The Landscape of Somatic Genetic Alterations in Breast Cancers from Carriers of Germline Pathogenic Variants in DNA-repair Genes

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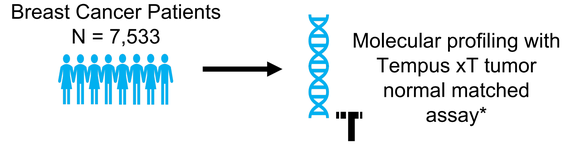
INTRODUCTION

- Hereditary breast cancer in carriers of germline pathogenic or likely pathogenic variants (PVs) in *ATM*, BRCA1, BRCA2, CHEK2, and PALB2 have unique clinicopathological characteristics compared to sporadic breast cancer.
- However, very little is known about the underlying differences in somatic genetic alterations between hereditary and sporadic breast cancer.

METHODS



Study Criteria:
- Patients with incidental germline PVs (g*ATM*, g*BRCA1*, g*BRCA2*, g*CHEK2*, g*PALB2*) OR sporadic breast tumors (defined as no germline PV in the selected genes).
- Breast cancer subtype determined by record of IHC positivity for ER, PR, HER2 OR sequencing-based detection of *ERBB2* (HER2) gene amplifications in the absence of available IHC data.

*Tempus xT assay - a targeted panel that detects single nucleotide variants, insertions and/or deletions, and copy number variants in 598-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.
** Statistical Analysis - comparisons were made by either Pearson's Chi-squared or Fisher's exact test, with false discovery rate (FDR) correction for multiple testing.

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KEY TAKEAWAYS

- The observed differences in the frequencies of *CCND1, ESR1, PIK3CA, TP53*, and other key genetic alterations between incidental hereditary and sporadic breast cancer highlight the unique tumor biology of breast cancer in germline PV carriers.
- This has significant implications for understanding tumorigenesis and identifying therapeutic strategies for the management of hereditary breast cancer.

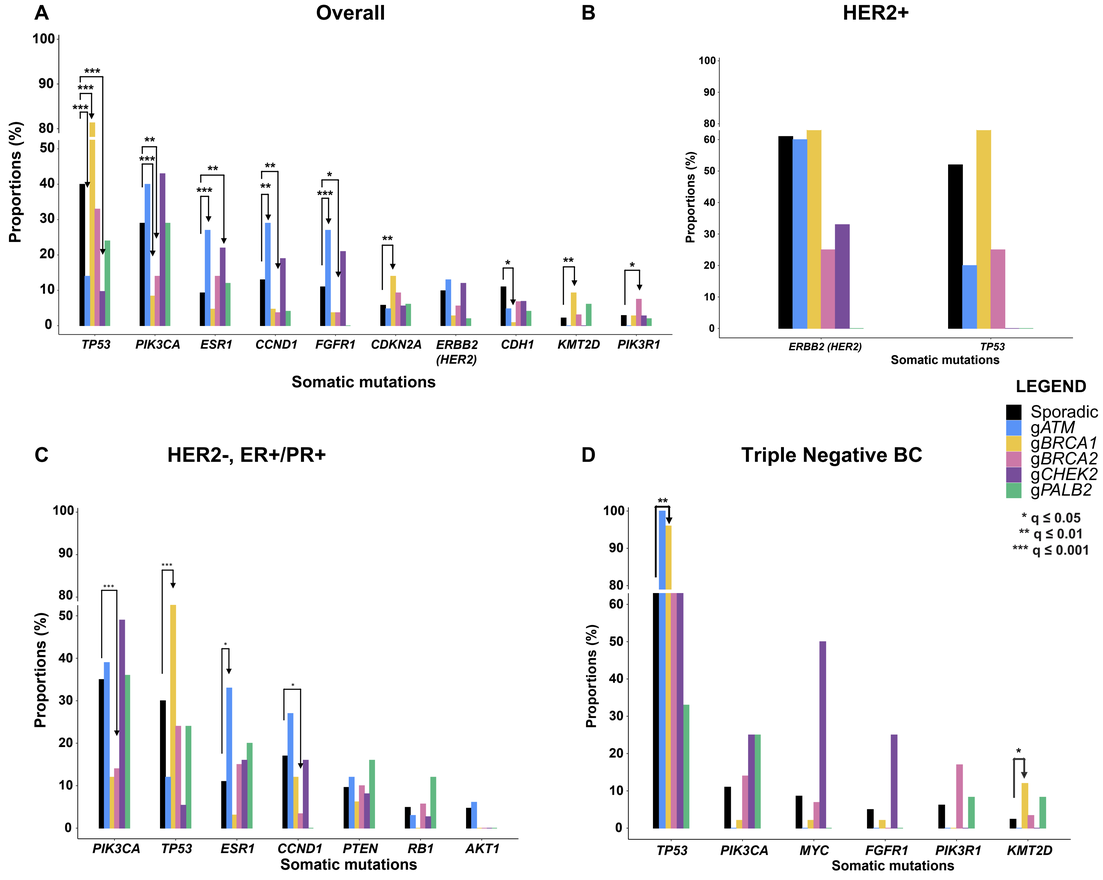
RESULTS

Table 1. Cohort Demographics

Characteristic	Overall, N = 7,533	sporadic, N = 7,081	*BRCA1*, N = 107	*BRCA2*, N = 161	*PALB2*, N = 49	*ATM*, N = 63	*CHEK2*, N = 72	p-value
Age at Diagnosis								<0.001
Median (IQR)	56 (46, 65)	56 (46, 65)	44 (35, 52)	51 (40, 60)	55 (49, 68)	51 (42, 61)	58 (49, 66)	
Gender								<0.001
Female	7,445 (99%)	7,008 (99%)	107 (100%)	149 (93%)	49 (100%)	62 (98%)	70 (97%)	
Male	85 (1.1%)	70 (1.0%)	0 (0%)	12 (7.5%)	0 (0%)	1 (1.6%)	2 (2.8%)	
Unknown	3	3	0	0	0	0	0	
Race								0.042
White	3,719 (73%)	3,514 (73%)	41 (65%)	68 (64%)	23 (70%)	32 (82%)	41 (87%)	
Black or African American	722 (14%)	688 (14%)	9 (14%)	18 (17%)	2 (6.1%)	4 (10%)	1 (2.1%)	
Asian	238 (4.7%)	220 (4.6%)	5 (7.9%)	7 (6.6%)	3 (9.1%)	2 (5.1%)	1 (2.1%)	
Other	416 (8.2%)	385 (8.0%)	8 (13%)	13 (12%)	5 (15%)	1 (2.6%)	4 (8.5%)	
Unknown	2,438	2,274	44	55	16	24	25	
Ethnicity								0.3
Not Hispanic or Latino	2,519 (84%)	2,376 (84%)	26 (79%)	61 (78%)	15 (71%)	16 (80%)	25 (83%)	
Hispanic or Latino	492 (16%)	453 (16%)	7 (21%)	17 (22%)	6 (29%)	4 (20%)	5 (17%)	
Unknown	4,522	4,252	74	83	28	43	42	
Smoking status								0.2
Never smoker	3,614 (65%)	3,421 (65%)	41 (55%)	70 (61%)	21 (60%)	33 (65%)	28 (53%)	
Current/former smoker	1,970 (35%)	1,835 (35%)	33 (45%)	45 (39%)	14 (40%)	18 (35%)	25 (47%)	
Unknown	1,949	1,825	33	46	14	12	19	
TMB								0.2
<10	6,593 (96%)	6,149 (96%)	105 (99%)	159 (99%)	48 (98%)	63 (100%)	69 (96%)	
>=10	242 (3.5%)	235 (3.7%)	1 (0.9%)	2 (1.2%)	1 (2.0%)	0 (0%)	3 (4.2%)	
Unknown	698	697	1	0	0	0	0	
Tumor receptor status								<0.001
ER+/PR+, HER2-	3,648 (63%)	3,433 (63%)	32 (38.6%)	88 (70.4%)	25 (64.1%)	33 (73.3%)	37 (74%)	
Triple-negative	1,297 (22.4%)	1,202 (22.1%)	48 (57.8%)	29 (23.2%)	12 (30.8%)	2 (4.5%)	4 (8%)	
HER2+	841 (14.6%)	809 (14.9%)	3 (3.6%)	8 (6.4%)	2 (5.1%)	10 (22.2%)	9 (18%)	
Unknown	1,747	1,637	24	36	10	18	22	

- The overall frequency of incidental germline PVs in each gene was 0.8% for g*ATM*, 1.4% for g*BRCA1*, 2.1% for g*BRCA2*, 1.0% for g*CHEK2*, and 0.7% for g*PALB2*.
- Among ER+/PR+, HER2- breast cancer, compared to sporadic tumors (Figure 1A):
  - *ESR1* mutations were significantly enriched in g*ATM* carriers (33% vs. 11 %, q-value 0.048),
  - *TP53* alterations were significantly enriched in g*BRCA1* PV carriers (69% vs. 30%, q-value < 0.001) but depleted in g*ATM* (12% vs. 30%, q-value 0.4) and g*CHEK2* PV carriers (5.4% vs. 30%, q-value 0.057)
  - *PIK3CA* (14% vs. 35%, q-value 0.001) and *CCND1* (3.4% vs. 17%, q-value 0.02) alterations were significantly lower in g*BRCA2* PV carriers.
- Among triple-negative breast cancer, compared to sporadic tumors (Figure 1B), *TP53* alterations were significantly higher in g*BRCA1* PV carriers compared to sporadic tumors (96% vs. 69%, q-value 0.004)

Figure 1. Proportion of Mutations According to BC Type



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