The genomic and transcriptomic landscape of PIK3R1-mutated breast cancers

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INTRODUCTION

Somatic mutations in *PIK3R1*, a tumor suppressor gene that encodes the regulatory subunit (p85α) of the PI3K signaling complex, are associated with poor outcomes in breast cancer. We previously developed an isogenic cellular system lacking p85α and investigated therapeutic approaches for breast cancers that lack functional p85α.[1] For instance, somatic loss of *PIK3R1* may sensitize breast cancer cells to MEK inhibition; previous work in patient-derived xenograft models confirmed this observation.[2] Here, we investigated the significance of *PIK3R1* mutations (*PIK3R1*^{MUT}) in breast cancer by using real-world data to characterize the genomic landscape of breast cancer patients with *PIK3R1*^{MUT} and examine genes that were co-mutated with *PIK3R1*. We also interrogated the effect of *PIK3R1*^{MUT} on corresponding mRNA expression levels, tumor mutational burden (TMB), and microsatellite instability (MSI) to better understand the molecular-level effects of this gene.

METHODS

We retrospectively analyzed next-generation sequencing (NGS) data from 3836 HER2 negative (HER2-) and 460 HER2 positive (HER2+) stage I-IV breast cancer patients with confirmed hormone receptor status (HR+/–).

Our cohort consisted of molecularly profiled, de-identified breast cancer cases using the Tempus xT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage and exome capture RNA-seq).[3]

This assay assesses mutations in both germline and somatic tissue and characterizes nucleotide variants, insertions/deletions, and copy number variants.

Table 1: Distribution of cohort by HR and HER2 status

Histology	n
HR+/HER2-	2782
HR-/HER2-	1054
HR+/HER2+	317
HR-/HER2+	143

[1]Turturro, S.B., *et al., Breast Cancer Res Treat* 2019; 177:325-33
[2]Cobleigh, MA, et al, Journal of Clinical Oncology 2021 39:15_suppl, e13062-e13062
[3]Beaubier, N., *et al., Oncotarget* 2019; 10:2384-2396

RESULTS

Table 2: *PIK3R1* mutation frequency across HR and HER2 subtypes

	PIK3R1^{MUT} n (%)	*PIK3R1*^{WT} n (%)	p-value[4]
Overall HER2-	n=87	n=3749	
HR+/HER2-	38 (44%)	2744 (73%)	< 0.001
HR-/HER2-	49 (56%)	1005 (27%)	
Overall HER2+	n=5	n=455	
HR+/HER2+	2 (40%)	315 (69%)	0.2
HR-/HER2+	3 (60%)	140 (31%)	

[4]Fisher's exact test

Distribution of *PIK3R1* mutational subtypes across HER2- samples

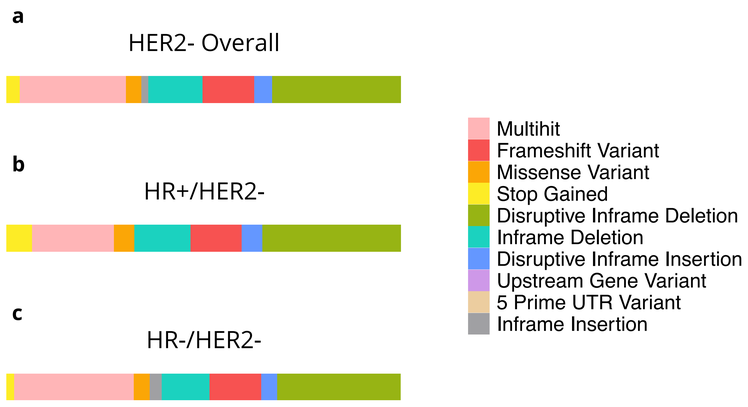

Figure 1. Distribution of variant types for all pathogenic/likely pathogenic *PIK3R1* variants detected in all HER2- (a), HR+/HER2- (b), and HR-/HER2- samples (c).

Table 3: Landscape of co-mutations in *PIK3R1*^{MUT} vs. *PIK3R1*^{WT} HER2- samples

	Genes	*PIK3R1*^{MUT} n (%)	*PIK3R1*^{WT} n (%)	p-value[5]	q-value[6]
		n=87	n=3749		
Positively correlated	*PTEN*	23 (26%)	206 (6%)	<0.001	<0.001
	NF1	13 (15%)	158 (4%)	<0.001	0.008
	TP53	50 (57%)	1455 (39%)	<0.001	0.021
Negatively correlated	*PIK3CA*	8 (9%)	1006 (27%)	<0.001	0.014

[5]Pearson's Chi-squared test; Fisher's exact test
[6]False discovery rate correction for multiple testing

***PIK3R1* gene expression in *PIK3R1*^{WT} vs. *PIK3R1*^{MUT} HER2- disease**

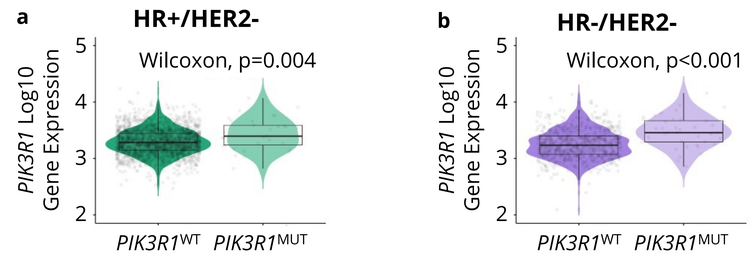

Figure 2. a. HR+/HER2-, p=0.004, q=0.024; Wilcoxon rank sum test with false discovery rate correction for multiple testing. **b.** HR-/HER2-, p<0.001, q <0.001; Wilcoxon rank sum test with false discovery rate correction for multiple testing. Median *PIK3R1* log10 gene expression was also higher in *PIK3R1*^{MUT} than in *PIK3R1*^{WT} HER2- disease overall (3.45 vs. 3.27; p<0.001, q<0.001; Wilcoxon rank sum test with false discovery rate correction).

- *PIK3R1* mutations are more common in HR- than HR+ disease.
- Mutations in *PIK3R1* tend toward mutual exclusivity with *PIK3CA* in HER2- disease.
- Mutations in *PTEN, NF1,* and *TP53* are enriched in *PIK3R1*^{MUT} HER2- disease.
- Median TMB was higher in *PIK3R1*^{MUT} than in *PIK3R1*^{WT} HR+/HER2- disease (4.7 vs. 3.1 mutations/MB; p=0.002, Wilcoxon rank sum test). Median TMB was not significantly different between *PIK3R1*^{MUT} and *PIK3R1*^{WT} HR-/HER2- disease (3.57 vs. 3.07; p=0.3, Wilcoxon rank sum test).
- MSI-high status was only observed in *PIK3R1*^{WT} HER2- samples, although this difference was not statistically significant (0.8% vs. 0%; p>0.9, Fisher's exact test).
- The percentage of patients with a high tumor mutational burden (TMB; ≥10 mutations/Mb) was not significantly different between *PIK3R1*^{MUT} and *PIK3R1*^{WT} HER2- disease (7% vs. 6.7%; p>0.9, Pearson's Chi-squared test).
- *PIK3R1* RNA expression was higher in *PIK3R1*^{MUT} than in *PIK3R1*^{WT} HER2- disease.

CONCLUSIONS

Our study used real-world evidence to build on previous pre-clinical and clinical studies and illustrates the importance of *PIK3R1*^{MUT} in breast cancer.

Certain mutations associated with poor outcomes and endocrine therapy resistance (*e.g., PTEN* and *NF1*) were more frequent in *PIK3R1*^{MUT} tumor samples.

PIK3R1 RNA expression was higher in *PIK3R1*^{MUT} than in *PIK3R1*^{WT} HER2- disease, suggesting that tumor cells compensate for a loss of *PIK3R1* protein function via overexpression of mutant *PIK3R1* RNA.

Overall, this study shows that *PIK3R1* may be an important therapeutic target in breast cancer.

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