

Clinical Characterization and Treatment Responsiveness of Rare EGFR L833V-containing Compound Mutations in Non-small Cell Lung Cancer: A Multi-Case Series

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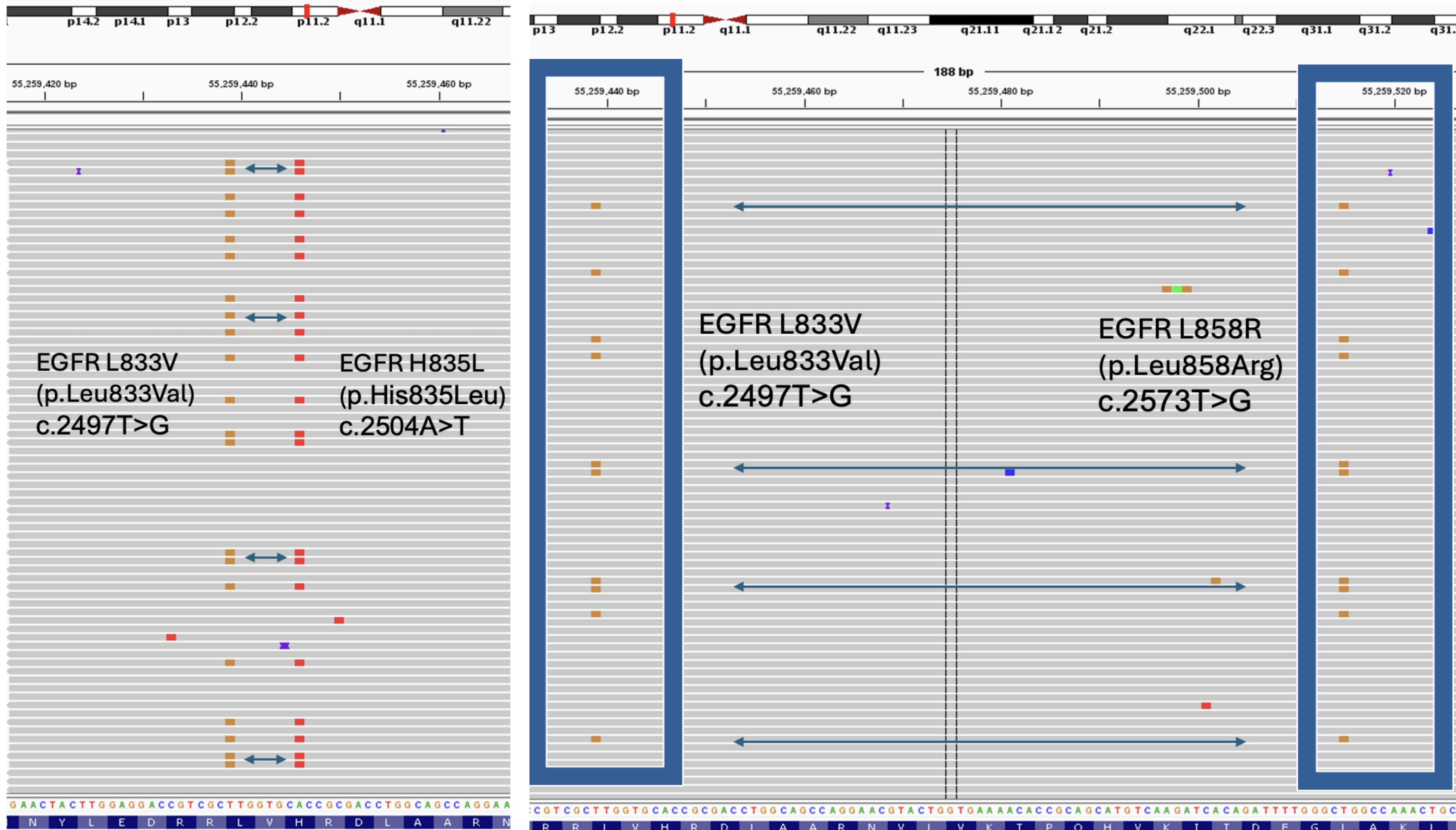
Introduction

Compound EGFR mutations, defined as two or more mutations on the same or different alleles, present a therapeutic challenge in non-small cell lung cancer (NSCLC). While the common exon 21 L858R point mutation and exon 19 deletions are highly sensitizing to EGFR tyrosine kinase inhibitors (TKI), the clinical impact of rare variants like L833V, particularly in tandem with other mutations, is poorly defined in current literature. This case series characterizes the clinical characteristics and treatment details of five NSCLC patients with EGFR L833V compound mutations.

Cases Description

We identified five institutional cases of EGFR L833V mutations, all occurring as compound mutations with another point mutation. All five cases show that L833V variant and its partner EGFR mutation exhibited near-identical variant allele frequencies.

Cis Architecture for EGFR L833V/H835L and EGFR L833V/L858R



Discussion

This series demonstrates a consistent allelic architecture for L833V compound mutations. Direct molecular phasing confirmed that the L833V variant exists strictly in *cis* with partner mutation (L858R or H835L). This illustrates co-inheritance of EGFR mutation on a single allele, where the *cis* configuration is likely the molecular basis for sensitizing effect observed in our patients. Our case series suggests that L833V does not negate the TKI sensitivity of its partner mutations. It compares favourably to standard practice by showing that these rare variants remain highly sensitive to 1st generation (erlotinib) and 3rd generation (aumolertinib, osimertinib) EGFR TKIs.

Conclusion

EGFR L833V compound mutations occurring in *cis* represent a highly TKI-sensitive molecular subset. This series provides critical real-world evidence supporting the efficacy of multiple TKI generations for this rare population, suggesting they should be managed similarly as other common sensitizing mutations.

References

1. Huang L, Zeng F, Huang P, et al. Mutational landscape and tyrosine kinase inhibitor sensitivity in EGFR L833 and H835 mutated non-small cell lung cancer. *Cancer*. 2025;e70063.

Ethics Approval: This research was approved by the Hospital Authority Central Institutional Review Board (HA Central IRB) with reference number CIRB-2026-168-5.

Age/Sex	EGFR Profile (VAF %)	Oncological journey	Current disease status
52/F	H835L (25.7%) / L833V (25.8%)	- Diagnosis via EBUS biopsy (pT2aN0) in Feb23 → RLL Lobectomy in Apr23, no adjuvant therapy - CT in Jun26 showed complete remission	Remission
75/F	H835L (39.5%) / L833V (39.5%)	- Diagnosis via FNAC of lung (pT1cN1) in Apr25 → LLL Lobectomy in Jul25, completed 4 cycles adjuvant pemetrexed-cisplatin in Nov25 - CT in May26 showed complete remission	Remission
70/F	L858R (18.0%) / L833V (18.0%)	- Diagnosis via FNAC of lung in Jul25 → RLL lobectomy in Dec25 (synchronous tumours L858R/L833V and L858R/ I744M mutation), treat as ypT3N0 - CT in Feb26 showed complete remission, started adjuvant osimertinib - CEA <1.8 µg/L in Jun26 (baseline 6.0 µg/L prior surgery)	Remission (on adjuvant treatment)
56/F	L858R (26.8%) / L833V (27.9%)	- Diagnosis via bronchoscopic biopsy (T4N3) in Oct24 → started aumolertinib 55mg daily in Dec24. CT in Jan25 showed responding disease → escalated to 110mg - Aumolertinib with pemetrexed-carboplatin x 6 cycles followed by maintenance pemetrexed given from Feb to Jun25, PET-CT showed static disease - LLL lobectomy + mediastinal LN dissection in Jun25 (ypT1N2 stage IIIA), followed by maintenance aumolertinib - CT in Oct25, May26 showed complete remission	Remission (on adjuvant treatment)
67/M	L858R (5.78%) / L833V (5.76%)	- Diagnosis via bronchoscopic biopsy (T3N2bM0) in Jan24 → completed radical chemoradiotherapy in Mar24. Consolidation durvalumab Q2W given for 13 cycles, PET-CT in Apr25 showed metastatic relapse in bone and lymph node - Given 1 cycle pemetrexed-carboplatin in Jun25 with poor marrow tolerance - Switched to erlotinib since Jun25 - CT scan in Mar26 showed partial response	Partial response

