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RESEARCH ARTICLE

High Detection Rate of Uncommon Driver Gene Mutations in Lung Squamous Cell Carcinoma: A Single-Center, Small-Sample Study and Clinical Implications in the Wuling Mountain Area of China

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Abstract

Objective: To investigate the characteristics and clinical significance of driver gene mutations in patients with lung squamous cell carcinoma (LUSC) from the Wuling Mountain area of China. **Materials and Methods:** Clinical data and molecular testing results, including next-generation sequencing (NGS), polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH), from 64 patients with LUSC treated at Tongren People's Hospital between September 2017 and April 2025 were retrospectively analyzed. Uncommon mutations were defined as alterations involving ALK, MET exon 14 skipping, BRAF, ERBB2, ROS1, and KRAS. Intergroup comparisons were performed using the chi-square test or Fisher's exact test. This retrospective study used only de-identified clinical data and involved no patient intervention or identifiable privacy risk; therefore, ethics committee approval was not required. **Results:** The overall driver gene mutation rate was 48.44% (31/64). Mutations potentially targetable with tyrosine kinase inhibitors (TKIs) were identified in 28.13% (18/64) of patients, of whom 44.4% harbored uncommon mutations. The mutation rate was significantly higher among patients from ethnic minority groups than among Han Chinese patients (44.4% vs. 19.4%, $P < 0.05$). Among the ethnic minority subgroups, the Miao group had the highest mutation rate (44.4%). **Conclusion:** A relatively high detection rate of uncommon driver gene mutations was observed among patients with LUSC from the Wuling Mountain area, particularly among those from ethnic minority groups. These findings support the consideration of comprehensive molecular profiling in patients with LUSC, with particular attention to patients from ethnic minority populations.

Keywords: Lung cancer; lung squamous cell carcinoma; driver gene mutations; uncommon mutations; ethnic minorities

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Introduction

Lung cancer (LC) is the second most commonly diagnosed malignancy worldwide and the leading cause of cancer-related mortality [1]. Epidermal growth factor receptor (EGFR) was one of the first tyrosine kinase receptors identified as being associated with tumorigenesis. The development of EGFR-targeted tyrosine kinase inhibitors (EGFR-TKIs) has demonstrated significant survival benefits for patients with EGFR-mutant LC and ushered in a new era of precision oncology [2, 3].

Advances in molecular diagnostic technologies, particularly the widespread application of next-generation sequencing (NGS), have facilitated the identification of an increasing number of driver gene alterations and corresponding therapeutic targets in LC [4]. Studies have shown that patients with actionable driver alterations, including EGFR, ALK, ROS1, and MET exon 14 skipping alterations, may achieve longer survival than those without identified driver alterations [5- 8]. Consequently, major

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clinical practice guidelines, including those of the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and Chinese Society of Clinical Oncology (CSCO), recommend molecular testing for patients with non-small cell lung cancer (NSCLC).

However, the prevalence of driver gene alterations varies substantially among histological subtypes. For example, EGFR mutation rates have been reported to range from 40% to 60% in lung adenocarcinoma (LUAD) [9], whereas they are considerably lower in lung squamous cell carcinoma (LUSC), ranging from 3.3% to 4.6% [10]. This marked difference has contributed to lower rates of molecular testing among patients with LUSC, with reported testing rates as low as 3.1% [11]. Accordingly, broad molecular profiling is not routinely performed in all patients with LUSC in current clinical practice [12], potentially limiting the identification of patients who could benefit from targeted therapies.

The NCCN guidelines recommend considering EGFR mutation testing in selected patients with LUSC, particularly never-smokers, patients diagnosed using small biopsy specimens, and those with mixed histological features [13]. Nevertheless, relatively few studies have specifically investigated the spectrum and clinical characteristics of driver gene alterations in LUSC. Therefore, we retrospectively analyzed the molecular testing results and clinical characteristics of 64 patients with LUSC treated at our institution. This study aimed to characterize the distribution of driver gene mutations in this population and to explore their potential clinical implications for targeted precision therapy in patients with LUSC.

Materials and Methods

Patient Information

All patients diagnosed with and/or treated for LUSC at Tongren People's Hospital between September 2017 and April 2025 were eligible for this retrospective analysis. Patient demographic characteristics, including age at diagnosis, sex, ethnicity, and molecular testing results, were collected through a review of the electronic medical record system.

Ethical Considerations

Because this was a retrospective study based exclusively on de-identified clinical data, with no patient intervention or identifiable personal information, formal approval by an institutional ethics committee was not required. All data were de-identified by the investigators before analysis.

Definition of Uncommon Mutations

Alterations involving ALK, MET exon 14 skipping, BRAF, ERBB2, ROS1, and KRAS were categorized as uncommon mutations.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Between September 2017 and April 2025, 367 patients with LUSC were admitted to Tongren People's Hospital. Molecular testing was performed in 64 patients, corresponding to a testing rate of 17.4%. The mean age of the study population was 61 ± 10 years. The cohort comprised 56 males (88%), with a mean age of 62 ± 10 years, and 8 females (12%), with a mean age of 56 ± 10 years. Regarding ethnicity, 39 patients were Han Chinese, 12 were Tujia, 7 were Miao, 4 were Dong, 1 was Gelao, and 1 was Derung. Detailed demographic characteristics are presented in Table 1.

Distribution of Gene Mutations

Molecular alterations were detected in 31 of the 64 patients, corresponding to an overall mutation rate of 48.44%. The identified mutated genes included EGFR, ALK, BRAF, MET exon 14, ERBB2, PIK3CA, TP53, and CDKN2A.

For the analysis of potentially targetable alterations, positive results for EGFR, ALK, MET exon 14 skipping, KRAS, BRAF, ROS1, and ERBB2 were classified as targetable, whereas non-targetable alterations and wild-type results were classified as negative. The mutation rate was significantly higher among patients from ethnic minority groups than among Han Chinese patients (44.4% vs. 19.4%, $P < 0.05$; Table 2). When analyzed by individual ethnic group, the Miao subgroup had the highest mutation rate, with an uncommon mutation rate of 44.4% (Figure 1).

Discussion

This retrospective analysis of 64 patients with LUSC identified driver gene alterations in 48.44% of cases, including alterations in EGFR, ALK, BRAF, MET exon 14, ERBB2, PIK3CA, TP53, and CDKN2A. Alterations potentially targetable with available TKIs were identified in 28.13% of patients. The proportion of LUSC patients undergoing molecular testing also increased from 1.0% in 2015 to 5.2% in 2024, with data available through April 2025, indicating a gradual increase in the use of molecular testing over time. This trend may reflect China's increasing healthcare capacity and the growing dissemination of precision oncology and targeted therapy approaches in lung cancer.

Eleven distinct gene alterations were identified in the study population, with potentially TKI-targetable alterations accounting for 28.13% of cases. Qian et al. [14], using a 68-gene NGS panel to analyze 204 Chinese LUSC surgical specimens, reported PIK3CA, PTEN, AKT1, TSVC1, and TSVC2 as the five most frequently mutated genes. Walter et al. [15], in an analysis of 32 German patients with LUSC, identified TP53, KRAS,

Table 1. Baseline Characteristics of Patients with Lung Squamous Cell Carcinoma (n = 64).

Characteristic	n	%
Age, years		
Mean ± SD	61 ± 10	—
Sex		
Male	56	87.5
Female	8	12.5
Ethnicity		
Han Chinese	39	60.9
Tujia	12	18.8
Miao	7	10.9
Dong	4	6.3
Gelao	1	1.6
Derung	1	1.6
Smoking status		
Yes	51	79.7
No	13	20.3
Clinical stage		
IIIB–IIIC	31	48.4
IVA–IVB	33	51.6
Specimen type		
Tissue	43	67.2
Blood	21	32.8
Detected gene alterations*		
EGFR	10	15.6
ALK	4	6.3
BRAF	1	1.6
MET exon 14	1	1.6
ERBB2	1	1.6
KRAS	1	1.6

Note. SD = standard deviation. Percentages were calculated using the total sample of 64 patients. Gene alteration categories are not mutually exclusive; therefore, their frequencies should not be summed to obtain the total number of mutation-positive patients.

EGFR, MET, and PIK3CA as the most frequently altered genes. In contrast, the most frequently altered genes in our cohort included EGFR, TP53, PIK3CA, and ALK. Differences between these findings may be attributable, at least in part, to differences in patient populations and molecular testing methodologies, as our study used a combination of NGS, PCR, and FISH. Notably, potentially TKI-targetable alterations accounted for 28.13% of patients, and 44.4% of these targetable alterations were classified as uncommon mutations, including ALK, BRAF, MET exon 14, ERBB2, and KRAS. This molecular profile differs from that typically observed in LUAD, in which common actionable alterations such as EGFR are more frequently identified [16].

The prevalence and distribution of genetic alterations may vary across ethnic groups [17, 18]. China has substantial ethnic diversity, providing an important context in which to investigate potential differences in the molecular characteristics of LUSC. In our cohort, the prevalence of potentially targetable alterations, particularly uncommon alterations, was significantly higher among ethnic minority patients than among Han Chinese patients ($P < 0.05$). However, no significant difference in EGFR mutation frequency was observed between the two groups, consistent with the findings of Zhou et al. [19]. In contrast, a study from the Ningxia Hui Autonomous Region reported a significantly lower EGFR mutation rate among Han Chinese patients than among Hui patients ($P < 0.05$) [20].

The mechanisms underlying potential ethnic differences in driver gene alterations remain unclear. Yang et al. [21], using whole-exome sequencing, identified population-specific genetic adaptations among several ethnic minority groups in Yunnan Province, China. The Di-Qiang, Dai, and Deang populations exhibited genetic signatures potentially associated with adaptation to hypertension, malaria-related diseases, and alcohol metabolism, respectively. These findings raise the possibility that population-specific genetic backgrounds may contribute to differences in the molecular profiles of LUSC among ethnic groups. Ma et al. [22] further proposed that non-Han populations living predominantly in mountainous regions, including areas at elevations exceeding 2,000 m, may experience distinctive environmental exposures, such as chronic hypoxia and increased ultraviolet radiation, which could potentially influence cancer susceptibility and molecular characteristics. However, these proposed mechanisms remain hypothetical and cannot be established from the present study. Further population-based genomic and epidemiological studies are required to determine whether genetic ancestry, environmental exposure, or their interaction contributes to the observed differences in mutation profiles.

Although our findings suggest differences in the distribution of driver gene alterations among Miao, Dong, Tujia, and Han patients with LUSC, several limitations should be considered. First, the present findings may not represent the true prevalence of driver gene alterations among these ethnic groups across China, as members of the same ethnic populations reside in multiple provinces and regions, and the potential effects of geographic variation remain uncertain. Second, the single-center design and relatively small sample size introduce the possibility of selection bias. The absence of data from other healthcare institutions in the Wuling Mountain region further limits the extent to which our findings can be generalized to the broader regional population. Third, molecular testing was performed using heterogeneous methodologies, including PCR, NGS, and FISH. Because molecular testing was not initially available in-house at our hospital, most early testing was performed by commercial third-party laboratories; in-house PCR testing began in July 2023. Differences in testing platforms, gene panels, and laboratory procedures may therefore have affected the detection of specific alterations and the comparability of results across patients. These methodological differences should be considered when interpreting the observed

Table 2. Distribution of Gene Alterations According to Ethnicity.

Ethnicity	Overall mutation status, n (%)	P value	EGFR status, n (%)	P value	Uncommon mutation status, n (%)	P value
	Positive	Negative		Positive	Negative	
Han Chinese	7 (19.4)	29 (80.6)	0.039	5 (14.7)	29 (85.3)	0.465
Ethnic minorities	11 (44.0)	14 (56.0)		5 (26.3)	14 (73.7)	
Total	18	43		10	43	

Note. Because the denominators in the supplied data differ across analyses, percentages should be checked against the original statistical output before submission. "Uncommon mutations" were defined as alterations in ALK, MET exon 14, BRAF, ERBB2, ROS1, and KRAS. P values were obtained using the chi-square test or Fisher's exact test, as appropriate.

mutation frequencies.

In conclusion, this study provides an initial characterization of the driver gene alteration spectrum among non-Han ethnic minority patients with LUSC, including Miao, Dong, and Tujia populations, in the Wuling Mountain region of China. Although potentially TKI-targetable alterations were identified in 28.13% of the study population, uncommon driver alterations represented a substantial proportion of these potentially actionable findings. ALK alterations were particularly notable among ethnic minority patients. Given the increasing availability of targeted therapies for uncommon and rare molecular alterations, our findings support consideration of broader molecular profiling in selected patients with LUSC, particularly those from ethnic minority populations.

However, because of the small sample size, single-center design, and heterogeneity of molecular testing methods, these findings should be considered hypothesis-generating rather than definitive evidence of ethnic differences in mutation prevalence. Larger, multicenter studies using standardized molecular testing platforms and comprehensive genomic profiling are needed to validate the observed patterns and clarify the contributions of genetic background and environmental factors. Such studies may help identify patients with LUSC who could benefit from molecularly guided treatment and further support the integration of precision oncology into the management of this histological subtype.

Clinical Implications

The findings have several potential implications for clinical practice. Although LUSC generally has a lower prevalence of actionable driver alterations than LUAD, the relatively high proportion of potentially targetable alterations observed in this cohort suggests that histological classification alone should not preclude molecular testing. In particular, the detection of uncommon alterations among patients from ethnic minority populations highlights the potential value of broader molecular profiling when clinically feasible. Identification of actionable alterations may provide additional treatment options for patients who would otherwise be managed primarily with chemotherapy, immunotherapy, or conventional approaches. However, the findings should not be interpreted as evidence that all patients with LUSC require identical molecular testing strategies, and testing decisions should remain consistent with current clinical guidelines, available tissue, clinical characteristics, and local resources.

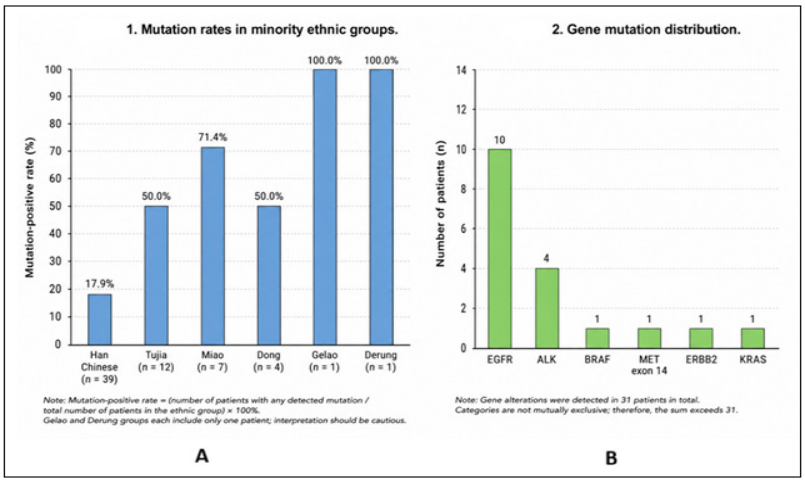

Figure 1. A, Mutation Rates according to Ethnic Group among Patients with Lung Squamous Cell Carcinoma. Mutation-positive rates are presented as percentages for Han Chinese, Tujia, Miao, Dong, Gelao, and Derung patients. The Gelao and Derung groups each comprised one patient; therefore, their rates should be interpreted cautiously. B, Distribution of Detected Gene Alterations among Patients with Lung Squamous Cell Carcinoma. The figure shows the number of patients with detected EGFR, ALK, BRAF, MET exon 14, ERBB2, and KRAS alterations. Gene categories were not mutually exclusive; therefore, the total number of detected alterations does not correspond to the number of mutation-positive patients.

Strengths and Future Research

The main strength of this study is its focus on a geographically and ethnically diverse population that has been relatively underrepresented in studies of the molecular characteristics of LUSC. The study also provides real-world molecular testing data from routine clinical practice and highlights the potential contribution of uncommon driver alterations that may otherwise remain undetected. Nevertheless, the small sample size and heterogeneous testing methods limit the precision of mutation frequency estimates. Future multicenter studies involving larger populations from the Wuling Mountain region and standardized comprehensive genomic profiling are warranted. Such studies should evaluate the relationship between ethnicity, geographic and environmental factors, molecular alterations, treatment selection, and clinical outcomes. Prospective studies would also be valuable for determining whether the identification of uncommon driver alterations translates into improved treatment response and survival.

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Statement of Transparency and Principles:

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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References

1. Cao W, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in china: A secondary analysis of the global cancer statistics 2020. Chin Med J (Engl). 2021;134(7):783-91. https://doi.org/10.1097/cm9.0000000000001474.
2. Voldborg BR, Damstrup L, Spang-Thomsen M, Poulsen HS. Epidermal growth factor receptor (egfr) and egfr mutations, function and possible role in clinical trials. Ann Oncol. 1997;8(12):1197-206. https://doi.org/10.1023/a:1008209720526.
3. Jeon H, Wang S, Song J, Gill H, Cheng H. Update 2025: Management of non-small-cell lung cancer. Lung. 2025;203(1):53. https://doi.org/10.1007/s00408-025-00801-x.
4. Shen Y, Chen JQ, Li XP. Differences between lung adenocarcinoma and lung squamous cell carcinoma: Driver genes, therapeutic targets, and clinical efficacy. Genes Dis. 2025;12(3):101374. https://doi.org/10.1016/j.gendis.2024.101374.
5. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, et al. Osimertinib with or without chemotherapy in egfr-mutated advanced nsclc. N Engl J Med. 2023;389(21):1935-48. https://doi.org/10.1056/NEJMoa2306434.
6. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in resected alk-positive non-small-cell lung cancer. N Engl J Med. 2024;390(14):1265-76. https://doi.org/10.1056/NEJMoa2310532.
7. Drilon A, Camidge DR, Lin JJ, Kim SW, Solomon BJ, Dziadziuszko R, et al. Repotrectinib in ros1 fusion-positive non-small-cell lung cancer. N Engl J Med. 2024;390(2):118-31. https://doi.org/10.1056/NEJMoa2302299.
8. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, et al. Tepotinib in non-small-cell lung cancer with met exon 14 skipping mutations. N Engl J Med. 2020;383(10):931-43. https://doi.org/10.1056/NEJMoa2004407.
9. Malapelle U, Pilotto S, Passiglia F, Pepe F, Pisapia P, Righi L, et al. Dealing with nsclc egfr mutation testing and treatment: A comprehensive review with an italian real-world perspective. Crit Rev Oncol Hematol. 2021;160:103300. https://doi.org/10.1016/j.critrevonc.2021.103300.
10. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: Meta-analyses by ethnicity and histology (mutmap). Ann Oncol. 2013;24(9):2371-6. https://doi.org/10.1093/annonc/mdt205.
11. Zhang T, Li J. Driven gene in patients with lung squamous cell carcinoma: Analysis of clinicopathologic characteristics and prognosis. Zhongguo Fei Ai Za Zhi. 2016;19(10):648-52. https://doi.org/10.3779/j.issn.1009-3419.2016.10.02.
12. Kalemkerian GP, Narula N, Kennedy EB, Biermann WA, Donington J, Leighl NB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American society of clinical oncology endorsement of the college of american pathologists/international association for the study of lung cancer/association for molecular pathology clinical practice guideline update. J Clin Oncol. 2018;36(9):911-9. https://doi.org/10.1200/jco.2017.76.7293.
13. National comprehensive cancer network. Nccn clinical practice guideline in oncolog y. 2015, http://www.nccn.org/professionals/physician_gls/pdf/nscl.Pdf.
14. Qian J, Chen R, Zhao R, Han Y, Yu Y. Comprehensive molecular characterizations of chinese patients with different subtypes of lung squamous cell carcinoma. Front Oncol. 2020;10:607130. https://doi.org/10.3389/fonc.2020.607130.
15. Walter J, Tufman A, Kumbrink J, Neumann J, Kahnert K, Sellmer L, et al. Clinicopathological characterization of next-generation sequencing detected mutations in lung cancers-a single-center experience. Transl Lung Cancer Res. 2024;13(4):799-810. https://doi.org/10.21037/tlcr-23-751.
16. Cho BC, Loong HHF, Tsai CM, Teo MLP, Kim HR, Lim SM, et al. Genomic landscape of non-small cell lung cancer (nsclc) in east asia using circulating tumor DNA (ctdna) in clinical practice. Curr Oncol. 2022;29(3):2154-64. https://doi.org/10.3390/curroncol29030174.
17. Liu L, Liu J, Shao D, Deng Q, Tang H, Liu Z, et al. Comprehensive genomic profiling of lung cancer using a validated panel to explore therapeutic targets in east asian patients. Cancer Sci. 2017;108(12):2487-94. https://doi.org/10.1111/cas.13410.
18. Noronha V, Budukh A, Chaturvedi P, Anne S, Punjabi A, Bhaskar M, et al. Uniqueness of lung cancer in southeast asia. Lancet Reg Health Southeast Asia. 2024;27:100430. https://doi.org/10.1016/j.lansea.2024.100430.
19. Zhou Y, Liu X, Guo Y, Li Z, Zhu S, Li Q, et al. Mutational characteristics of chinese han and ethnic minorities in southwestern china: A propensity score matched analysis.

Ann Transl Med. 2022;10(14):782. https://doi.org/10.21037/atm-22-987.
20. Yuan lz, zhou w, meng fz. An analysis of egfr mutation and clinicopathologic characteristics in hui and han patients with non-small-cell lung cancer. Ningxia medical journal 2017;39:484-7.
21. Yang Z, Chen H, Lu Y, Gao Y, Sun H, Wang J, et al. Genetic evidence of tri-genealogy hypothesis on the origin of ethnic minorities in yunnan. BMC Biol. 2022;20(1):166. https://doi.org/10.1186/s12915-022-01367-3.
22. Ma Y, Li Q, Du Y, Chen W, Zhao G, Liu X, et al. Oncogenic genetic alterations in non-small-cell lung cancer (nsclc) in southwestern china. Cancer Manag Res. 2020;12:10861-74. https://doi.org/10.2147/cmar.S266069.