Whole transcriptomic analysis of HR+ breast cancer in Black women classified as Basal-Type by BluePrint

Sonya Reid[1], Tuya Pal[1], Xiao-Ou Shu[1], Ann L. Tezak[1], Kent Hoskins[2], Dipali Sharma[3], Jennifer Wei[4], Yen Huynh[4], Shiyu Wang[4], Josien Haan[5], Andrea Menicucci[4], Patricia Dauer[4], William Audeh[4], FLEX Investigators Group

1. Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; 2. Division of Hematology/Oncology, University of Illinois at Chicago, Chicago, IL; 3. Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; 4. Agendia Inc., Irvine, CA; 5. Agendia NV, Amsterdam, Netherlands

Background

- Breast cancer is now the leading cause of cancer-associated deaths among Black women, and they are 41% more likely to die from breast cancer compared with White women[a,b]. Few studies have evaluated if tumor biology differences contribute to this disparity in outcomes.
- BluePrint, an 80-gene molecular subtyping assay categorizes tumors as Luminal, HER2, or Basal-Type. Together with MammaPrint, a 70-gene assay that determines the risk of distant recurrence, tumors are classified as Luminal A or Luminal B. Similar to triple negative breast cancer (**TNBC**), hormone receptor-positive (**HR+**) tumors classified by BluePrint as Basal-Type (HR+/Basal) are more aggressive, higher grade, are over-represented among young Black women and have worse clinical outcomes[c].
- TNBC is associated with low ACKR1 expression, which encodes the Duffy antigen and correlates with worse breast cancer outcomes[d,e].
- Given the over-representation and worse outcomes among Black women with HR+/Basal tumors, we compared differentially expressed genes (**DEGs**) by race and subtype.

Methods

Patients: This study includes 455 Black women and 2202 White women (reference group) with stage **I-III** breast cancer (N = 2657). All patients received BluePrint testing and are participants of the ongoing BEST study (5R01CA204819) at Vanderbilt University Medical Center or FLEX study (NCT03053193).

Molecular Classification: Of the 455 included Black women, 315 had Luminal B (HR+/Luminal) and 140 had Basal tumors (66 HR+/Basal and 74 HR-/Basal). White women within FLEX (n = 2202) were included as a reference group with HR+/Luminal (n = 1825), HR+/Basal (n = 158), or HR-/Basal (n = 219) tumors.

Whole Transcriptome analysis: Differential gene expression analysis (**DGEA**) was performed using Limma R package. Black and White women were age-matched, resulting in 314 HR+/Luminal, 66 HR+/Basal and 74 HR-/Basal tumors within each race included in the DGEA. Significant DEGs had an adjusted p-value < 0.05 and absolute log2 fold change > 1.

Statistical analysis: Two-tailed proportional z-test was used to assess differences in subtype proportion by race.

Results

Figure 1. Frequency of BluePrint molecular subtype and HR status among Black and White women

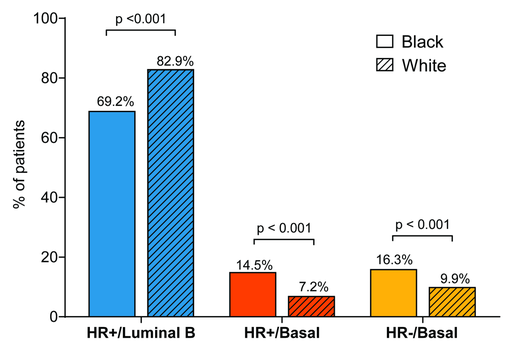
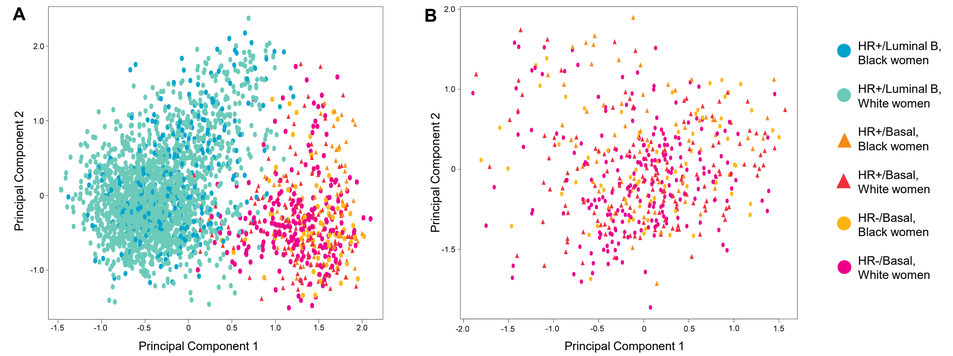


Figure 2. Multidimensional scaling plots colored by race and all BluePrint subtypes (A) and within BluePrint Basal-Type breast cancer (B)



- Black women had a significantly higher proportion of HR+/Basal (14.5%; p < 0.001) and HR-/Basal (16.3%; p < 0.001) tumors compared to White women (7.2% and 9.9%, respectively) (**Figure 1**).
- In a multidimensional scaling analysis, HR+/Basal tumors cluster with HR-/Basal (TNBC) rather than with HR+/Luminal tumors (**Figure 2A**). Within BluePrint Basal tumors, there is no distinct clustering between HR status and/or race (**Figure 2B**).

Figure 3. Differential gene expression in Black women for all groups (A), within Luminal B vs. HR+/Basal breast cancer (B) , and within HR+/Basal vs. HR-/Basal breast cancer (C) . Significant DEGs are indicated by color: upregulated genes are blue and downregulated genes are red.

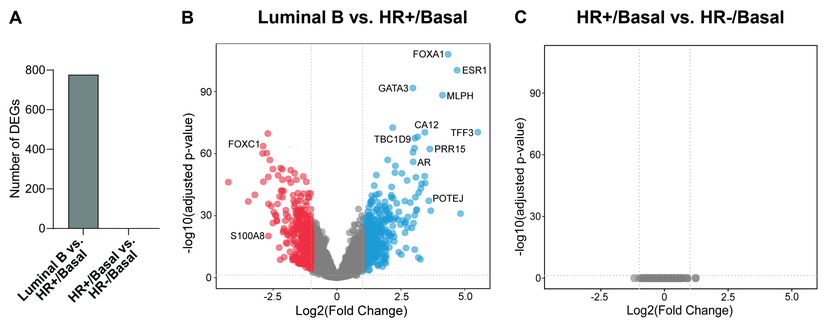
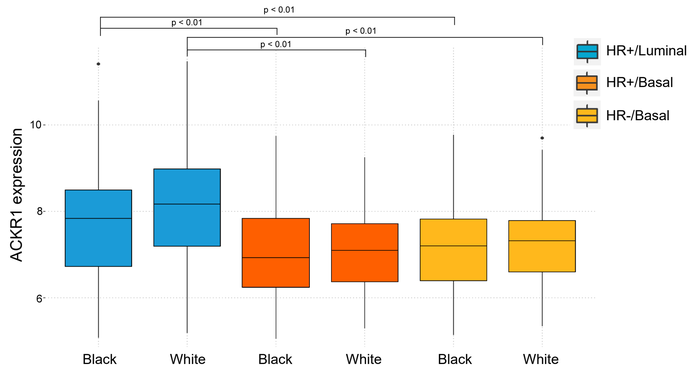


Figure 4. Duffy gene (ACKR1) expression in Black and White women by HR status and BluePrint subtype. Adjusted p-values for each comparison are in the table.



- While a DGEA comparing HR+/Basal with HR+/Luminal tumors resulted in over 700 DEGs within Black women (**Figure 3A**), no DEGs were identified when comparing HR+/Basal tumors with HR-/Basal (**Figure 3B**).
- ACKR1 expression was significantly higher in White women with HR+/Luminal tumors than Black women. In contrast, ACKR1 expression in HR+/Basal tumors was comparable to HR-/Basal tumors, regardless of race (**Figure 4**).

Conclusions

In this racially diverse cohort, transcriptomic analyses suggest that **HR+/Basal tumors are biologically analogous to TNBC, independent of race**. Molecular profiling identified racial disparities in the proportion of HR+/Basal tumors and underscores the need for diverse representation in clinical trials. With an over-representation of HR+/Basal tumors in Black women and evidence of worse outcomes, these data suggest that patients with HR+/Basal tumors should not be treated uniformly with HR+/Luminal tumors and highlight the importance of further genomic classification for patients with HR+ tumors.

References

a. Giaquinto et al. CA Cancer J Clin, 2022.
b. Siegel et al. CA Cancer J Clin, 2022.
c. Reid et al. SABCS, 2021.
d. Jenkins et al. Cancer Epidemiol Biomarkers Prev, 2019.
e. Martini et al. Sci Reports, 2021.

ASCO 2022 Abstract #517