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Fusion genes as drug resistance in EGFR mutant lung cancer –*Nature Communications*– Collaborative Team of Dana-Farber Cancer Institute and National Cancer Center Japan

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Highlights

- Fusion genes as drug resistance mechanism were comprehensively studied in EGFR mutant lung cancer which account for about half of adenocarcinoma in Asian countries.
- Through multimodal evaluation of putative fusion oncogenes, we identified only a minority of them have a role as functional drug resistance which could be overcome by combination therapies.
- Our results partially reveal the complex nature of fusion oncogenes as potential drug resistance and highlight approaches that can be undertaken to determine their functional significance.

Summary

Activating mutations in epidermal growth factor receptor (EGFR) gene are detected in up to 50% of Asian patients with lung adenocarcinoma. The standard treatment for these cancers is the use of EGFR tyrosine kinase inhibitors (TKIs). Despite a robust initial response to TKIs, lung cancers inevitably acquire resistance to these drugs. In vitro and clinical data on oncogenic fusion genes as a mechanism of resistance have been limited to the study of only representative genes.

New research by the collaborative team of Dr. Pasi A. Jänne from Department of Medical Oncology, Dana-Farber Cancer Institute (Boston, USA) and Dr. Yoshihisa Kobayashi from Division of Molecular Pathology, National Cancer Center Japan (Tokyo, Japan) undertook a comprehensive systematic validation of all fusion genes detected by the DNA-based hybrid capture next generation sequencing in 504 patients with EGFR mutant lung cancer, as underappreciated mediators of TKI resistance. Suspected fusions are aligned with the clinical response to EGFR-TKIs, validated by RNA-seq, and through CRISPR-Cas9 genome-edited in vitro cell models. We demonstrate that both functional and non-functional fusion oncogenes in terms of drug resistance are present in EGFR mutant cancers. In vitro models found effective combination therapies to overcome fusion genes and revealed a wide variety of further resistance mechanisms to these combination therapies. Our genomic and functional studies of fusion oncogenes as potential drug resistance mechanisms to EGFR inhibitors provides insight into the biological complexity of fusion oncogenes. Understanding the complex biology is vital for developing further assays, clinical indications, and for leveraging effective combination therapy to overcome drug resistance.

Publication

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DE, Ribeiro MF, Sacardo KP, Saddi R, Macedo MP, Blasco RB, Li J, Kurppa KJ, Nguyen T, Voligny E, Ananda G, Chiarle R, Katz A, Tolstorukov MY, Sholl LM, Jänne PA.
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