

EGFR, *ERBB2* and *ERBB4* fusions are recurrent alterations in multiple cancer types

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Gene fusions involving the HER family of genes, *EGFR*, *ERBB2* and *ERBB4* are rare, but potentially amenable to treatment with targeted therapies. The incidence of these fusions across cancers has not yet been comprehensively described. We sought to assess the frequency and characteristics of fusions involving the HER family of genes. We utilized publicly available next generation sequencing data to assess the frequency of gene rearrangements involving *EGFR*, *ERBB2* and *ERBB4*. We queried the TCGA PanCancer Analyses, MSK IMPACT and AACR GENIE data bases through cBioPortal (accession dates 6/18/20, 8/8/20, 8/8/20 respectively). The overall frequency of each type of fusion by data set is displayed in Table 1. We found that *EGFR* fusions were most frequent in glioblastoma multiforme, oligoastrocytoma and astrocytoma. *ERBB2* fusions were found most often in breast cancer, stomach adenocarcinoma and cervical adenocarcinoma. *ERBB4* fusions were the least common overall, but most frequently found in breast cancer and non-small cell lung cancer. We assessed fusion partners in each category and the most common *EGFR* and *ERBB2* fusions were *EGFR-SEPT14* and *ERBB2-PPP1R1B*, respectively. We evaluated these fusions for co-occurrence of mutations in tumor suppressor genes within the TCGA datasets. Interestingly, we found that *TP53* mutations cooccurred with *ERBB2* fusions more often than in samples without *ERBB2* fusions (74% in *ERBB2* fusions vs. 36% of non-*ERBB2* fusion samples). *EGFR*, *HER2* and *HER4* fusions are individually rare events but collectively represent up to 1% of all cancers, a significant number of patients with potentially actionable genomic alterations.

Table 1. Frequency of *EGFR*, *ERBB2* and *ERBB4* fusions.

Fusion	Overall Frequency	TCGA PanCancer (N= 10,967)	MSK IMPACT (N= 10,945)	AACR GENIE (N=96,324)
EGFR	0.6% (752)	0.3% (27)	0.8% (88)	0.6% (637)
ERBB2	0.1% (173)	0.5% (50)	<0.1% (10)	0.1% (113)
ERBB4	<0.1% (45)	<0.1% (7)	<0.1% (4)	<0.1% (34)