Identifying recurrent gene amplifications in breast cancer for antibody-drug-conjugate development (PS3-04-13)

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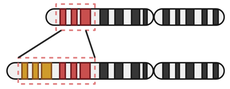
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BACKGROUND

Background: We hypothesized genes with frequent copy number amplifications (CNA) in breast cancer resulting in overexpression of membrane proteins could serve as potential targets for novel antibody drug conjugates (ADC).

MATERIALS AND METHODS

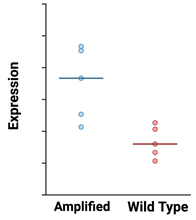
1 cBioPortal FOR CANCER GENOMICS



Copy number amplification Frequency > 15%

Amplification defined as copy number alteration equals 2 (maximum) in GISTIC 2.0. N = 3970 patients.

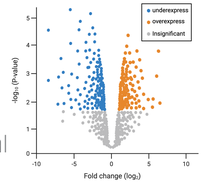
2



Over-expression in Amplified cancers

Wilcoxon rank-sum test FDR < .0001

3

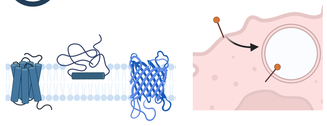


TCGA GTExPortal

mean Log_2 Fold change > 1 in cancer compared 21 normal tissue

(DESeq2 for differential expression)

4



Literature review for membrane protein and internalization

Figures in methods section were generated using biorender at https://www.biorender.com/

RESULTS

- 719 genes are amplified with higher mRNA expression in amplified cancers: all breast (553 genes), ER+ (3 genes), HER2+ (142 genes), TNBC (21 genes).
- 228 of these show higher expression in breast cancer than in normal tissues.
- 13 of these are membrane proteins with known ability for internalization.

RESULTS

CNA profile of breast cancer

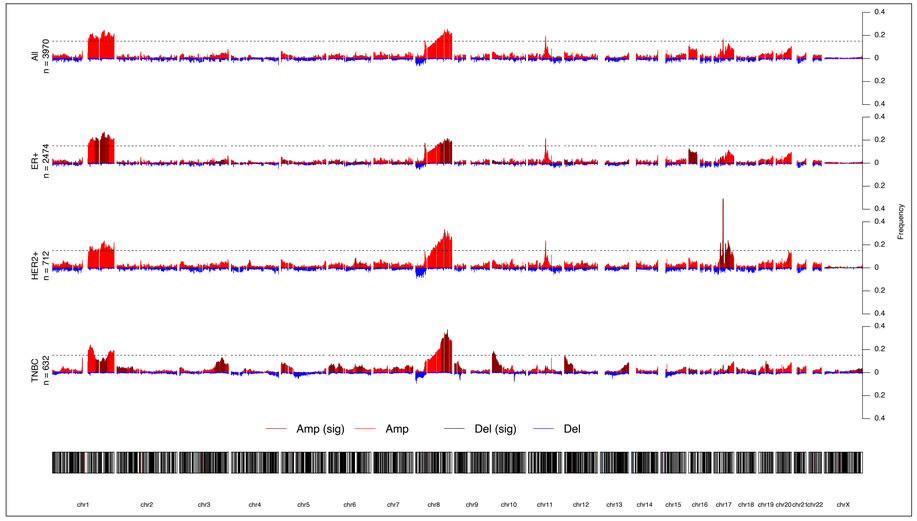


Fig. 1 CNA profile of breast cancer. Genome-wide copy number aberration frequencies across all breast cancers and in clinical subtypes. The dashed line represents the 15% frequency threshold. Sig: significant for Chi-square or Fisher's Exact test with FDR < .0001. X-axis genome aligned by chromosome number.

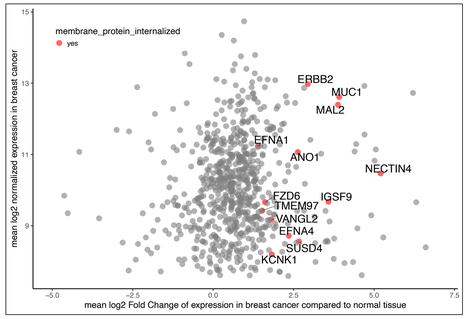


Fig. 2 Mean Expression levels and fold change of expression compared to normal tissue of the recurrent amplified genes. Top ADC candidates are shown in red.

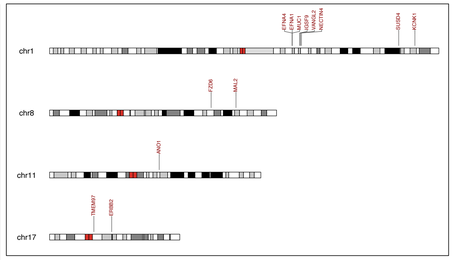


Fig. 3 Chromosome position of the top ADC candidates from Fig. 2.

RESULTS

Table 1. Characterization of candidate genes with recurrent amplification for antibody-drug-conjugate development

Gene	ER+ frequency (significant difference compared to non-ER+ subtype)	HER2+ frequency (significant difference compared to non-HER2+ subtype)	TNBC frequency (significant difference compared to non-TNBC subtype)	Amplification Frequency (all breast)	Mean log2 expression Fold Change (breast cancer expression compared to normal tissue)
NECTIN4	0.20	0.16	0.21	0.20	5.20
MUC1	0.20	0.17	0.21	0.20	3.91
MAL2	0.19	0.29	0.33 (sig)	0.23	3.87
IGSF9	0.21	0.18	0.21	0.21	3.58
ERBB2	0.06	0.60 (sig)	0.06	0.16	2.93
SUSD4	0.24 (sig)	0.18	0.14	0.21	2.66
ANO1	0.19	0.23	0.05	0.18	2.62
EFNA4	0.20	0.17	0.21	0.20	2.35
KCNK1	0.20	0.16	0.17	0.18	1.81
VANGL2	0.19	0.15	0.20	0.19	1.80
FZD6	0.16	0.22	0.26	0.18	1.61
TMEM97	0.03	0.18 (sig)	0.02	0.06	1.52
EFNA1	0.20	0.17	0.21	0.20	1.39

CONCLUSIONS

- *We have identified several novel potential targets for ADC development in breast cancer.*

References

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2. Mermel, Craig H., et al. "GISTIC2. 0 facilitates sensitive and confident localization of the targets of focal somatic copy-number alteration in human cancers." *Genome biology* 12.4 (2011): R41.
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4. Love, Michael I., Wolfgang Huber, and Simon Anders. "Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2." *Genome biology* 15.12 (2014): 550.