Somatic Mutational Landscape of Laryngeal Squamous Cell Carcinoma: Implications for Tumor Progression and Precision Medicine

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INTRODUCTION

•Laryngeal squamous cell carcinoma (LSCC) is the most common malignancy of the larynx, with ~12,650 new cases and 3,880 deaths expected in the U.S. in 2024.

•Prognosis remains poor for advanced disease, and survival has plateaued despite advances in chemoradiotherapy

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•Genomic profiling has identified recurrent mutations (e.g., TP53, FAT1, NOTCH1, KMT2D), but sex-specific and metastasis-specific alterations are poorly characterized.

•This study leverages the AACR Project GENIE dataset to define the somatic mutational landscape of LSCC and explore associations with tumor progression, metastasis, and precision therapy.

METHODS

•Retrospective cross-sectional genomic analysis of 135 LSCC tumor samples from the AACR Project GENIE database (2017–2024).

•Clinical and genomic data extracted from cBioPortal (v16.1), including somatic mutation data and demographic variables.

•Comparative analyses performed by tumor site (primary vs. metastatic) and sex using chi-squared and Mann-Whitney U tests.

•Co-occurrence and mutual exclusivity assessed to identify potential molecular subtypes.

RESULTS

Cohort Characteristics

- 135 samples from 130 patients: 89.2% male, 71.5% White.
- 59.2% primary tumors, 39.2% recurrent/metastatic.

Top Somatic Mutations

- TP53 (89.6%), KMT2D (27.4%), FAT1 (20.7%), NOTCH1 (20.7%).

Metastasis-Associated Mutations

- ATP8B1 ($p < 0.001$) and SAMD9L ($p < 0.001$) were exclusively found in metastatic samples.
- DMD ($p = 0.049$) was exclusive to primary tumors.
- KMT2D was significantly more frequent in primary tumors ($p = 0.027$).

Sex-Specific Differences

- CDK8 mutations were seen only in females ($p = 0.011$).
- ATP8B1 ($p = 0.013$) and EPHB2 ($p = 0.024$) were seen only in males.

Mutual Exclusivity

- KMT2D and TP53 mutations showed significant mutual exclusivity ($p = 0.018$), suggesting distinct molecular subtypes.

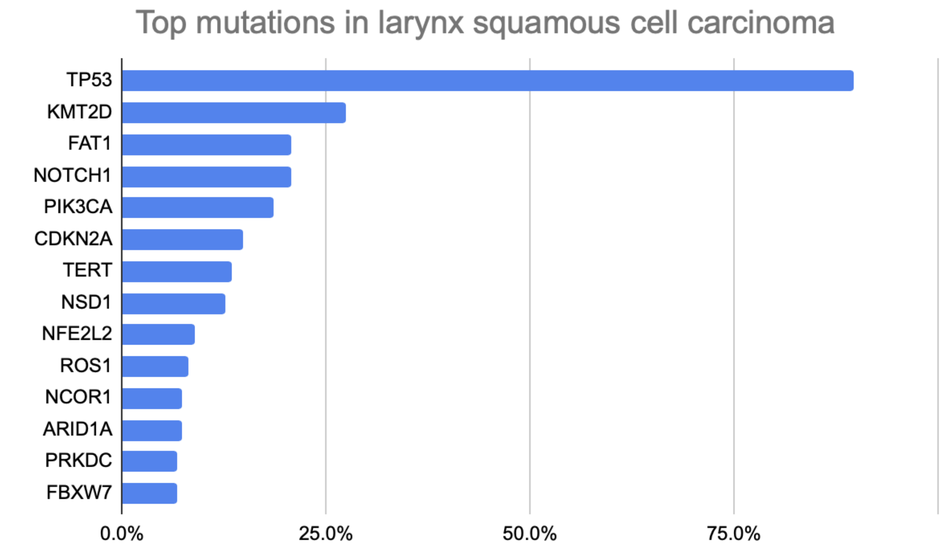

Figure 1. Bar Chart Illustrating Top Somatic Mutations in Larynx Squamous Cell Carcinoma Patients

DISCUSSION

•LSCC demonstrates marked genomic heterogeneity, dominated by TP53 alterations but also involving chromatin-modifying genes such as KMT2D.

•The mutual exclusivity of TP53 and KMT2D suggests biologically distinct molecular subtypes, which may inform targeted therapy development.

•The discovery of ATP8B1 and SAMD9L in metastatic disease implicates these genes as potential biomarkers for tumor dissemination and therapeutic targeting.

•Gender-specific mutations (CDK8 in females; ATP8B1 and EPHB2 in males) may reveal sex-linked oncogenic pathways, though further validation is needed given the small female sample size.

•These findings underscore the value of comprehensive genomic profiling in guiding precision oncology for LSCC.

CONCLUSION

•TP53 remains the dominant driver in LSCC, but distinct genomic alterations define primary vs. metastatic and male vs. female disease.

•ATP8B1 and SAMD9L represent promising biomarkers for metastatic disease, while CDK8 and EPHB2 highlight potential sex-specific therapeutic targets.

•Genomic stratification of LSCC may support the development of personalized treatment strategies and targeted therapies to improve patient outcomes.

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