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 tumors types) submitted to Caris Life Sciences (Phoenix, AZ) were molecularly profiled by next-generation sequencing of DNA (NextSeq, 592-gene panel; or NovaSeq, whole exome) and RNA (whole transcriptome). Gene fusion partners, 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).

Fusion	Caris Life Sciences (N= 64,354)	Public data sets: TCGA PanCancer (N= 10,967)	Public data sets: MSK IMPACT (N= 10,945)	Public data sets: AACR GENIE (N=96,324)	Overall Frequency
EGFR	0.1% (59)	0.3% (27)	0.8% (88)	0.6% (637)	0.6% (752)
ERBB2	0.2% (114)	0.5% (50)	<0.1% (10)	0.1% (113)	0.1% (173)
ERBB4	0.2% (108)	<0.1% (7)	<0.1% (4)	<0.1% (34)	<0.1% (45)

Figure 1 – Overall *ERBB* family fusion incidence in the Caris Life Sciences and public data sets.

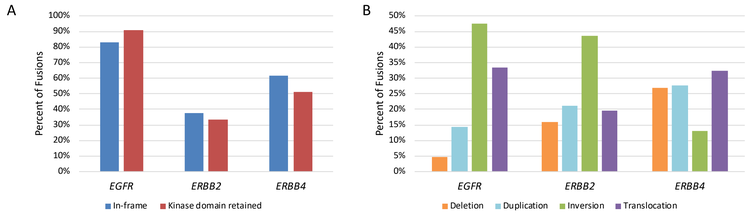


Figure 2 – Characteristics of fusions detected in the Caris Life Sciences cohort. (A) Proportion of ERBB fusions that were in-frame or retained the ERBB kinase domain. (B) Distribution of fusion topologies determined from analysis of fusion breakpoints.

EGFR Fusions

Fusion Partner	Caris LS	Public data sets: TCGA	MSK IMPACT	AACR GENIE	Total
EGFR-SEPT14	20	13	2	12	27
SEPT14-EGFR				17	17
EGFR-PSPH	4				
EGFR-VSTM2A	3	1		2	3
EGFR-LAMA2				3	3
VOPP1-EGFR	1			3	3
SEC61G-EGFR	2	2			2
EGFR-GBAS				2	2
EGFR-SEC61G				2	2
EGFR-TNS3				2	2
EGFR-VOPP1				2	2
VSTM2A-EGFR	1			2	2
ELDR-EGFR				2	2
ZNF713-EGFR				2	2
EGFR-GRB2	2				
LANCL2-EGFR	2				

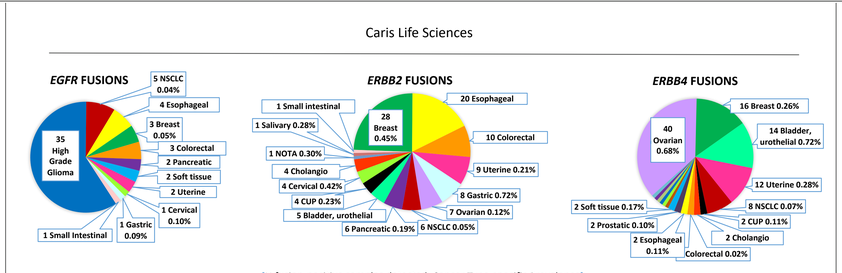
ERBB4 Fusions

Fusion Partner	Caris LS	Public data sets: TCGA	MSK IMPACT	AACR GENIE	Total
IKZF2-ERBB4	20				
ERBB4-IKZF2	13				
LANCL1-ERBB4	3				
KANSL1L-ERBB4	3				
ERBB4-TRIM33				3	3
ERBB4-PARD3B			1	1	2
ERBB4-PXMP2			1	1	2
AGAP1-ERBB4	2				
KLF7-ERBB4	2				
ERBB4-FN1	2				

ERBB2 Fusions

Fusion Partner	Caris LS	Public data sets: TCGA	MSK IMPACT	AACR GENIE	Total
ERBB2-PPP1R1B	3	10		1	11
ERBB2-IKZF3	10	6		4	10
ERBB2-CTTN		8			8
GRB7-ERBB2	2		2	4	6
ERBB2-GRB7	2				
C17orf37-ERBB2			2	2	4
GP2-ERBB2	5				
ERBB2-PSMB3		3			3
JUP-ERBB2	3				
ERBB2-GSDMA	3				
ERBB2-GSDMB	2				
ERBB2-TCAP	1	1		1	2
ERBB2-WIPF2		1		1	2
RARA-ERBB2			1	1	2
ERBB2-SHC1	2				
SHC1-ERBB2			1	1	2
ERBB2-CDK12	10			2	2
ERBB2-PGAP3	10			2	2
PGAP3-ERBB2	8				
ERBB2-STARD3	5			2	2
ERBB2-IGFBP4	2				
ERBB2-MED1	2				
ERBB2-MED24	2				
ERBB2-PLXDC1	2				
ERBB2-RAPGEFL1	2				
IKZF3-ERBB2	1			2	2

Figure 3 – Recurrent fusion isoforms detected in Caris Life Sciences (Caris LS) and public data sets.



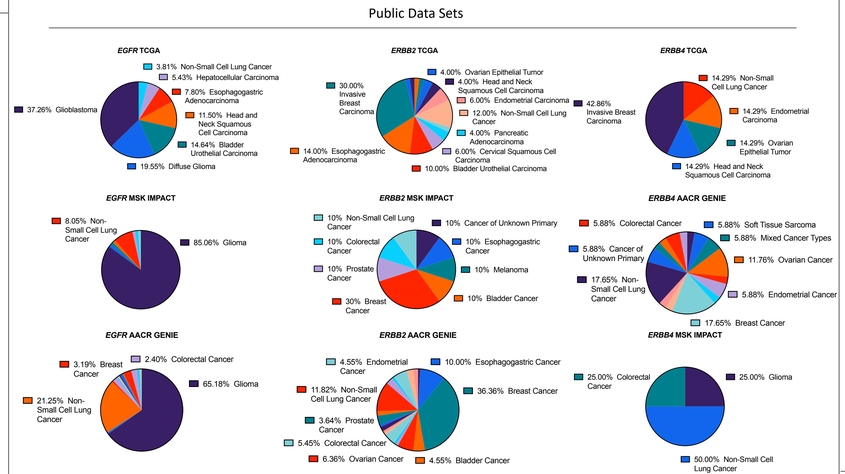


Figure 4 – *HER* family fusion frequency by cancer type

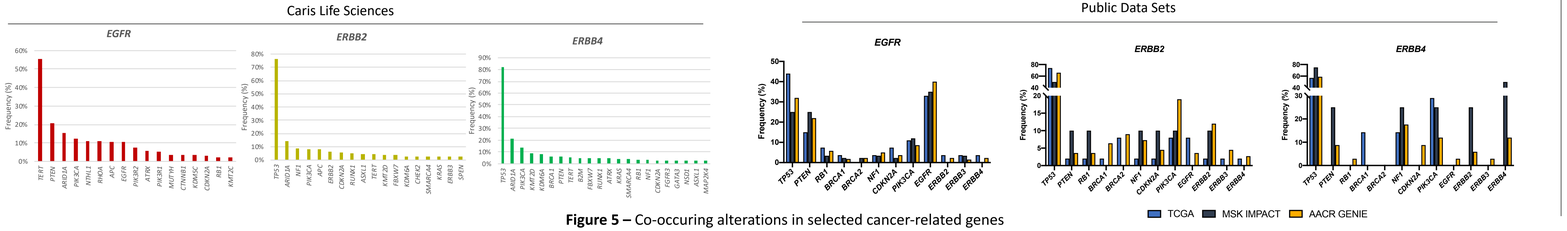


Figure 5 – Co-occuring alterations in selected cancer-related genes

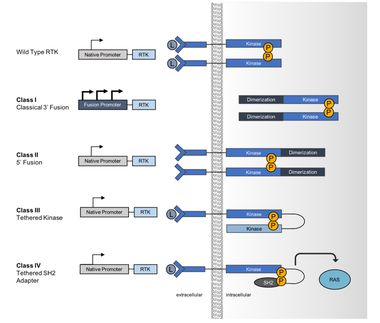


Figure 6 – Proposed mechanisms of activation of HER family fusions and proposed classification nomenclature.

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 182,590 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 >60% across public datasets.
- HER family fusions are excellent candidates for targeted therapies.

References

1. The results shown here are in part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.
2. Cerami et al. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. Cancer Discovery. May 2012 2; 401.
3. Gao et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci. Signal. 6, pl1 (2013).
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5. Zehir et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017 Jun;23(6):703-713. doi: 10.1038/nm.4333. Epub 2017 May 8. Erratum in: Nat Med. 2017 Aug 4;23 (8):1004. PMID: 28481359; PMCID: PMC5461196.

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