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ORIGINAL ARTICLE

Genomic and transcriptomic profiling reveals prognostic nucleoporin alterations in head and neck squamous cell carcinoma

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ABSTRACT

Objective: To characterize the mutational and expression landscape of nucleoporin (NUP) genes and evaluate their prognostic significance in head and neck squamous cell carcinoma (HNSCC).

Methods: This retrospective bioinformatic cross-sectional study utilized publicly available data from The Cancer Genome Atlas (TCGA). Thirty-eight nucleoporin genes were identified using the Human Genome Organisation Gene Nomenclature Committee database and relevant literature. Genomic alterations were analyzed in the TCGA HNSCC PanCancer Atlas cohort (n=523) using cBioPortal. Gene expression profiles were evaluated in the TCGA HNSC cohort (n=564) through the UCSC Xena platform. Overall survival was assessed in 500 HNSCC patients using KaplanMeier Plotter. Statistical significance was set at $p<0.05$.

Results: Genetic alterations in nucleoporin genes were identified in 41.1% of HNSCC cases. POM121L12 exhibited the highest alteration frequency (8%), followed by NUP155 (6%). Differential expression analysis revealed significant upregulation of NUP37, NUP62, NUP62CL, NUP85, NUP107 and NUP155, whereas SEC13, RANBP2 and DDX19B were significantly downregulated. Survival analysis demonstrated that elevated expression of NUP37 (HR 1.33; 95% CI: 1.02-1.75; p=0.037) and NUP54 (HR 1.31; 95% CI: 1.00-1.71; p=0.05) was associated with poorer overall survival. Conversely, increased NUP210L expression was associated with improved survival (HR 0.75, 95% CI: 0.570.98; p=0.031).

Conclusion: Nucleoporin genes exhibit frequent genomic and transcriptomic dysregulation in HNSCC. NUP37, NUP54 and NUP210L emerged as potential prognostic biomarkers, highlighting the nuclear pore complex as a promising target for future mechanistic and therapeutic investigations.

Keywords: Nuclear Pore Complex Proteins (MeSH); Nucleoporins (MeSH); Neoplasms (MeSH); Head and Neck Neoplasms (MeSH); Carcinoma, Squamous Cell (MeSH); Neoplasms, Squamous Cell (MeSH); Squamous Cell Carcinoma of Head and Neck (MeSH); Integrative Genomics (Non-MeSH); Biomarkers (MeSH); Biomarkers, Tumor (MeSH); Mutation (MeSH); Gene Expression (MeSH); Transcriptome (MeSH); Computational Biology (MeSH); Prognosis (MeSH); Survival Analysis (MeSH).

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INTRODUCTION

The Nuclear pore complex (NPC) is a 110MDa massive molecular assembly of about 30 unique Nucleoporins (Nups), organized in a total of approximately 1000 protein subunits.[1,2] As a primary gateway for nucleocytoplasmic transport, the NPC facilitates passive diffusion of small molecules and the active receptor-mediated transport of large macromolecules, including proteins and RNA.[3]

Beyond transport, Nups like NUP98, NUP50 and NUP153, regulate nuclear architecture and gene expression by associating with active chromatin remodeling complexes. In this way, they modulate genomic organization, transcriptional programs and DNA repair mechanisms.[4]

Given their fundamental roles, the structural or functional disruptions of Nups are linked to many human diseases, ranging from developmental syndromes to cancers.[5] In hematologic malignancies, chromosomal translocations involving NUP98 and NUP214 can trigger abnormal transcriptional programs that contribute to leukemogenesis.[6] Moreover, Nup96, a product derived from NUP98 processing, has been found to regulate mRNA export of cell cycle-related genes; its disruption can lead to the unscheduled nuclear retention of tumor suppressor transcripts or the overexpression of cell cycle regulators, creating a protumorogenic environment.[7]

Recent studies have revealed that several nucleoporins participate in key oncogenic signaling pathways. For instance, NUP62 has been implicated in the hyperactivation of the Wnt/β-catenin pathway by facilitating the nuclear entry of β-catenin, a process essential for the proliferation of various solid tumours.[8] Similarly, the RanGAP1/RanBP2 complex plays a crucial role in stabilizing the GSK3β-Snail axis; by regulating the nuclear-cytoplasmic portioning of Snail, these Nups promote the epithelial-mesenchymal transition (EMT) and metastasis spread.[9] These observations indicate that nucleoporins may also have

important roles in the development and progression of solid tumors. In squamous cell carcinoma specifically, NUP 62 overexpression has been shown to enhance the nuclear import of the oncogenic transcription factor p63, further promoting an aggressive cellular phenotype and resistance to apoptosis.[10]

Head and neck squamous cell carcinoma (HNSCC) remains a global health challenge with over 900,000 cases annually. Despite multimodal treatment, 5-year survival rate is about 50% due to late diagnosis and frequent recurrence.[11] While individual Nups have been studied, a systematic investigation of the entire nucleoporin family in HNSCC is lacking. As the NPC functions as a highly integrated structural and functional unit, analyzing the full range of Nup genes is essential to distinguish key drivers from passenger alterations. To address this gap, we conducted a comprehensive genomic and transcriptomic analysis of nucleoporin genes in HNSCC using The Cancer Genome Atlas (TCGA) dataset (n=523). This study aimed to systematically characterize the mutational and expression landscape of nucleoporins and evaluate their potential prognostic significance in HNSCC.

METHODS

It was a retrospective bioinformatic cross-sectional design to characterize the genomic and transcriptomic landscape of Nucleoporin genes in HNSCC. Data were retrieved and analyzed using integrated clinical and genomic databases, including the cBioportal for cancer genomics, the UCSC Xena platform, and the Kaplan-Meier Plotter. Only publicly available, de-identified TCGA datasets were used in this study; therefore, separate ethical approval was not required. All data processing and reporting adhered strictly to the TCGA publication guidelines.The analysis was conducted from April 2024 to May 2024, utilizing the most recent updates of the TCGA Pan Cancer Atlas and Pan Cancer Survival cohorts available as of 2024. The ethical approval was obtained from the Ethics Board of Khyber Medical University, Peshawar (Reference #: DIR/KMU-EB/EP/000772 dated: April 27, 2021) prior to starting this study.

Data Acquisition and statistical procedures:

Gene Selection and Identification: Nucleoporins comprise the structural components of the nuclear pore complex. To ensure a systematic collection, we identified an initial panel of candidates using the Human Genome Organisation (HUGO) Gene Nomenclature Committee (HGNC) "Nuclear Pore Complex" hierarchy (Group ID: 554) https://www.genenames.org/. From this group, we specifically filtered for genes belonging to the Nucleoporins subgroup (Subgroup ID: 1051) characterized by their structural role within the NPC. This selection was corroborated with established published literature,[12 13] resulting in a final study panel of 38 genes listed in Table 1. Non-Nup components of the pore complex were excluded.

All of the 38 genes were then analyzed for the genetic alterations, changes in expression, and overall survival in HNSCC patients.

Genetic alteration analysis: Genomic alteration data for the Head and Neck Squamous Cell Carcinoma (HNSCC) cohort (n=523; TCGA PanCancer Atlas) were retrieved and analyzed via cBioportal for Cancer Genomics (https://cancergenome.nih.gov/publications/guidelines).[14] To characterize the mutational landscape of 38 selected Nup genes, we analyzed nonsynonymous mutations, including missense mutations, truncating mutations, and in-frame mutations. Copy number alterations (CNA) were determined using the GISTIC 2.0 algorithm, and significant CNAs were then defined as high-level amplifications and deep deletions. The integrated mutational and CNA landscape was visualized using OncoPrints, representing the frequency and type of alterations across the patient cohort.

Changes in gene expression: RNA-Sequencing (RNA-Seq) data were retrieved from the UCSC Xena platform utilizing the TCGA HNSC cohort (n=564). To ensure technical consistency and minimize potential batch effects, differential expression analysis was performed by comparing primary tumour tissues directly against matched normal solid tissue samples from the same patients.[15] Expression levels were quantified as log2 (FPKM+1). Global expression patterns for the 38 Nup genes (Table 1) were visualized using heatmaps. Furthermore, for individual gene comparisons, box plots were created to assess differential expression between the primary tumor and the matched normal solid tissue. Statistical significance was determined using Welch's t-test, with a p-value threshold of < 0.05 considered statistically significant.

Patient survival plots: Overall survival analysis (OS) was performed using the Kaplan-Meier Plotter (Pan-Cancer platform) on the cohort of 500 HNSCC patients.[16] To ensure high-fidelity transcriptomic analysis, the 'Jetset' algorithm was employed for optimal probe selection. Patients were stratified into high and low expression subgroups based on median expression levels of each Nup gene, providing a balanced and justified distribution for statistical comparison. Survival curves were estimated using the Kaplan-Meier method, and the statistical significance of differences between the high and low expression subgroups was determined using the log-rank test. Hazard ratios with 95% confidence interval (CI) were extracted to quantify the mortality risk. Results were considered statistically significant at a threshold of $P < 0.05$. This exploratory analysis prioritized genes showing consistent prognostic trends across the cohort.

RESULTS

Mutations in genes encoding nucleoporins in HNSCC: Analysis of the TCGA HNSCC cohort (n=523) revealed 41.1 % of patients (215 out of 523) exhibited at least one genetic alteration in the 38 selected Nucleoporin genes (Figure 1b). While individual Nup genes relatively showed low mutation frequencies (ranging from 0.2% in SEC13 and NUP50 to 8% in POM121L12), as shown in Figure 1a, the aggregate landscape suggests that Nup alterations are a common feature in a significant subset of HNSCC cases.

The most prevalent genetic mutation observed was nonsynonymous mutations (green), accounting for approximately 17 % of the total patient cohort. This was followed by gene amplification (red) at approximately

Table I: Nucleoporins and genes encoding them

Nucleoporin Protein Name	Gene symbol
NUCLEOPORIN 85	NUP85
NUCLEOPORIN 160	NUP160
NUCLEOPORIN 107	NUP107
NUCLEOPORIN 98/96	NUP98
NUCLEOPORIN 133	NUP133
SEC13	SEC13
SEH1 LIKE NUCLEOPORIN	SEH1L
NUCLEOPORIN 37	NUP37
NUCLEOPORIN 43	NUP43
ELYS	AHCTF1
NUCLEOPORIN 42	NUPL2/NUP42
RAN BINDING PROTEIN 2	RANBP2
NUCLEOPORIN 214	NUP214
NUCLEOPORIN 88	NUP88
ALADIN WD REPEAT NUCLEOPORIN	AAAS
GLE1	GLE1
NUCLEOPORIN 62	NUP62
NUCLEOPORIN 62 C-TERMINAL LIKE	NUP62CL
RAE1	RAE1
NUCLEOPORIN 93	NUP93
NUCLEOPORIN 188	NUP188
NUCLEOPORIN 205	NUP205
NUCLEOPORIN 35	NUP35
NUCLEOPORIN 155	NUP155
TPR	TPR
NUCLEOPORIN 153	NUP153
NUCLEOPORIN 50	NUP50
NDC1	NDC1
NUCLEOPORIN 210	NUP210
NUCLEOPORIN 210L	NUP210L
POM121	POM121
POM121 transmembrane nucleoporin like 2	POM121L2
POM121 transmembrane nucleoporin like 12	POM121L12
POM121 transmembrane nucleoporin C	POM121C
NUCLEOPORIN 58/45	NUPL1/NUP58
NUCLEOPORIN 54	NUP54
DOX 19	DOX19B

The data in this table are sourced from previous studies by one of the coauthors[12,13]

15% and multiple alterations (grey) in 8% of cases. Deep deletions (blue) and structural variants (purple) were less frequent, occurring in approximately 1.5% and 0.2 % of patients, respectively. The high prevalence of amplifications and mutations suggests that genetic gains and missense variants are the primary drivers of Nup genomic instability in HNSCC. These alterations occurred alongside known driver mutations in TP53, PIK3CA and TP63,[17] indicating that Nup alterations are integrated into the broader genomic landscape of Head and Neck tumorigenesis.

This genomic instability was not only limited to HNSCC. Analysis of the TCGA PanCancer Atlas revealed variations in Nup alteration frequencies across all cancer types studied (Figure 2). Notably, Skin Cutaneous Melanoma exhibited the highest alteration rate at over 60% mostly driven by the nonsynonymous mutations, whereas Thyroid Carcinoma showed the lowest at under 10%, thus exhibiting a more stable nucleoporin genomic profile. These findings suggest that nucleoporin alterations may play a broader role in cancer biology beyond HNSCC.

Alterations in nucleoporin expression in HNSCC: To investigate the expression profile of the Nucleoporin genes in HNSCC, we analyzed transcriptomic data from the TCGA Head and Neck Squamous Cell Carcinoma (HNSC) Cohort. We compared 520 primary HNSCC tumor samples against 44 normal solid tissue samples obtained from the same cohort. To ensure statistical robustness for parametric testing, raw RNA Seq counts were Log2 (x+1) transformed to stabilize variance.

Welch's t-test revealed significant dysregulation across multiple genes encoding Nucleoporins expression (Figure 3a). A varying trend was observed with both significant overexpression and underexpression identified among the selected nucleoporin genes. Specifically, marked upregulation was observed in NUP37, NUP62, NUP62CL, NUP85, NUP107, and NUP155 genes (Figure 3a and b). Among these, NUP37 and NUP62 showed the most prominent increases. This is biologically significant as these genes are often associated with accelerated mitotic progression and the nucleocytoplasmic transport of oncogenic signaling proteins in aggressive epithelial tumours.

Conversely, significant loss of expression was detected in SEC13, RANBP2, and DDX19B. The reduction in mRNA levels of RANBP2, a SUMO E3 ligase, is particularly noteworthy as its depletion may contribute to the genomic instability frequently observed in HNSCC. To validate the sensitivity and accuracy of this expression analysis, CRISP3 and MMP11 were utilized as positive control benchmarks, as they are established markers of HNSCC progression.[18] As expected, both genes exhibited high-magnitude overexpression in tumour


NUP85 0.8%
NUP160 2%
NUP107 4%
NUP98 1.2%
NUP133 2%
SEC13 0.2%
SEH1L 1.2%
NUP37 0.8%
NUP43 1%
AHCTF1 4%
NUP42 1.2%
RANBP2 3%
NUP214 2.8%
NUP88 1.4%
AAAS 1.2%
GLE1 1.2%
NUP62 1%
NUP62CL 1%
RAE1 0.8%
NUP93 1.8%
NUP188 1.6%
NUP205 3%
NUP35 2%
NUP155 5%
TPR 3%
NUP153 1.4%
NUP50 0.2%
NDC1 0.8%
NUP210 1.4%
NUP210L 2%
POM121 2.2%
POM121L2 0.4%
POM121L12 8%
POM121C 0.8%
NUP58 1%
NUP54 1.4%
DDX19B 0.6%
TP53 71%
PIK3CA 29%
TP63 18%
Genetic Alteration
Inframe Mutation (putative driver)
Missense Mutation (putative driver)
Missense Mutation (unknown significance)
Splice Mutation (putative driver)
Splice Mutation (unknown significance)
Truncating Mutation (putative driver)
Truncating Mutation (unknown significance)
Structural Variant (putative driver)
Structural Variant (unknown significance)
Amplification
Deep Deletion
No alterations

Figure: 1A

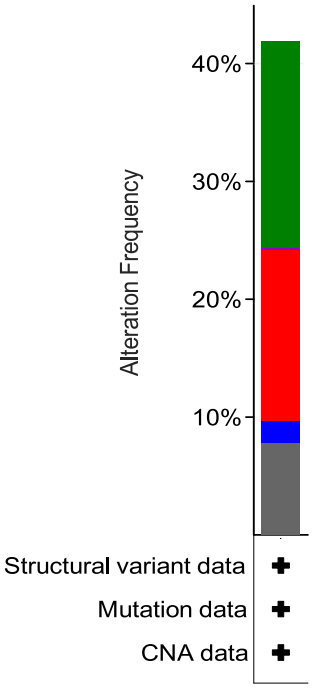

Figure: 1B

Figure 1: (a) Genetically mutated Human Nucleoporin genes (NUPs) encoding nucleoporin proteins in HNSCC patients. Various genetic alterations in NUPs detected in HNSCC. 523 HNSCC patients are represented by horizontal bars in figure. Multiple color pallets in the figure signifies, missense mutations, inframe mutations and truncating mutations The figure's various color palettes are representative of genetic inframe mutations (maroon), missense mutations (green), splice mutations (orange) truncating mutations (black), genetic amplification (red) and deep deletions (blue). TP53, PIK3CA and TP63 have been utilized as positive control benchmarks. (b) Alteration frequency of all the NUP genes in HNSCC patients is over 40%. In the figure green color represents %age of mutations, red represents %age of amplification, blue represents %age of deep deletions while grey represents %age of multiple alterations in NUPs genes in HNSCC patients

samples compared to normal tissue, confirming that our statistical pipeline correctly identifies known dysregulated signatures in this dataset.

Impact of nucleoporins expression on patient overall survival in HNSCC: To evaluate the clinical significance of Nucleoporin dysregulation, we analyzed the impact of gene expression levels on the overall survival of HNSCC patients using Kaplan-Meier survival curves. Patients were stratified into low and high expression groups based on the median split of the mRNA expression data.

Our analysis identified specific nucleoporins as significant prognostic indicators. High expression of NUP37 was significantly associated with poor overall survival of HNSCC patients, yielding a Hazard Ratio (HR) of 1.33 (95% CI: 1.02-1.75; log-rank P=0.037). Similarly, overexpression of NUP54 also correlated with decreased survival probability with a Hazard Ratio (HR) of 1.31 (95% CI: 1.0–1.71; log-rank P=0.05) (Figure 4). The poor prognosis linked to NUP37 and NUP54 may stem from their roles in accelerating the nuclear import of transcription factors and signaling proteins that drive the PI3K/Akt pathway, a central mediator of tumor cell survival and therapeutic resistance in HNSCC.

In contrast, overexpression of NUP210L was significantly correlated with better

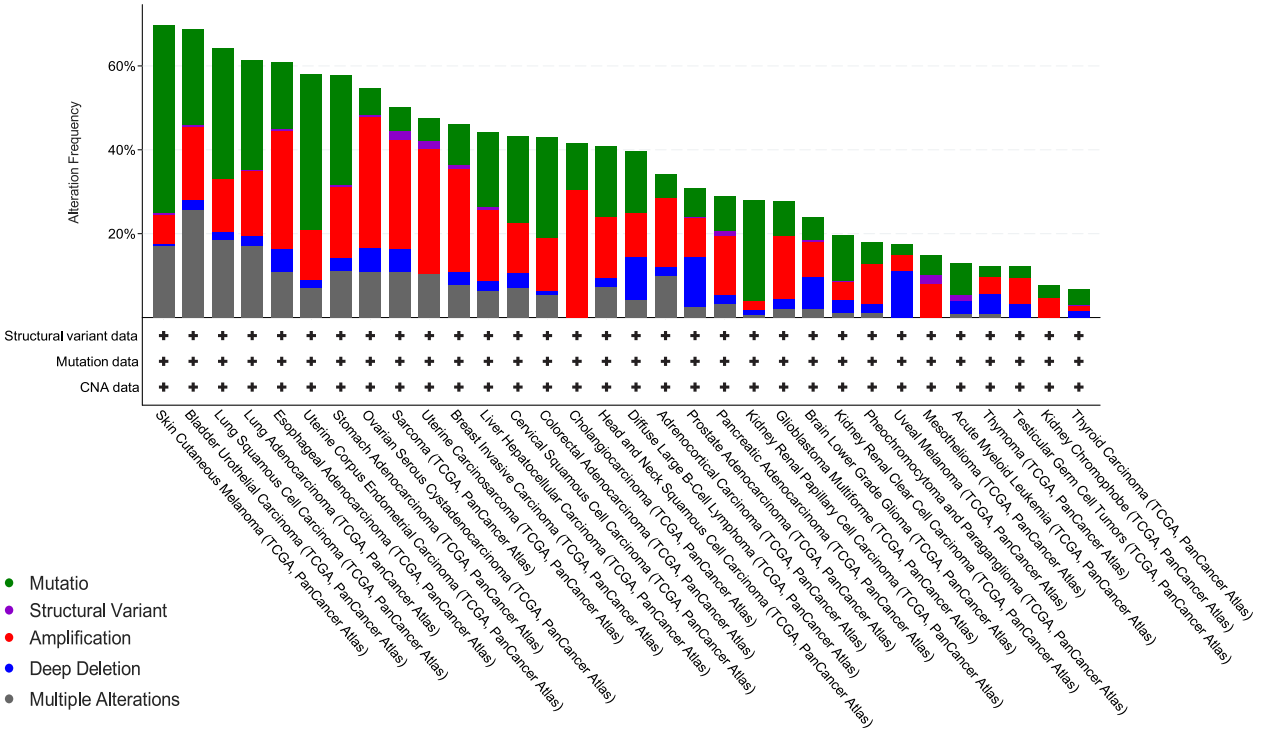

Figure 2: TCGA Pan-Cancer atlas studies representing NUP genes mutations in different types of cancers. Among 32 studies, 10967 samples / 10953 patients were queried. NUP genes mutations found in approximately 40% of HNSCC samples.

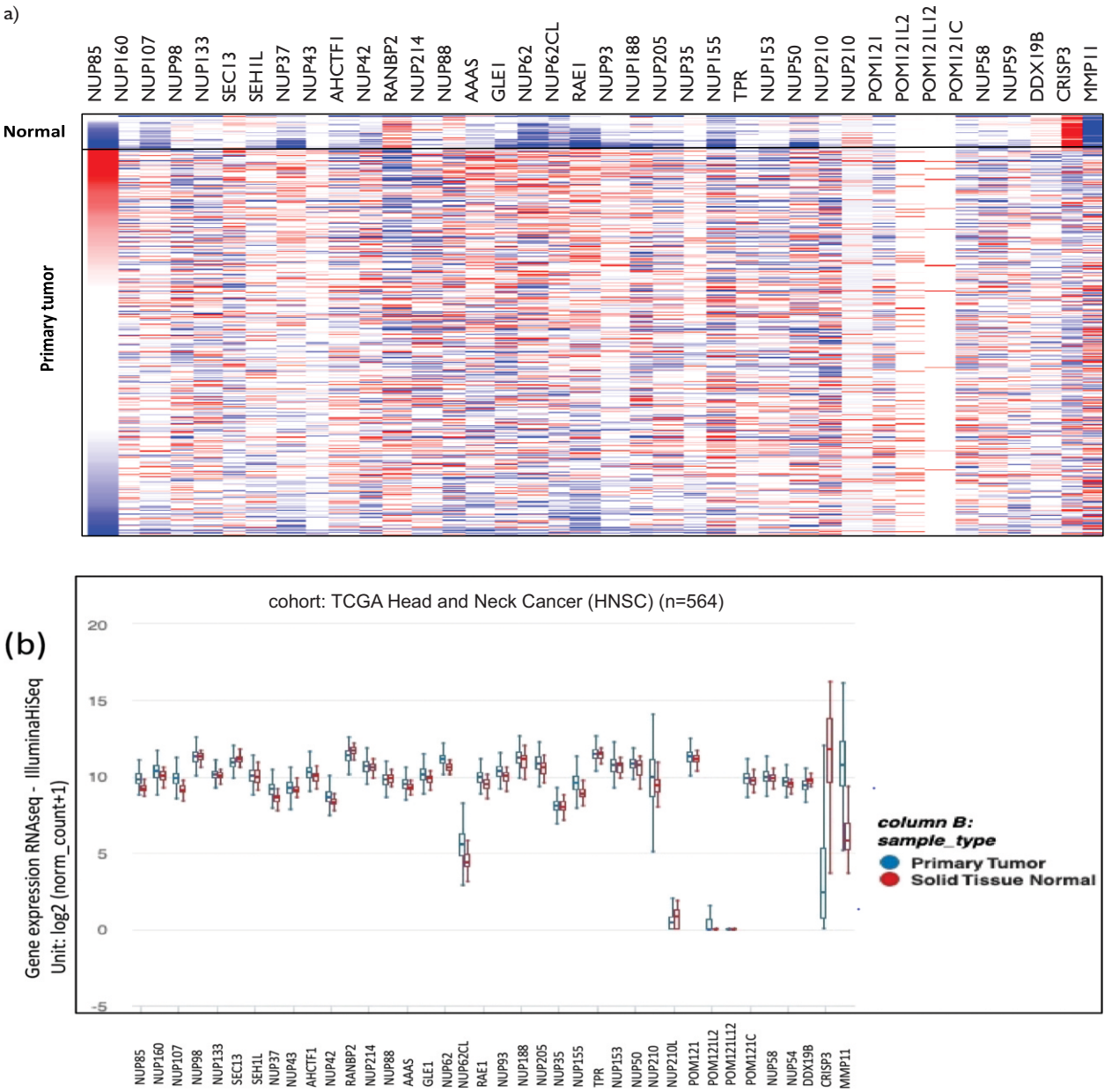

Figure 3: (a) Heat map representing the expression levels of NUP genes in TCGA HNSCC dataset. Up/Down regulation of NUPs have been signified by Red/Blue bars respectively. Primary tumor in 520 samples of HNSCC has been compared with normal solid tissue of 44 matched HNSCC patients from the same dataset. CRISP3 and MMP11 have been utilized as reference genes. (b) Box plots showing expression levels of Nucleoporin genes enlisted in Table 1 in TCGA HNSCC dataset. Comparison of NUPs expression level in primary tumor versus matched normal solid tissue of same HNSCC patients has been presented. Level of significance has been detected by Welch's t-test. P value of <0.05 is significant. NUP85 p=8.882e-16** (t=11.24), NUP160 p=0.00006574** (t=4.304), NUP107 p=0.000** (t=12.42), NUP98 p= .8864 (t=-0.1434), NUP133 p=0.003329** (t=3.042), SEC13 p=0.0008556** (t=-3.497, SEH1L p=0.07772* (t=1.798), NUP37 p=1.752e-13** (t=9.651), NUP43 p=0.01007* (t=2.644), AHCTF1 p=0.000001441** (t=5.367), RANBP2 p=0.00002662** (t=-4.590), NUP214 p=0.1408 (t=1.493), NUP88 p=0.1226 (t=-1.565), AAAS p=0.000001589** (t=5.222), GLE1 p=1.194e-7** (t=5.922), NUP62 p=2.220e-16** (t=11.29),NUP62CL p=1.415e-10** (t=7.885), RAE1 p=2.634e-10** (t=7.800), NUP93 p=2.730e-7** (t=5.889), NUP188 p=0.002895** (t=3.131), NUP205 p=0.0001690** (t=4.041), NUP35 p=0.2855 (t=1.077), NUP155 p=9.992e-14** (t=9.543), TPR p=0.04259 (t=2.075), NUP153p=0.1227 (t=1.567), NUP50 p=0.001029**(t=3.501), NUP210 p=0.002307** (t=3.127), NUP210L p=0.05086 (t=-2.004), POM121 p=0.001074** (t=3.442), POM121L2 p=0.000008682** (t=4.688), POM121L12 p=0.003777** (t=2.909), POM121C p=0.0002417** (t=3.909), NUP54 p=0.00006633** (t=4.264), DDX19B p=9.236e-14** (t=-8.759), CRISP3 p=1.088e-20** (t=-15.56) MMP11 p=0.000** (t=19.98)

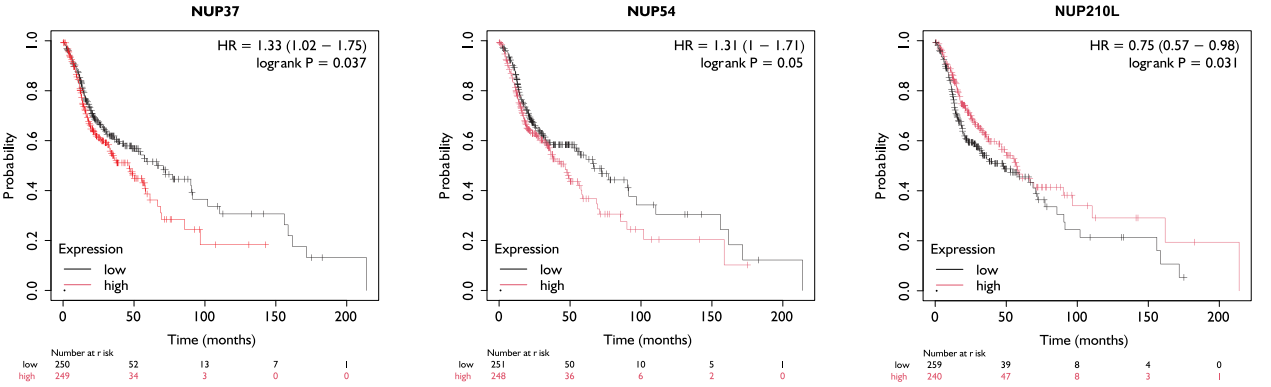

Figure 4: Significant correlation of genes encoding Nucleoporins with overall survival of HNSCC patients. Overall survival analysis is represented by Meier-Kaplan plot. On x-axis overall survival rate has been displayed while on y-axis time period after diagnosis in months has been shown. Groups with overexpression are presented by red color curve while those with low expression has been presented by black color curve.

patient survival, exhibiting a protective effect with a Hazard Ratio (HR) of 0.75 (95% CI: 0.57–0.98; log-rank P = 0.031) (Figure 4). This improved outcome may be attributed to NUP210L role in maintaining tissue-specific cellular differentiation; its downregulation is frequently observed in more aggressive, undifferentiated HNSCC phenotypes. Notably, these prognostic associations remained significant after multiple testing corrections and were consistent across patient subgroups, including those stratified by HPV status, an important clinical confounder in HNSCC.

No statistically significant associations with overall survival were observed for the remaining NUP genes under the current study parameters (Supplementary Figure-1).

DISCUSSION

The present study provides one of the first comprehensive genetic and molecular mapping of Nucleoporin genes in HNSCC, highlighting their probable participation in cancer development. Our systematic analysis revealed significant somatic mutations and abnormal expression patterns among various Nup genes. Notably, the POM121L12 gene showed the highest mutation rate (8%), followed by Nup155 (6%). Furthermore, we identified a consistent upregulation of a specific subset of nucleoporins, including Nup62, Nup85, Nup107, Nup37, Nup62CL, Nup155, and Nup210, establishing a distinct molecular signature for Nup dysregulation in this malignancy. Critically, our data demonstrates that while overexpression of NUP37 and NUP54 correlates with poor patient survival, NUP210L overexpression is significantly associated with improved survival outcomes, suggesting a complex divergent role for different Nups in HNSCC progression.

Our findings align with and expand upon emerging evidence regarding the oncogenic roles of the Nuclear Pore Complex (NPC). The high mutation rate of the POM121L12 gene is particularly significant; as a vital component for NPC assembly,[19] its alteration likely destabilizes nuclear envelope integrity. Similar to findings in colorectal cancer,[20] our data suggests that POM121L12, in cooperation with Nup155,[21] may drive oncogenic signaling in HNSCC. Furthermore, Nup62 overexpression, observed in our cohort, mirrors its known role in promoting HNSCC progression by facilitating nuclear import of oncogenic transcription factor p63, which maintains squamous cells in an undifferentiated proliferative state.[10]

Crucially, our study supports the non-canonical roles of Nups beyond simple gatekeeping. For instance, Nup155 regulates p21 translation within the p53 pathway in hepatocellular carcinoma and enhances invasion and migration in non-small cell lung cancer via PTEN/AKT signaling.[22] Similarly, we observed Nup155 overexpression in HNSCC, suggesting it may act as a signaling scaffold in this context as well.

Likewise, Nup37, a core component of the Nup107-160 sub-complex, activates YAP/TEAD signaling essential for early development.[23] Its overexpression has been linked to tumor proliferation, migration, and invasion in hepatocellular carcinoma and glioma,[24] as well as to poor survival outcomes in OSCC and NSCLC.[25] Our data similarly identified Nup37 upregulation correlated with poor prognosis in HNSCC, underscoring its potential as a prognostic biomarker and therapeutic target.

Another NPC component, Nup54, also showed elevated expression associated with poor patient survival. Previous research indicates that Nup54 facilitates nuclear import of co-activator CARM1, which activates Notch2 transcription and promotes gastric tumorigenesis.[26]

These findings open an avenue for targeted therapy, for example, importazole disrupts POM121–importin β-mediated nuclear import and reduces tumor aggressiveness,[27] while selinexor, an FDA-approved exportin-1 inhibitor, restores nuclear localization of tumor suppressors and induces apoptosis.[13] Given the pronounced dysregulation of Nups in HNSCC, specific targeting of these components could offer a novel precision medicine intervention.

However, there are certain limitations in this study. Being more of a genomic and computational study, it is inadequate to fully describe the biochemical convergence of the pathways, like the Nup155-PTEN/AKT axis, which requires further functional validation. Furthermore, the inherent heterogeneity of HNSCC subsets may influence Nup expression profiles, a factor that was not fully stratified in this analysis.

To overcome these constraints, future research will utilize CRISPR-Cas9 gene silencing and co-immunoprecipitation (Co-IP) in HNSCC cell lines to move beyond correlation and establish a direct

causal link between Nup alterations and tumour phenotype.

CONCLUSION

Our findings imply that the NPC undergoes functional reprogramming during HNSCC progression, making it a dynamic participant in tumorigenesis rather than a passive gateway. The identification of NUP37, NUP54, and NUP210L as survival-linked biomarkers offers a novel toolkit for risk stratification and highlights the NPC as a bottleneck for therapeutic intervention. Moving forward, we will focus on the mechanistic intersection of Nup155 and the p53/p21 pathway while leveraging AI-assisted drug discovery to identify small molecules targeting the Nup107-160 sub-complex, aiming to translate these molecular insights into targeted interventions for aggressive HNSCC.

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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

SZ: Study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

RM: Conception and study design, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

WS & SS: Conception and study design, critical review, approval of the final version to be published

MMK: Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DECLARATION

During the preparation of this study, we have used AI in order to improve English readability.

After using this tool authors edited and reviewed the draft and take the full responsibility of the content for publication.

SUPPLEMENTARY INFORMATION

Supplementary information accompanies this paper at: https://www.kmuj.kmu.edu.pk/article/view/24190