Intrinsic Subtype Distributions Across Inherited Breast Cancer Genes: An Opportunity to Refine Treatment

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INTRODUCTION

- 5-10% of breast cancers are inherited, primarily due to germline pathogenic/likely pathogenic variants (GPVs) in inherited DNA repair pathway genes, such as *BRCA1*, *BRCA2*, *PALB2*, *ATM* and *CHEK2*.
- We compared intrinsic breast cancer subtypes among females with GPVs in these genes and conduct subgroup analyses among hormone receptor (HR) subtypes including HR positive (estrogen and/or progesterone receptor positive), HER2 negative (HER2-), or HR-/HER2- breast cancers compared to sporadic breast cancers.

METHODS

Breast Cancer Patients
N = 4,972

Molecular profiling with Tempus xT tumor normal matched or tumor-only assay*

- Inclusion Criteria:
  - › GPVs in *BRCA1*, *BRCA2*, *PALB2*, *ATM* or *CHEK2* detected incidentally the xT assay or a validated germline test
  - › Tumor testing including whole transcriptome RNA expression analysis.
- Exclusion Criteria:
  - › GPV in more than one of the above-mentioned genes

Molecular Subtyping:

- PAM50 subtyping conducted to determine intrinsic subtypes (i.e., Luminal A, Luminal B, Basal, HER2-enriched).

Analyses:

- Intrinsic subtype distribution was compared across the 5 inherited breast cancer genes and to sporadic cases.
  - › In the overall cohort
  - › In the subgroup with HR+/HER2- disease

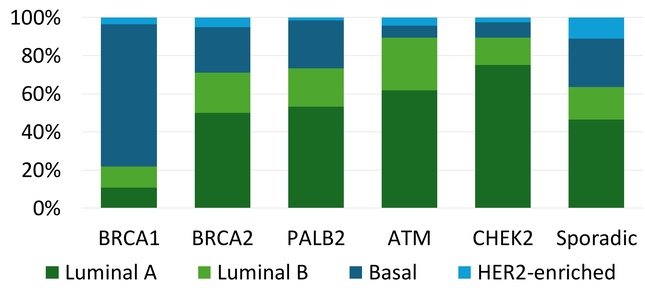
*Tempus xT assay - a targeted panel that detects single nucleotide variants, insertions and/or deletions, and copy number variants in 598-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.
** Statistical Analysis - Statistical comparisons were conducted using the Kruskal-Wallis rank sum test for continuous variables and the Pearson's Chi-squared test or Fisher's exact test for categorical variables, with false discovery rate (FDR) correction for multiple testing applied where appropriate.

RESULTS

Table 1: Demographic and Clinical Characteristics of the Study Population

	Overall N=4,988	Sporadic N=4,553	*BRCA1* N=98	*BRCA2* N=126	*PALB2* N=74	*ATM* N=54	*CHEK2* N=83
Age at Diagnosis, Median (IQR)	56 (47, 65)	57 (47, 65)	47 (37, 58)	49 (39, 58)	53 (46, 60)	52 (42, 60)	57 (49, 64)
Race							
White	2,532 (73%)	2,277 (73%)	54 (68%)	62 (67%)	51 (82%)	32 (84%)	56 (89%)
Black	487 (14%)	447 (14%)	14 (18%)	17 (18%)	3 (4.8%)	4 (11%)	2 (3.2%)
Other	294 (8.5%)	269 (8.6%)	7 (8.9%)	8 (8.6%)	5 (8.1%)	1 (2.6%)	4 (6.3%)
Asian	161 (4.6%)	146 (4.7%)	4 (5.1%)	6 (6.5%)	3 (4.8%)	1 (2.6%)	1 (1.6%)
Unknown	*1,514*	*1,414*	*19*	*33*	*12*	*16*	*20*
Stage							
Early (Stage I-III)	942 (19%)	753 (16.5%)	50 (51%)	45 (36%)	44 (59%)	15 (28%)	35 (42%)
Late (Stage IV)	4,046 (81%)	3,800 (83.5%)	48 (49%)	81 (64%)	30 (41%)	39 (72%)	48 (58%)
Intrinsic Subtype							
Luminal A	1,810 (47%)	1,631 (46%)	9 (11%)	50 (50%)	34 (53%)	29 (62%)	57 (75%)
Luminal B	669 (17%)	602 (17%)	9 (11%)	21 (21%)	13 (20%)	13 (28%)	11 (14%)
Basal	1,006 (26%)	895 (25%)	62 (75%)	24 (24%)	16 (25%)	3 (6.4%)	6 (7.9%)
HER2-enriched	404 (10%)	391 (11%)	3 (3.6%)	5 (5%)	1 (1.6%)	2 (4.3%)	2 (2.6%)
Unknown	*1,099*	*1,034*	*15*	*26*	*10*	*7*	*7*
Receptor Status							
HR+/HER2-	2,500 (64%)	2,271 (64.6%)	26 (30%)	69 (68%)	48 (73%)	31 (76%)	50 (77%)
HR-/HER2-	855 (22%)	757 (21.5%)	56 (65%)	24 (24%)	13 (20%)	1 (2%)	3 (5%)
HER2+	57 (14%)	489 (13.9%)	4 (5%)	8 (8%)	5 (8%)	9 (22%)	12 (18%)
Unknown	*1,112*	*1,036*	*12*	*25*	*8*	*13*	*18*

Figure 1: Distribution of Subtypes Across Breast Cancers

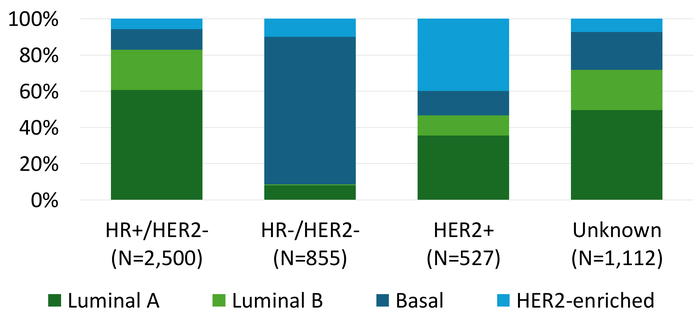


- As shown in **Figure 1**, the distribution of the four intrinsic subtypes showed:
  - › Basal subtype encompassed a majority in *BRCA1* carriers (75%) and was less common in *ATM* (6.4%) and *CHEK2* (7.9%) carriers.
  - › Luminal A subtype encompassed a higher proportion in *ATM* (62%) and *CHEK2* (75%) carriers, compared to *PALB2* (53%), *BRCA2* (50%) and *BRCA1* (11%) carriers.
- As shown in **Table 2**, among the HR+ subgroup, Basal and Luminal B subtypes were over-represented among *BRCA1* tumors (45%; n=10 and 32%; n=7, respectively) compared to sporadic tumors (11%; n=207 and 22%; n=398 respectively). Among the HR+ Luminal A subtype, *CHEK2* tumors were over-represented (80%; n=37) while *BRCA1* tumors were under-represented (23%; n=5), compared to sporadic tumors (60%; n=1093).

Table 2: Distribution of Subtypes in HR+ Breast Cancers

	BRCA1 N=22	*BRCA2* N=58	*PALB2* N=43	*ATM* N=29	*CHEK2* N=46	Sporadic N=1,813
Intrinsic Subtype						
Luminal A	5 (23%)	39 (67%)	28 (65%)	19 (66%)	37 (80%)	1,093 (60%)
Luminal B	7 (32%)	12 (21%)	11 (26%)	9 (31%)	7 (15%)	398 (22%)
Basal	10 (45%)	5 (8.6%)	4 (9.3%)	1 (3.4%)	2 (4.3%)	207 (11%)
HER2-enriched	-	2 (3.4%)	-	-	-	115 (6.3%)

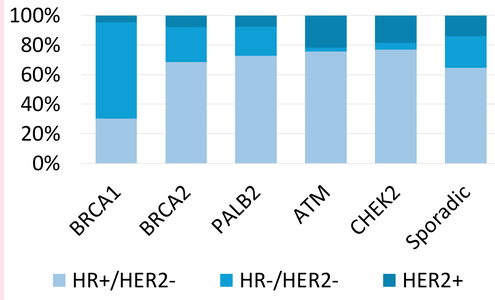
Figure 2: Distribution of Subtypes by Receptor Status



RESULTS

- As shown in **Figure 4**, triple-negative breast cancers (HR-/HER2-) were overrepresented in *BRCA1* carriers (65%) while HR+/HER2- breast cancers were overrepresented in *BRCA2*, *PALB2*, *ATM*, and *CHEK2* carriers (68%, 73%, 76%, and 77%, respectively).

Figure 4: Distribution of Receptor Status Across Breast Cancers



CONCLUSIONS

- Our findings demonstrate significant differences in the distribution of intrinsic subtypes across inherited breast cancer genes, with:
  - › Basal subtype seen predominantly in *BRCA1* carriers and under-represented in both *ATM* and *CHEK2* carriers.
  - › Among the HR+ subgroup, the Basal subtype remained over-represented in *BRCA1* carriers and the Luminal B subtype was also over-represented.
- Identification of non-Luminal A tumors based on intrinsic subtyping may be of both prognostic and predictive importance, with consideration of more aggressive treatment.
- Consequently, our findings highlight the importance of intrinsic tumor subtyping to identify aggressive tumors over-represented among females with inherited breast cancer due to *BRCA1*, *BRCA2*, and *PALB2* GPVs.

FUTURE DIRECTIONS

- Analysis of somatic mutation profiles underway
- Survival analysis by gene/subtype underway

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