Mutational Landscape of Non-Small Cell Lung Cancer in The United States

M. Elsayed[1] , A. Allam[1] , M. Khalafallah[2] , O. Aboshady[3] , M. Gouda[4]
[1]Student Research Unit, Faculty of Medicine, Menoufia University, [2]Department of Clinical Ophthalmology, Faculty of Medicine, Menoufia University, [3]Department of Pharmacology, Faculty of Medicine, Menoufia University, [4]Department of Clinical Oncology, Faculty of Medicine, Menoufia University

Background

- Mutational landscape studies, facilitated by next-generation sequencing technologies, can improve our understanding of cancer pathogenesis and help identify potentially targetable alterations. In this study, we aimed to provide an overall description of the mutational landscape in non-small cell lung cancer (NSCLC) using publicly available sequencing data.

Methods

- We used the American Association for Cancer Research's Project Genomics Evidence Neoplasia Information Exchange (GENIE) [GENIE Cohort v11.0-public study] to obtain sequencing data for patients diagnosed with NSCLC. Mutational profiles were described according to race (White, Black, or Asian) and histopathology (adenocarcinoma or squamous cell carcinoma). We used the OncoKB to assess the actionability of frequently mutated genes in the studied cohort.

Results

- We included 16,498 samples (13,927 White, 1,304 Black, and 1,267 Asian; 12,790 adenocarcinoma, and 1,546 squamous cell carcinoma). TP53 was the most frequently mutated gene, with half of the analyzed samples (49.6%) containing at least one TP53-related molecular alteration. TP53 mutation rate was higher in cases with squamous cell carcinoma compared to cases with adenocarcinoma (76.7% vs. 45.6%; p<0.001). It was the most frequent mutated gene regardless of tumor stage, primary (44.8%) and metastatic (57%). In race-dependent subgroup analysis, mutations in EGFR gene occurred in about 53.3% of Asian cases to rank as the most frequently mutated gene in this subgroup (Figure). Most of the frequently mutated genes in NSCLC (especially in the squamous cell carcinoma subgroup) are still not actionable (Table).

Figure: Commonly mutated genes in NSCLC

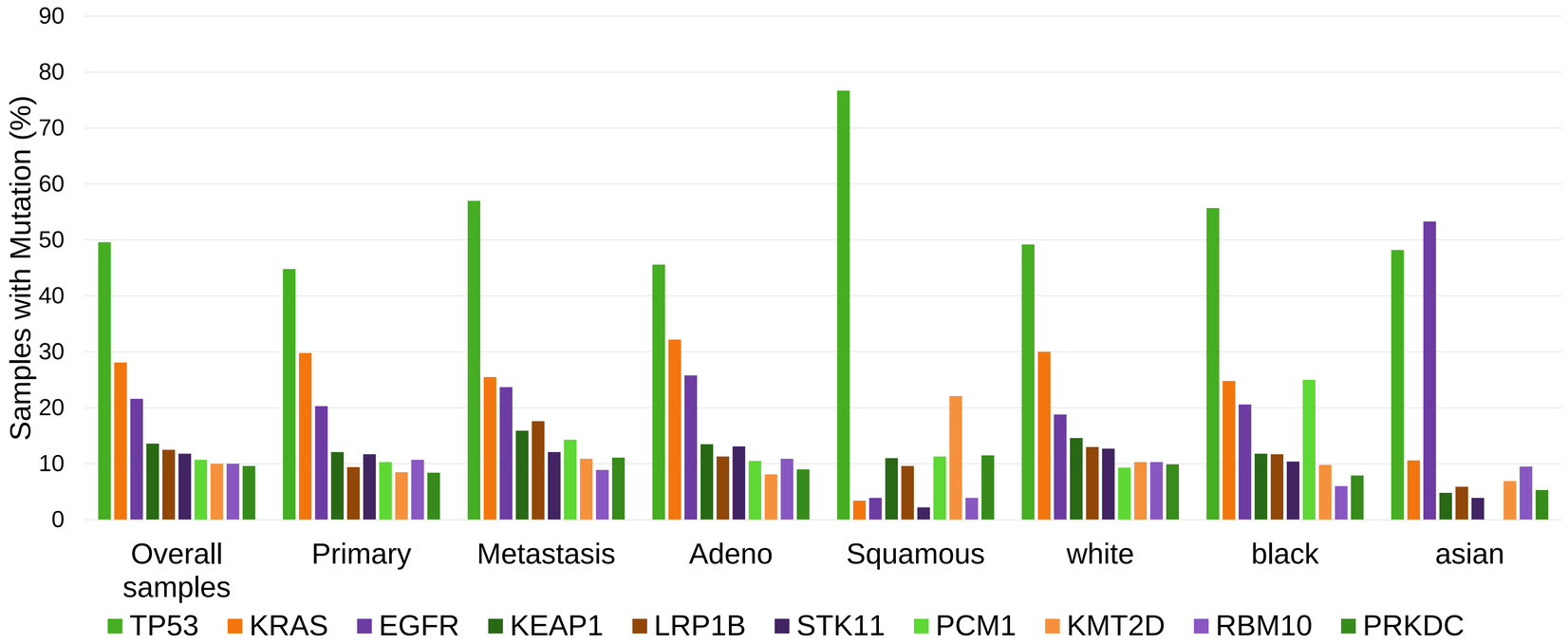

Table: Actionable genes in NSCLC

Adenocarcinoma	Squamous cell	White	Black	Asian
TP53 (45.6%)	TP53 (76.6%)	TP53 (49.2%)	TP53 (55.7%)	EGFR (53.3%)
KRAS (32.2%)	KMT2D (22.1%)	KRAS (30%)	PCM1 (25%)	TP53 (48.2%)
EGFR (25.8%)	PRKDC (11.5%)	EGFR (18.8%)	KRAS (24.8%)	KRAS (10.6%)
KEAP1 (13.5%)	PCM1 (11.3%)	KEAP1 (14.6%)	EGFR (20.6%)	RBM10 (9.5%)
SKT11 (13.1%)	KEAP1 (11%)	LRP1B (13%)	KEAP1 (11.8%)	KMT2D (6.9%)

Actionable gene
Non-actionable gene

Correspondence: M. Elsayed, email: mostafaahmed8799@gmail.com

Conclusion

- Despite progress in the targetability of NSCLC, many of the most frequently mutated genes are still not actionable. Genomic profiling has the potential to identify potential targets of interest, which could guide individualized treatment plans to address the current high burden of NSCLC.

Acknowledgment

- AACR Project GENIE is a publicly accessible cancer registry of real-world data assembled through data sharing between 19 leading international cancer centers.
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