.

Smoking and Alcohol History
Approximately 76.7% of patients indicated a history of smoking or were current smokers. Additionally, approximately 66.7% of patients reported habitual alcohol intake. The significant correlation of these modifiable risk factors with HNSCC underscores the necessity for focused public health initiatives to reduce these hazards in at-risk groups.

Tumor Stage at Diagnosis
The analysis indicates that around 48.67% of patients were diagnosed at stage IVA, signifying advanced disease at presentation. This elevated proportion indicates potential diagnostic delays, perhaps attributable to asymptomatic lesions in the early stages or insufficient access to screening. Understanding the stage can also guide treatment approaches and underscore the necessity for more early detection techniques.

Lung Squamous Cell Carcinoma (LUSC)
The LUSC cohort represents a specific subtype of lung cancer, which also has distinctive demographic characteristics.

Age Distribution
Like HNSCC, LUSC incidences primarily impact those aged 60 to 75 years, predominantly middle-aged to older adults. This discovery associates the heightened prevalence of lung cancer with aging demographics and their prolonged exposure to toxins, particularly tobacco smoke.

Gender Representation
LUSC likewise indicates a predominantly male population, although the ratio of diagnosed men to women may differ somewhat from that of HNSCC. Historically, lung cancer has been more common in men due to elevated smoking rates; however, this disparity has diminished in recent years as smoking rates among women have risen.

Smoking History
A notable link occurs between smoking and LUSC, similar to HNSCC. A significant proportion of patients with LUSC are either former or current smokers, underscoring the pivotal role of tobacco exposure in the etiology of this cancer type. This observation highlights the necessity for extensive smoking cessation initiatives, especially aimed at high-risk populations.

Comorbid Conditions
The demographic profile of LUSC patients often includes numerous comorbidities, including as chronic obstructive pulmonary disease (COPD) and cardiovascular problems, which may influence management and treatment outcomes. Understanding these associated illnesses is essential for developing complete care strategies for LUSC patients. The demographic data from the HNSCC and LUSC databases offer vital insights regarding age, gender, risk factors and disease stages, which are crucial for tailoring preventive and intervention strategies. The prevalent tendencies of elevated prevalence in older males, frequent associations with smoking and late-stage diagnosis highlight the imperative for targeted public health actions to address these diseases and improve early identification and treatment options.

The COL28A1 gene has attracted considerable interest for its possible involvement in head and neck squamous cell cancer (HNSCC). The data illustrated through oncoprint and lollipop plots offers a visual depiction of alterations in this gene among HNSCC patients.

Interpretation of Oncoprint Data
The oncoprint (Figure 1(a)) illustrates a summary of the mutation profile of the COL28A1 gene in HNSCC cases. Each row generally signifies a distinct patient, whereas the columns denote particular mutations. The existence of several mutations in the COL28A1 gene indicates a potentially significant involvement for this gene in the etiology of HNSCC. These mutations may modify gene activity or protein structure, facilitating tumor formation and progression. Examining the number and categories of mutations can yield information into the basic characteristics of HNSCC tumors and guide prospective treatment strategies.

Interpretation of Lollipop Plot
The lollipop plot (Figure 1(b)) illustrates the precise locations of mutations at the amino acid level inside the COL28A1 protein. The X-axis denotes the quantity of individuals with mutations at specific loci, whilst the Y-axis illustrates the corresponding amino acid positions of these mutations. The density of mutations in particular locations may signify "hotspot" areas essential for the protein's function or stability. Examining the correlation between these mutations and clinical outcomes may enhance the comprehension of their significance in HNSCC prognosis and treatment.

Recent studies have underscored the significance of COL28A1 in HNSCC, indicating that mutations in this gene may substantially affect cancer biology. A study examining the effects of these mutations on tumor microenvironment interactions is essential for comprehending their ramifications [23]. Recent research has demonstrated that changes in type I collagen deposition, possibly associated with COL28A1 mutations, promote cancer stem cell traits in HNSCC, highlighting the significance of extracellular matrix

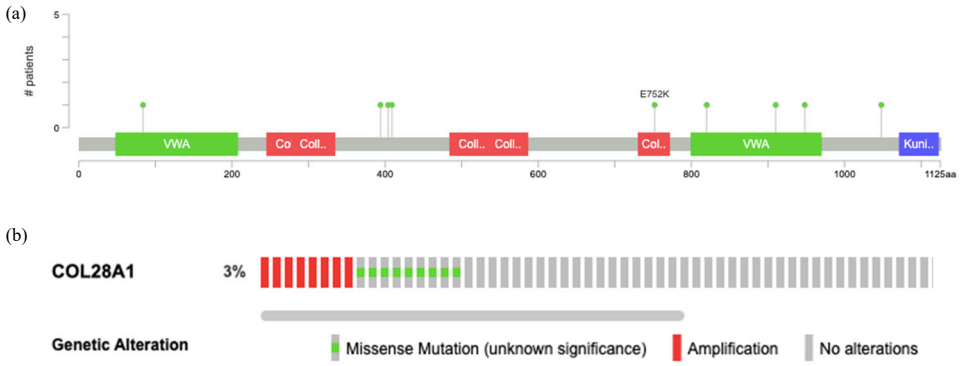

Figure 1(a-b): (a) Oncoprint data demonstrating several mutations in the *COL28A1* gene in HNSCC patients and (b) Lolipop plot demonstratng the placement of mutations in the *COL28A1* gene, the X-axis represents the number of patients and the Y-axis represents the position of the amino acid

components in tumor dynamics [24]. These advancements emphasize the necessity for additional investigation of COL28A1 mutations, both as indicators for prognostic assessment and as targets for innovative therapeutic approaches in HNSCC treatment.

Interpretation of COL28A1 Expression in HNSCC

The presented findings related to the COL28A1 gene in head and neck squamous cell carcinoma (HNSCC) patients underscore its potential significance in tumor biology and prognosis.

Box Whisker Plot Analysis

The box whisker plot (Figure 2(a)) depicts the expression levels of the COL28A1 gene in HNSCC patient tissues relative to normal tissues, indicating a p-value of 2.09×10^-1. This signifies that there is no statistically significant disparity in the expression of COL28A1 between primary tumor tissues and normal tissues. Despite diversity in expression levels among the samples, the lack of substantial differences indicates that COL28A1 may not serve as a main marker for differentiating tumor from normal tissue in this cohort [25].

Kaplan-Meier Survival Analysis

Subsequent analysis utilizing the Kaplan-Meier technique (Figure 2(b)) offers essential insights into the correlation between COL28A1 expression levels and survival outcomes in HNSCC patients. The research indicates a notable disparity in survival rates between low/medium and high expression groups, with the high-expression group demonstrating a worse prognosis, evidenced by a p-value of 0.0029. This discovery suggests that elevated expression of COL28A1 is associated with adverse clinical outcomes, indicating its potential function as an oncogenic component in HNSCC. These results underscore the importance of evaluating COL28A1 expression as a potential biomarker for patient classification and targeted therapy approaches in clinical contexts [26].

Implications for Oncogenic Properties

The suggestion that COL28A1 has carcinogenic characteristics is essential for comprehending its function in HNSCC. The varying expression levels correlate with distinct survival outcomes, suggesting a potential mechanism by which COL28A1 may affect tumor growth or the tumor microenvironment. Increased COL28A1 levels may promote cellular characteristics associated with malignancy, including proliferation, invasion, or resistance to apoptosis, thus exacerbating disease severity. Although COL28A1 expression does not markedly distinguish initial tumors from normal tissue, its correlation with lower survival rates in HNSCC patients underscores its potential as a key marker of tumor aggressiveness. Additional research is necessary to investigate the molecular mechanisms involved and examine the therapeutic implications related to COL28A1 expression levels.

Interpretation of the Pathogenicity and Stability Predictions for COL28A1 Mutations in HNSCC

The examination of mutations in the COL28A1 gene in patients with head and neck squamous cell carcinoma (HNSCC) provides critical insights into their possible pathogenicity and impact on protein stability. The results are based on forecasts obtained from the PolyPhen and I-Mutant tools, which evaluate the functional consequences of detected mutations (Table 1).

Pathogenicity Assessment

The PolyPhen prediction scores indicate (Figure 3) the likelihood that an amino acid substitution will affect the function of the COL28A1 protein:

High Probability of Damage

Several mutations, such as G404R, E948Q, G409E, E394Q and R910H, obtained scores between 0.799 and 1.000, classifying them as "probably damaging." These alterations are anticipated to dramatically impair normal protein

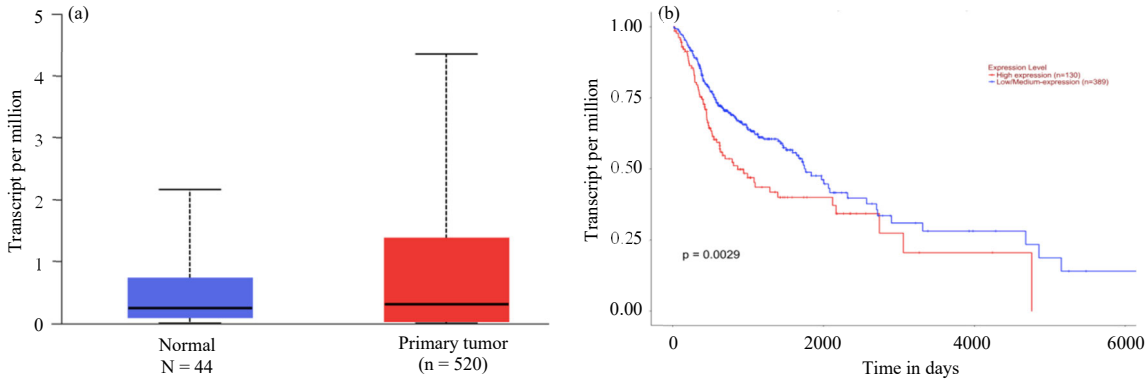

Figure 2(a-b): (a) Box Whisker plot demonstrating the expression of the *COL28A1* gene in HNSCC patients (p-value = 2.09 x 10^{-01}). No significant expression was observed in the primary tumor tissues when compared to the normal tissues and (b) Kaplan Meier survival analysis showed a significant difference in survival among the low/medium and high expression groups. The high-expression group exhibited a poor prognosis (p-value = 0.0029) compared to the low/medium-expression group, implying that the *COL28A1* gene could have an oncogenic property, A p-value less than 0.05 was considered to be significant

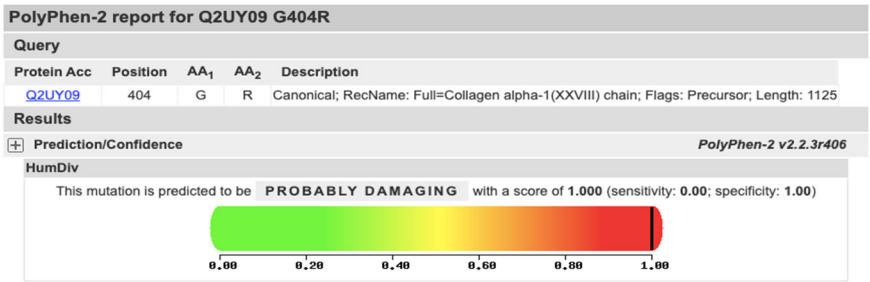

Figure 3: PolyPhen -2 Report

Table 1: The predictions about the pathogenicity and stability of the functional role of COL28A1 protein in the presence of mutations identified in HNSCC patients

Mutations	PolyPhen score	Polyphen prediction	IMutant score	IMutant prediction
G404R	1.000	Probably damaging	-0.59	Decreased stability
G84C	0.927	Possibly damaging	-1.87	Decreased stability
T1048P	0.000	Benign	-0.19	Decreased stability
E394Q	0.799	Possibly damaging	-0.72	Decreased stability
E948Q	1.000	Probably damaging	-0.49	Decreased stability
G409E	0.978	Probably damaging	0.74	Increased stability
R910H	1.000	Probably damaging	-0.91	Decreased stability
F820L	0.012	Benign	-1.45	Decreased stability
E752K	0.259	Benign	-1.46	Decreased stability

Polyphen prediction scores: 0.95 -1.000, Probably damaging, 0.5-0.94, Possibly damaging, <0.5, Benign, Imutant Prediction scores: A DDG value <0 indicates decreased stability, DDG value >0 indicates increased stability

function, potentially contributing to the carcinogenic characteristics linked to COL28A1 in HNSCC. The G404R mutation, scoring 1.000, indicates a significant modification that is likely to negatively impact protein activity.

Variable Impact

Mutations such as G84C and E394Q scored between 0.799 and 0.927, classifying them as "possibly damaging." While these changes might alter protein stability or interactions, their effects may not be as severe as those classified as "probably damaging." The presence of these mutations reinforces the need for further investigation into their role in tumor pathology [27].

Benign Mutations

In contrast, the T1048P, F820L and E752K mutations exhibited low PolyPhen scores, signifying they are "benign." T1048P received a score of 0.000, indicating it is improbable to affect COL28A1 function. These data suggest that such mutations do not influence the cancer phenotype observed in HNSCC patients.

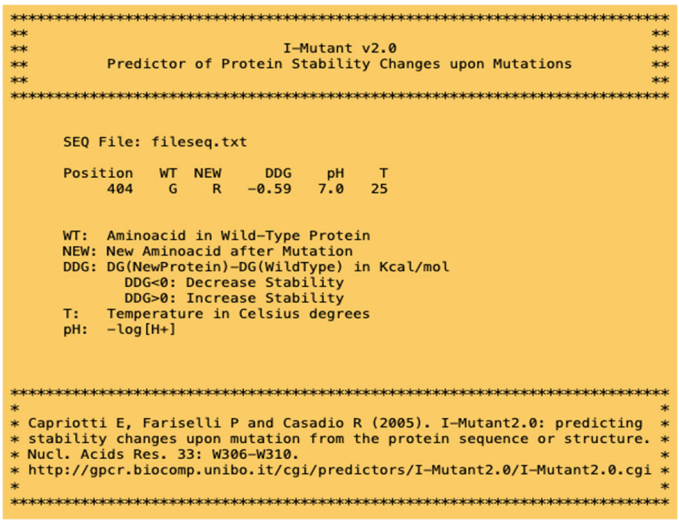

Figure 4: Stability changes upon mutations

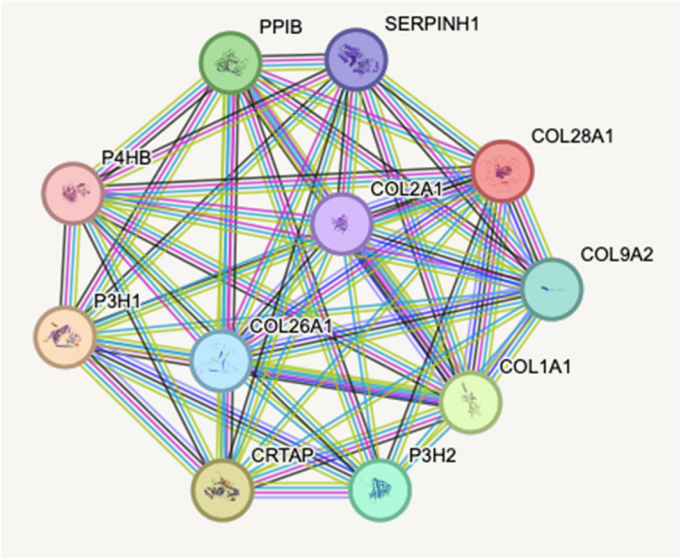

Figure 5: Protein - Protein interaction network of COL28A1

Stability Predictions

The I-Mutant stability scores (Figure 4) further elucidate the implications of these mutations on the COL28A1 protein's structural integrity:

Decreased Stability

The majority of mutations had a negative ΔΔG (DDG) value, signifying reduced protein stability. Prominent instances encompass G404R (-0.59) and G84C (-1.87), wherein the destabilizing influence may result in protein misfolding and functional impairment, so substantiating possible disease processes in HNSCC. This diminished stability may promote cancer growth by impairing protein functioning and interactions within the tumor microenvironment.

Increased Stability

Notably, the G409E mutation exhibited a positive DDG value (0.74), suggesting increased stability. This mutation's effect implies a possible compensatory mechanism within the protein structure that could influence COL28A1's functional role. It raises questions about how variations in stability may alter the protein's interactions (Figure 5) with other cellular components [28].

The assessment of mutations in COL28A1 with PolyPhen and I-Mutant not only supports its possible pathogenic function in HNSCC but also highlights the intricacy of genetic variations affecting tumorbehavior. The differentiation between detrimental and benign mutations facilitates the identification of modifications that require more

functional investigation. Comprehending these variances might inform therapeutic methodologies and patient management techniques, particularly for customized treatment options for HNSCC.

DISCUSSION

Head and neck squamous cell carcinoma (HNSCC) remains one of the most prevalent cancers worldwide, contributing to approximately 4% of all adult malignancies in Europe, with an estimated 140,000 new cases reported annually. The incidence is notably higher in males (6%) than in females (2%), with geographical variations in morbidity rates. Despite advancements in treatment modalities such as surgery, radiation and chemotherapy, the five-year survival rate for HNSCC remains unsatisfactory, starting at around 60% for localized disease and declining with regional or distant metastasis. Poor outcomes are often attributed to the aggressive behavior of malignant tumors, which exhibit extensive local invasion and frequent metastasis to cervical lymph nodes [29].

Alcohol and tobacco consumption are well-established risk factors for HNSCC, contributing to malignancies of the oral cavity, hypopharynx and larynx [30]. However, accumulating evidence highlights the role of genetic alterations in influencing tumor progression, prognosis and treatment response.

In the present study, analysis of OncoPrint data revealed a 3% incidence of genetic abnormalities involving the COL28A1 gene in patients with HNSCC. These alterations predominantly included missense mutations and gene amplifications. Elevated expression of COL28A1 was associated with a poorer prognosis, as evidenced by the Kaplan-Meier survival analysis. This suggests that COL28A1 may contribute to HNSCC carcinogenesis and hold potential as a prognostic biomarker.

COL28A1 mutations have also been reported in other malignancies, including endometrial, gastric and lung cancers. COL28A1 encodes a protein involved in extracellular matrix (ECM) remodeling, a crucial process for maintaining tissue architecture and facilitating cellular signaling. Mutations within this gene may disrupt ECM integrity, promoting tumor progression and resistance to therapy. Targeting COL28A1 interactions with integrin receptors, which mediate cell adhesion and signaling, may offer a therapeutic opportunity to inhibit tumor-promoting pathways. Inhibitors designed to disrupt the interaction between COL28A1 and tumor cells may reduce cancer cell invasiveness and metastasis [31].

Combining chemotherapy with ECM modulators represents another potential strategy for targeting COL28A1-altered tumors. By modifying ECM stiffness and composition, these agents may enhance the efficacy of conventional chemotherapeutics. Furthermore, employing gene-editing technologies such as CRISPR to correct COL28A1 mutations could restore normal gene function and potentially reverse tumorigenic characteristics. Ongoing studies exploring these approaches underscore the potential for precision medicine to improve outcomes in HNSCC patients [32].

Comparison of COL28A1 mutations with other well-known genetic drivers in HNSCC reveals important distinctions. For instance, mutations in TP53-observed in over 50% of HNSCC cases-frequently involve missense mutations and deletions that disrupt its tumor-suppressive functions [33]. Although COL28A1 mutations are less frequent than TP53 alterations, their impact on ECM remodeling highlights a unique pathogenic role that may contribute to HNSCC progression.

PolyPhen and I-Mutant analyses in this study identified several pathogenic COL28A1 mutations, such as G404R and G409E, categorized as "probably damaging" with high pathogenicity scores (1.000 and 0.978, respectively) [32]. These mutations demonstrated decreased protein stability (e.g., G404R with a -0.59 DDG value), potentially impairing ECM homeostasis and supporting tumor aggressiveness [27].

Mutations in genes such as PIK3CA and CDKN2A are also frequently implicated in HNSCC. PIK3CA mutations are known to enhance PI3K signaling, promoting cell proliferation and survival. Although COL28A1 mutations may similarly influence tumor behavior, the more established roles of TP53, PIK3CA and CDKN2A in driving tumorigenesis have clearer clinical implications. Further research is required to elucidate the precise oncogenic role of COL28A1 in comparison to these established genetic markers [34].

The presence of COL28A1 mutations should also be contextualized within the broader framework of HNSCC progression, which frequently involves early mutations in genes such as NOTCH1, CDKN2A and KMT2D. These alterations influence cellular proliferation, differentiation and immune response regulation, further complicating the interplay between genetic mutations in HNSCC [34].

The emerging understanding of COL28A1 mutations offers promising insights into their potential as biomarkers for diagnosis, prognosis and treatment prediction in HNSCC. Further exploration of COL28A1 in clinical settings may identify novel therapeutic targets and improve early detection strategies. Integrating genetic profiling into clinical decision-making could enable tailored treatment approaches for patients harboring COL28A1 mutations, ultimately improving survival outcomes [35-38].

CONCLUSION

The present study identifies COL28A1 as a potential biomarker with significant implications for HNSCC progression, prognosis and treatment response. Elevated COL28A1 expression correlated with poor prognosis, indicating its potential clinical relevance. COL28A1's role in

ECM remodeling and its interactions with integrin receptors suggest it may contribute to HNSCC aggressiveness and resistance to therapy.

Targeting COL28A1 using small molecule inhibitors or non-coding RNAs may offer therapeutic strategies to modulate its expression, potentially improving survival outcomes in HNSCC patients. Further studies exploring COL28A1's role in combination treatments, immunotherapy and molecular targeting approaches are essential to establish its potential as a clinical target in personalized medicine for HNSCC.

Limitations and Future Scope

This study acknowledges several limitations. Genomic data analysis inherently relies on complex bioinformatics tools and interpretation, which require expertise to ensure accuracy and clinical relevance. Further validation using independent datasets is necessary to confirm the reliability of the findings. Additionally, while this study identifies COL28A1 as a potential biomarker in HNSCC, experimental studies exploring its mechanistic role in tumor progression are warranted.

Future research should investigate COL28A1's role in combination therapies, particularly ECM modulators or integrin inhibitors, to enhance treatment efficacy. Studies involving CRISPR-based gene correction may offer potential strategies for reversing tumor-promoting effects caused by COL28A1 mutations. Moreover, expanding research into COL28A1's interactions with immune cells may provide insights into its role in immune evasion mechanisms in HNSCC.

Ethical Considerations

This study was conducted in accordance with established ethical guidelines and standards for biomedical research. The genomic and transcriptomic data used in this study were obtained from publicly accessible databases such as The Cancer Genome Atlas (TCGA) and cBioPortal, ensuring compliance with data-sharing policies. As this study exclusively utilized publicly available data, no direct involvement of human participants was required and therefore, no informed consent was necessary. All data handling procedures adhered to relevant ethical standards to maintain data integrity and participant confidentiality.

Conflict of Interest

The authors declare no conflicts of interest in relation to this study. There were no financial, professional, or personal relationships that could have influenced the research findings.

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