Deep Mutational Scanning of EGFR Reveals Potential Domain-Specific TKI Sensitivities in Lung Cancer

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The epidermal growth factor receptor, EGFR, is frequently activated in lung cancer by genomic alterations including missense mutations. The different mutation spectra in these diseases are reflected in divergent responses to EGFR inhibition: significant patient benefit in lung cancer, but limited in glioblastoma. Here, we report a comprehensive mutational analysis of EGFR function. We performed saturation mutagenesis of EGFR and assessed function of ~22,500 variants in a human EGFR-dependent lung cancer cell line. This approach revealed enrichment of erlotinib-insensitive variants of known and unknown significance in the dimerization, transmembrane, and kinase domains. Multiple EGFR extracellular domain variants, lacking approved targeted therapies, were sensitive to dacomitinib. In summary, this comprehensive screen reveals novel functional EGFR variants and suggests broader clinical investigation of EGFR inhibition for cancers harboring extracellular domain mutations.