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ORIGINAL ARTICLE

GENOMIC AND TRANSCRIPTOMIC ALTERATIONS IN THE ELN GENE NETWORK AND THEIR ASSOCIATION WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) are a common form of cancer that arises in the mucosal surfaces of various anatomical locations, including the larynx, oral cavity, and nasal cavity. The *ELN* gene plays a crucial role in elastin synthesis, a protein responsible for maintaining the elasticity of skin, blood vessels, and ligaments, thereby preventing cell senescence. Genetic alterations in the *ELN* gene family may contribute to the development and progression of HNSCC.
Objectives: This study aims to investigate the alterations in the *ELN* gene family and their potential association with HNSCC.
Materials and Methods: Computational analyses were performed using publicly available databases, including UALCAN, cBioPortal, and STRING, to identify genetic changes in HNSCC patients. The study focused on mutations (missense and truncating), gene amplification, and deep deletions within the *ELN* gene family.
Results: The analysis revealed a high frequency of alterations in *ELN* family member 11, occurring in 5% of HNSCC patients. Additionally, a significant variation in *ELN* gene expression was observed between normal samples and different cancer grades. Kaplan-Meier survival analysis indicated an insignificant difference for the *MFAP2* gene but a significant difference for the *FN1* gene between normal and primary tumour groups in HNSCC.
Conclusion: These findings suggest a potential link between *ELN* gene alterations and HNSCC, emphasizing the necessity for further experimental validation to confirm these preliminary observations and elucidate the underlying mechanisms.

Keywords: **Elastin, ELN gene, computational analysis, Gene expression, Squamous cell carcinoma**

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) from the mucosal surfaces of the oral cavity, nasal passages, pharynx, and larynx and was one of the most aggressive malignancies. Patients with HNSCC continue to have a dismal prognosis despite improvements in therapies and diagnostic methods; the five-year survival rate was often only 50%. This outcome is often attributed to late-stage diagnosis, high rates of recurrence, and the complex molecular heterogeneity of the disease[2]. Consequently, there is a need to better understand the molecular underpinnings of HNSCC to develop more effective diagnostic, prognostic, and therapeutic strategies[3].

One promising area of research for understanding the complexities of HNSCC involved the study of genomic and transcriptomic changes. Genomic alterations refer to changes in the DNA sequence, such as mutations, amplifications, and deletions, while transcriptomic alterations pertain to changes in gene expression levels[4]. Together, these alterations can significantly impact cellular function and contribute to cancer development and progression. Among the myriad of genes implicated in cancer, the *ELN* gene network, which encodes for proteins essential in maintaining tissue elasticity, has garnered attention for its potential role in HNSCC[5].

Tropoelastin, the precursor to elastin, a crucial extracellular matrix protein that give tissues like skin, blood vessels, and ligaments their elastic qualities, which is encoded by the *ELN* gene. Elastin provides resilience and flexibility, allowing tissues to stretch and recoil[6]. In addition to its structural role, elastin also participates in various cellular processes, including cell signaling, proliferation, and migration. Alterations in the *ELN* gene or its regulatory network can disrupt these functions, potentially contributing to tumorigenesis[7].

Recent data points to a potential role for the *ELN* gene network in the etiology of HNSCC. Studies have identified various genomic alterations in the *ELN* gene, such as amplifications, deletions, and point mutations, which could affect the normal function of elastin and its associated pathways. Moreover, transcriptomic analyses have revealed differential expression patterns of *ELN* and related genes in Colorectal cancer tissues compared to normal tissues. These findings hint at a complex interplay between the *ELN* gene network and the molecular mechanisms driving Colorectal cancer[8]. To elucidate the role of the *ELN* gene network in HNSCC, it is crucial to integrate genomic and transcriptomic data. This integrated approach allows for a comprehensive understanding of how alterations at the DNA level translate into changes in gene expression and, subsequently, cellular behavior. By using sequencing technologies and advanced bioinformatics tools, researchers can map the genomic and transcriptomic changes in the *ELN* gene network, find important driver mutations, and discover potential treatment targets[9].

Additionally, understanding the importance of *ELN* gene changes in predicting HNSCC outcomes is crucial. Prognostic biomarkers can help classify patients by their risk of recurrence or disease progression, allowing for more personalized treatment plans[10]. Previous studies have suggested that alterations in gene network may correlate with clinical outcomes in HNSCC patients[11,12]. For instance, differential expression of *ELN* has been associated with varying survival rates, indicating its potential as a prognostic marker[13]. In addition to its prognostic value, the *ELN* gene network may also offer novel therapeutic opportunities. Targeting specific genomic alterations or modulating the expression of key genes within this network could pave the way for innovative treatments. For example, drugs that restore normal elastin function or inhibit pathways disrupted by *ELN* alterations could prove beneficial in managing HNSCC[14]. The objective of this study was to examine changes in the *ELN* gene network's transcriptome and genome and how they relate to HNSCC.

MATERIALS AND METHODS

Sample data set

An online tool designed for gathering, examining, and deciphering genetic data is the cBioPortal database. It provides information on genetic changes in diverse samples and genes as well as comprehensive patient descriptions from a range of cohorts. There are 530 cases of head and neck squamous cell carcinoma in the Cancer Genome Atlas (TCGA) Firehose Legacy dataset, of which 504 samples have data on copy number modification and sequencing. For every sample, the database contains the entire profile of the genes that have been deleted, amplified, and modified.

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Analysis of Oncoprint data

Every chosen gene frequency distribution was covered in depth by the Oncoprint data, which also includes information on the type of variation, modifications to the amino acids that code for proteins, gene amplifications, deletions, insertions, frameshifts, and splice site alterations. This data provides a baseline for monitoring mutations or variations, gene expression, and patient survival based on the changed genes using a variety of computational methods[15].

Analysis of the protein-protein interaction network

A database of anticipated and known protein-protein interactions which may involve functional or structural relationships called the STRING database. These relationships are the result of information compiled from several main databases and computer forecasts. Highest frequency alteration of genes within the entire family was selected for further analysis, focusing on gene expression and survival curves[16].

Analysis of gene expression and survival

Analysis of the *ELN* gene, its expression profile and tumour grading were performed similar to the previous study by Tharany et al., in 2021 using the UALCAN database. Using the Comprehensive Perl Archive Network (CPAN) module in a PERL script, the Kaplan-Meier survival analysis was carried out and the correlation of survival between groups was calculated with the p-value[17].

RESULTS

Protein protein interaction analysis

The primary connections of *ELN* with genes like these are disclosed by the protein interaction network such as *LOX, MFAP4, FBN1, MFAP2, FN1, VTN, DCN, BGN, GLB1, and FBLN5*, which play key roles in various biological processes. A p-value, which indicates the significant difference between the normal and HNSCC sample groups, was used to illustrate the expression score. The examination of functional enrichment revealed 45 edges and 11 nodes. A PPI (Protein-Protein Interaction) enrichment value of 3.04 x 10^{-13} indicated a string statistical significance. This value indicates the connections between proteins in the network and the biological interactions (Figure 1).

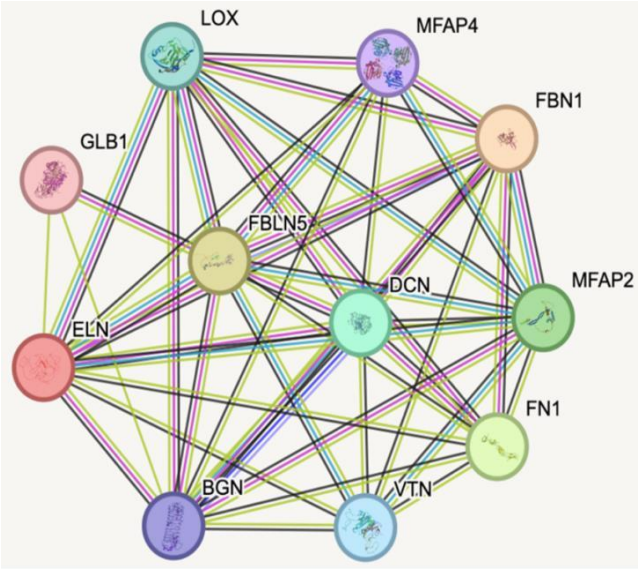

Figure 1. Protein interaction network of *ELN* gene in Homo sapiens (STRING version 12.0)

Analysis of Oncoprint data

Eleven genes had changes identified by the oncoprint data analysis, with *FN1* (5%) having the greatest frequency of Deep deletion, truncating and missense mutation (Figure 2) (Table 1). This was followed by *ELN FBLN5, BGN, FBN1* with 2-4% alteration.

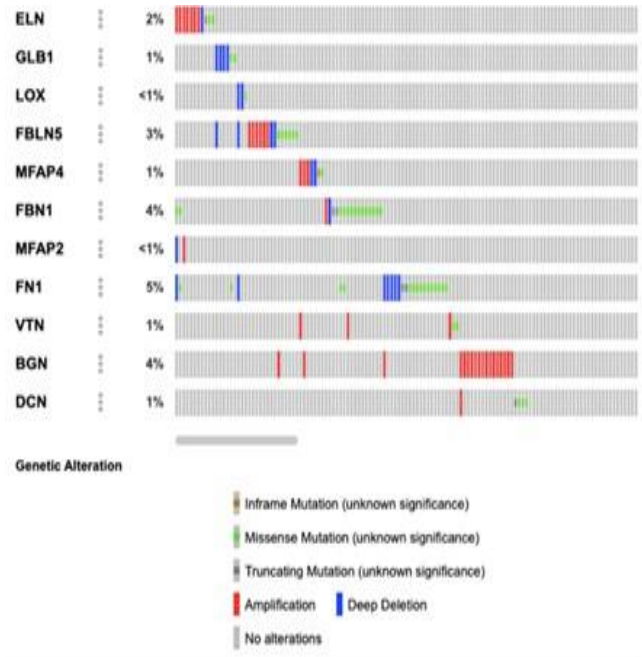

Figure 2. Oncoprint data demonstrating the alterations in the *ELN* gene network

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Table 1. The ELN gene interaction network's genetic changes

Gene	Protein encoded	Frequency of alteration (%)	Type of alteration
ELN	Elastin	2	Gene amplification, Deep deletion, inframe and missense mutation
GLB1	Beta-galactosidase	1	Deep deletion, missense mutation
LOX	Protein-lysine 6-oxidase	<1	Deep deletion, missense mutation
FBLN5	Fibulin-5	3	Deep deletion, missense mutation
MFAP4	Microfibril-associated glycoprotein 4	1	Deep deletion, inframe and missense mutations, and gene amplification
FBN1	Fibrillin-1	4	Missense mutation, truncating, deep deletion, and gene amplification
MFAP2	Microfibrillar-associated protein 2	<1	Gene amplification, Deep deletion
FN1	Fibronectin	5	Missense mutation, truncating, and deep deletion
VTN	Vitronectin V10 subunit	1	Gene amplification, missense mutation
BGN	Biglycan	4	Gene amplification
DCN	Decorin	1	Gene amplification, truncating and missense mutation

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Analysis of the protein-protein interaction network

The primary connections of *ELN* with genes like these are disclosed by the protein interaction network such as *GLB-1, LOX, FBLN 5, MFAP 4, FBN 1, MFAP 2, FN1, VTN, BGN, DCN*. The *MFAP2* and *FN1* genes demonstrated <1% and 5% gross alterations, respectively. Strong evidence was found between the *MFAP2* gene amplification and the gene expression profile, suggesting that primary tissues had higher *MFAP2* expression than normal tissues (p-value =1.62 x 10^{-12}). A p-value, which indicates the significant difference between the normal and HNSCC sample groups, is used to illustrate the expression score (Table 2). An examination of functional enrichment revealed a network with 55 edges and 11 nodes. This indicates that these proteins exhibit a higher degree of interaction among themselves, suggesting that they form a biologically interconnected group. These interactions point to a potential collective functional role or involvement in related biological processes, emphasizing the significance of their co-occurrence within the same biological pathway or system.

Table 2. Gene expression profile and survival of genes included in the ELN gene network

Gene	Gross alteration	Gene expression profile	P value
ELN	Gene amplification, Deep deletion	Insignificant	5.25 x 10^{-1}
GLB1	Deep deletion	Upregulated	1.14 x 10^{-7}
LOX	Deep deletion	Upregulated	2.68 x 10^{-12}
FBLN5	Deep deletion	Insignificant	1.03 x 10^{-1}
MFAP4	Gene amplification, Deep deletion	Downregulated	1.12 x 10^{-2}
FBN1	Gene amplification, Deep deletion	Insignificant	4.06 x 10^{-1}
MFAP2	Gene amplification, Deep deletion	Upregulated	1.62 x 10^{-12}
FN1	Deep deletion	Upregulated	1.62 x 10^{-12}
VTN	Gene amplification	Insignificant	8.83 x 10^{-1}
BGN	Gene amplification	Upregulated	1.62 x 10^{-12}
DCN	Gene amplification	Insignificant	4.41 x 10^{-1}

Gene expression and survival analysis

Significant alterations in gene expression were seen in six out of ten genes within the *ELN* gene network (p-value < 0.05). Of these, there were notable variations in the survival rates of HNSCC patients for two main genes (Figure 1). The HNSCC group's *MFAP2* gene expression profile showed a substantial increase when compared to the normal group (p-value = 1.62 x 10^{-12}).

In patients with HNSCC, low/medium and high *MFAP2* expression showed statistically significant differences in survival outcomes, according to Kaplan-Meier survival analysis (p-value = 0.031), with high *MFAP2* expression associated with poorer prognosis (Figure 3).

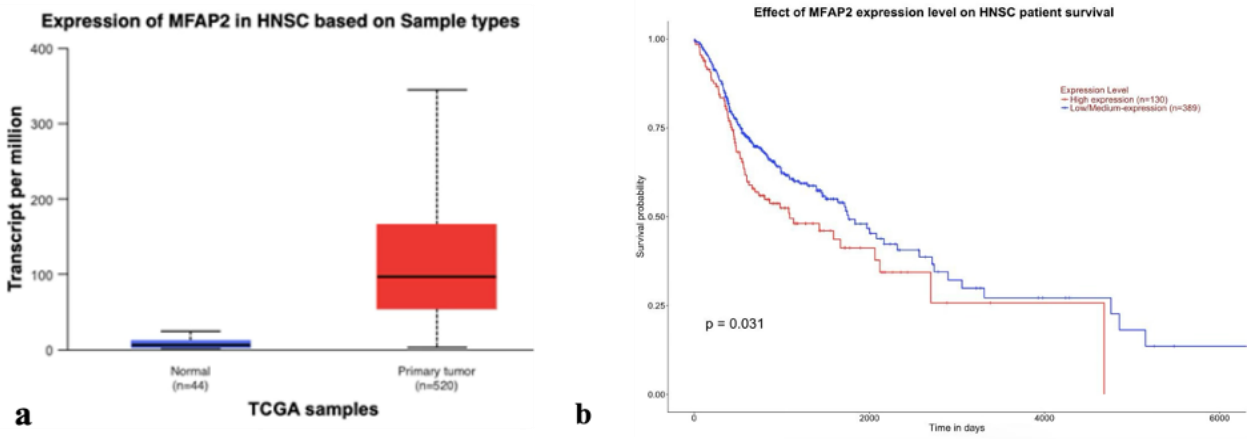

Figure 3. (a) The *MFAP2* gene expression profile. The HNSCC group had a substantial upregulation of the *MFAP2* gene in comparison to the normal (p-value = 1.62 x 10^{-12}), (b) The Kaplan-Meier Analysis of survival in the low/medium and high expression of *MFAP2* gene in HNSCC groups (p-value = 0.031). Patients presenting with high expression of *MFAP2* demonstrated a poor prognosis.

With p-values of 1.62 x 10^{-12} for *MFAP2* and *FN1*, the gene expression profiles of both genes between normal and primary tumor samples showed significant changes. There was a notable variation in the probability of survival according to the expression levels of *MFAP2* and *FN1*, even if the current finding does not support sex predilection of these genes with HNSCC. *MFAP2 and FN1* presented with significant survival probabilities of p = 0.031 and p = 0.051 respectively. (p-value less than 0.05 was considered to be significant) (Figure 3).

Comparing the HNSCC group to the normal group, the gene expression profile of *FN1* also revealed a notable increase (p-value = 1.62 x 10^{-12}). The analysis showed a near significance in survival outcomes between low/medium and high *FN1* expression in HNSCC patients (p-value = 0.051), with high *FN1* expression tending to be associated with a poorer prognosis (Figure 4).

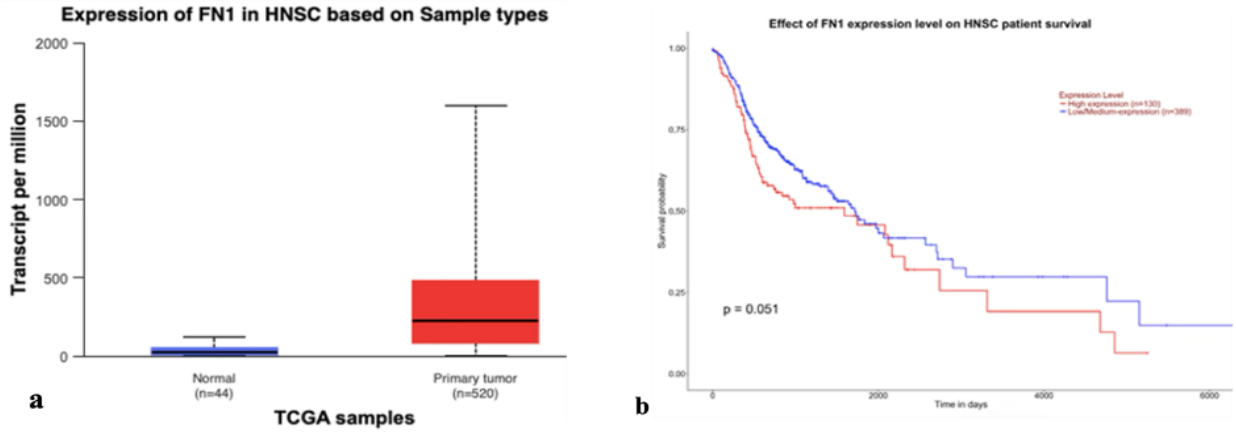

Figure 4. (a) *FN1* gene expression profile. When comparing the HNSCC group to the normal group, it was discovered that the *FN1* gene was substantially elevated (p-value = 1.62 x 10^{-12}), (b) Kaplan-Meier Survival analysis between various expression level of *MFAP2* gene in HNSCC groups (p-value = 0.051). Patients presenting with high expression of *MFAP2* demonstrated a poor prognosis.

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DISCUSSION

Our findings provide new insights into the molecular mechanisms underlying HNSCC and highlight the prognostic significance of specific gene alterations. Our analysis revealed that *ELN* interacts with several key genes, including *LOX*, *MFAP4*, *FBN1*, *MFAP2*, *FN1*, *VTN*, *DCN*, *BGN*, *GLB1*, *and FBLN5*. These genes are involved in various biological processes critical for maintaining tissue elasticity and integrity. It is possible that these proteins interact more frequently among themselves, indicating a physiologically linked group, based on the significant PPI enrichment p-value (3.04×10^{-13}). This aligns with previous studies by Halsey et al. (2023) and Ozsvar et al. (2021), which emphasized the importance of elastin and its associated proteins in cellular processes and tissue structure[6,7]. This finding suggests that the mechanisms driving *ELN* gene alterations may have broader implications beyond HNSCC, supporting the notion of shared pathways in different cancer types. Eleven genes had substantial changes found in our Oncoprint data study, with *FN1* having the highest prevalence of missense, truncating, and deep deletion mutations (5%).

The examination of the gene expression profile showed that the genes *FN1* and *MFAP2* were substantially increased in HNSCC tissues as opposed to normal tissues. A Kaplan-Meier survival study revealed that patients with HNSCC who expressed high levels of *MFAP2* had a worse prognosis (p-value = 0.031), corroborating previous studies by Guo et al. (2021) and Zhou et al. (2022)[13,18]. Similarly, high *FN1* expression tended to correlate with poorer survival outcomes (p-value = 0.051), although this result was near significant. These findings suggest that *MFAP2* and *FN1* could serve as prognostic biomarkers for HNSCC, aiding in the stratification of patients based on their risk of recurrence or disease progression. Our research contributes to the knowledge regarding the molecular causes of HNSCC. Previous research by Kleszcz et al., 2023 has highlighted the complexity and heterogeneity of HNSCC at the molecular level[3]. Our findings align with these studies, emphasizing the need for a comprehensive understanding of genomic and transcriptomic alterations in developing effective diagnostic, prognostic, and therapeutic strategies. Moreover, our identification of specific gene alterations in the *ELN* gene network, such as those in *MFAP2* and *FN1*, aligns with the work of Farah (2021) and Wang et al. (2022), who analysed the role of these genes in maintaining tissue structure and function[4,19]. Our study also highlights the potential of targeting these alterations for therapeutic purposes, supporting the therapeutic implications discussed by Eberly et al. (2024)[10].

Research should focus on longitudinal studies to monitor the temporal changes in the *ELN* gene network and their correlation with disease progression, treatment response, and recurrence in HNSCC patients. This work provides important new information on the possible connection between HNSCC and changes in the *ELN* gene. However, these findings need to be confirmed through experimental validation, highlighting the necessity for further research to establish the biological significance and clinical relevance of these genetic changes.

CONCLUSION

Our research offers fresh perspectives on the transcriptomic and genomic changes in the *ELN* gene network and how they relate to HNSCC. Key driver mutations and putative prognostic biomarkers, like *FN1* and *MFAP2*, have been found, which highlights the significance of these genes in the pathophysiology of HNSCC. Future research should focus on validating and exploring targeted therapies that restore normal *ELN* function or inhibit disrupted pathways. This integrated approach holds the potential to improve the clinical management of HNSCC, ultimately leading to better patient outcomes.

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DECLARATIONS

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Conflict of interest
All the authors declare that there was no conflict of interest in the present study

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