Incidence of ERBB gene fusions (EGFR, ERBB2, ERBB4) across tumor types

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Introduction

Gene fusions involving receptor tyrosine kinases are established oncogenes in multiple cancer types. Gene fusions can be successfully targeted with small molecule inhibitors. ALK, ROS1, RET, and NTRK fusions all have FDA approved targeted inhibitors. HER family fusions (EGFR, ERBB2, ERBB4) have been previously described, however, there has not been a comprehensive study of their frequency. HER family fusions are important potential candidates for targeted therapies. In this study, we sought to comprehensively analyze the frequency and molecular features of EGFR, ERBB2, and ERBB4 fusions. We assessed HER family fusion partners, genomic features, cancer types and co-occurring mutations.

Methods

Tumor samples (n=64,354; representing >40 tumor types) submitted to Caris Life Sciences (Phoenix, AZ) were molecularly profiled by next-generation sequencing of DNA (IexNextSeq, 592-gene panel; or NovaSeq, whole exome) and RNA (whole transcriptome). Gene fusions, in out-of-frame status, retention of ERBB kinase domain, topology of fusion breakpoints, and co-alterations were characterized for each ERBB fusion transcript detected. Fusion prevalence was further examined in public data sets (TCGA, MSK-IMPACT and AACR GENIE).

Conclusions

• HER fusions are rare, recurrent genomic alterations across multiple cancer types.
• We identified 811 EGFR fusions, 287 ERBB2 fusions and 153 ERBB4 fusions across 182,950 tumor samples.
• Collectively, EGFR, ERBB2, and ERBB4 fusions represent up to 1% of cancer patients.
• We identified an increased frequency of TP53 mutations co-occurring with HER family fusions in >70% of Caris Life Sciences data and >80% of public datasets.
• HER family fusions are excellent candidates for targeted therapies.

References

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