

P2.1563: High Allele Frequency EGFR T790M Suggesting Germline Mutation in Two Sisters with Lung Adenocarcinoma

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INTRODUCTION

EGFR mutations are key drivers in non-small cell lung cancer (NSCLC) and predictive biomarkers of response to targeted therapy. Most EGFR mutations are somatic; however, rare germline variants, including EGFR T790M, have been associated with hereditary lung cancer risk, particularly in never-smokers. We report two sisters with advanced lung adenocarcinoma harboring the same EGFR L858R/T790M co-mutation, with T790M allele frequencies >50%, raising suspicion for a germline origin.

CASE PRESENTATION

Two sisters diagnosed with advanced lung adenocarcinoma. The first patient, a 59-year-old never-smoker, presented with dyspnea, cough, and fatigue and was diagnosed with stage IV disease with pleural metastases. Molecular testing revealed an EGFR co-mutation consisting of exon 21 p.L858R and exon 20 p.T790M, with allele frequencies of 4% and 54%, respectively. The second patient a 63 year old women, presented with similar clinical features and was also diagnosed with stage IV EGFR-mutant lung adenocarcinoma. Molecular analysis showed the same co-mutation (p.L858R and p.T790M) with allele frequencies of 3.6% and 52.06%, respectively. In both cases, testing was performed using real-time PCR. The high allele frequency of T790M (>50%) raises suspicion for a germline origin.

DISCUSSION AND CONCLUSION

Although EGFR T790M is commonly associated with acquired resistance to EGFR tyrosine kinase inhibitors, germline T790M mutations have been described and are linked to inherited lung cancer predisposition. Studies such as the INHERIT EGFR study have demonstrated a high prevalence of germline mutations among patients with baseline T790M. The identification of this variant has important implications for genetic counseling and familial risk assessment.

Conclusion:

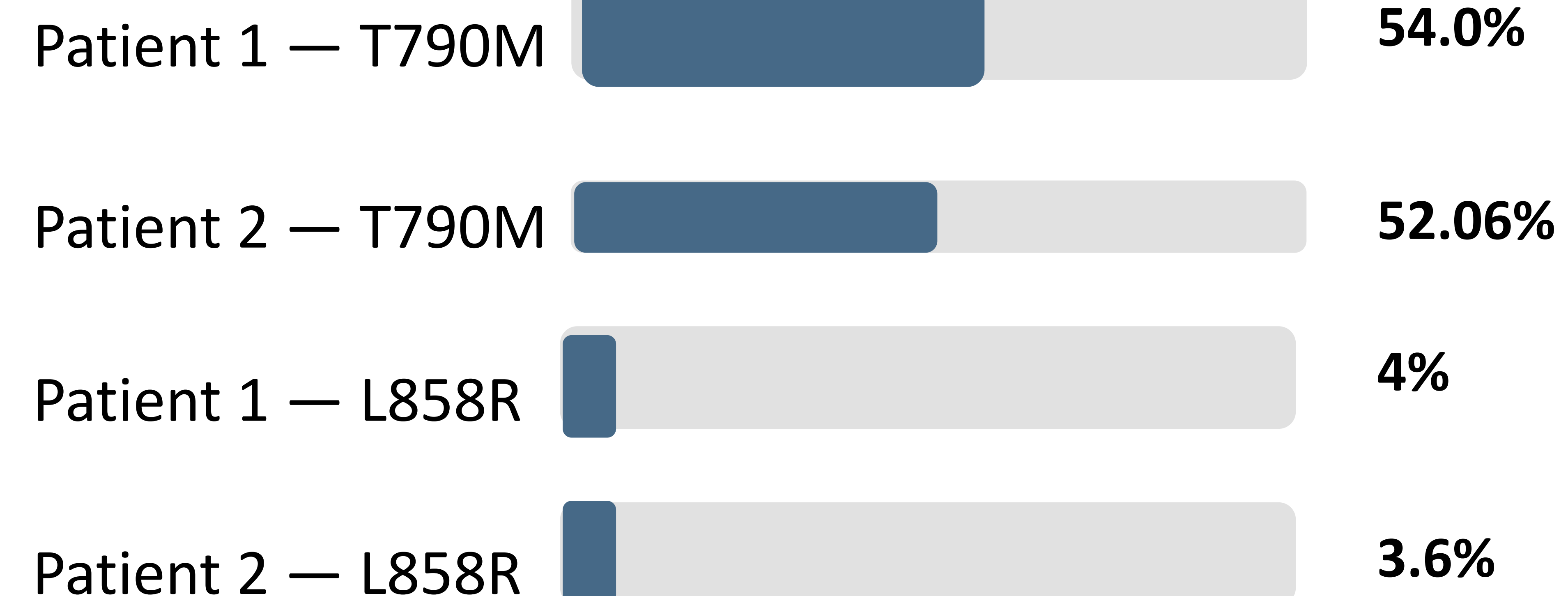
This report highlights the possibility of germline EGFR T790M mutation in familial lung cancer. These findings support the need to consider germline testing in selected patients and emphasize the importance of integrating hereditary risk assessment into routine oncologic care.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

GENE: EGFR MUTATION



Información Clínica:

Paciente
Nombre:
Fecha de nacimiento: 11/05/1970
Género: Femenino
Número de caso: TMR15-4287
Número AZ: 02024

Médico

MD: George Oblitas Alca
Institución: UOMP
Indicación: NM Pulmón

Determinación molecular tumoral

Muestra

Tipo de muestra: cfDNA
Fecha de recepción muestra: 27/06/2023
Fecha de reporte: 06/07/2023

Gen analizado

EGFR

Resultados:

DOS VARIANTES PATOGENICAS FUERON ENCONTRADAS EN EL GEN EGFR					
GEN	VARIANTE	EXON	TIPO	FRECUENCIA	CLASIFICACION
EGFR	c.2573T>G (p.Leu858Arg)	21	Missense	3.68%	Patogénica
EGFR	c.2369C>T (p.Thr790Met)	20	Missense	52.06%	Patogénica

Se han detectado las variantes patogénicas c.2573T>G (p.Leu858Arg) y c.2369C>T (p.Thr790Met) en el gen EGFR. Una variante patogénica es un cambio en la secuencia del ADN de un gen que afecta su funcionamiento.

Los resultados indican que dos variantes patogénicas en el gen EGFR fueron detectadas en la muestra analizada. La prueba realizada en el ADN libre tumoral (cfDNA o ctDNA) permite detectar una variante somática.

No se encontraron más variantes en el gen analizado. Se detectó la variante EGFR T790M.

Metodología

Para la determinación tumoral de los genes estudiados se ha empleado la tecnología AmpliSeq en combinación con la secuenciación de NGS (Next Generation Sequencing) de Illumina (San Diego, USA) para la determinación de variantes en el gen EGFR. El cfDNA o ctDNA de la muestra fue extraído utilizando el kit comercial QIAamp Circulating Nucleic Acid Kit de Qiagen (Alemania). La secuenciación fue realizada en el sistema MiSeq de Illumina con valores de $\geq 95\%$ de bases cubiertas a una uniformidad de cobertura de 20%.

El límite de detección predeterminado (LOD) se estableció en un 0.5% de frecuencia alélica (VAF). La evaluación de mutaciones fue realizada con BaseSpace Variant Interpreter el cual permite la variación. Las variantes son evaluadas mediante la plataforma VarSome Clinical (Saphentor, Suiza). La interpretación acerca de la patogenidad de las variantes sigue las últimas recomendaciones del Colegio Americano de Genética Médica (ACMG), ESMO Scale for Clinical Actionability of molecular Target (ESCAT).