Genomic Drivers of Racial Disparity in HR-Positive Early Breast Cancer

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Background

- African American (AA) women with hormone-receptor positive (HR+) breast cancer experience the greatest disparity in survival of all breast cancer subtypes. Later stages of diagnoses have been attributed to racial differences in social determinants of health[1]. Nearly all breast cancer disparities research has focused on triple-negative breast cancer (TNBC) among Black women, but HR+ breast cancer is three times more common than TNBC.
- AA women with HR+, early-stage breast cancer (EBC) are 80% more likely to die and 30% more likely to have biologically aggressive HR+ tumors compared with Non-Hispanic White (NHW) women[2].
- Genomic sub-typing studies of HR+ EBC reveal that compared with NHW women, AA women have a higher prevalence of the aggressive luminal B and HR+ basal subtypes. However, the molecular mechanisms underlying this racial difference are unknown.
- We analyzed genomic profiles of HR+/HER2- primary tumors in a diverse cohort of EBC patients to identify molecular drivers of the aggressive HR+ tumor phenotype that disproportionately affects AA women.

Introduction

- The molecular drivers of aggressive tumor biology in HR+ EBC in AA women are yet to be comprehensively elucidated. The goal of this study is to continue to identify genetic biomarkers associated with survival disparity in early-stage, HR+ breast cancer among US AA women.

Methods

- HR+/HER2- EBC treated at the University of Illinois Chicago (UIC) between 2018-2021 underwent NGS profiling of the primary tumor in the Laboratory of Genomic Medicine at UIC for DNA and RNA somatic driver alterations with the Oncomine Comprehensive Assay v3 (OCAv3), which includes 161 driver genes and detects SNVs, CNVs, indels, and gene fusions.
- Enrichment of alterations according to self-identified race was tested with Fisher's exact tests and odds ratios with 95% confidence intervals (CI). Publicly available data from The Cancer Genome Atlas (TCGA) was downloaded from the Genomic Data Commons portal (https:/ portal.gdc.cancer.gov) to validate findings.

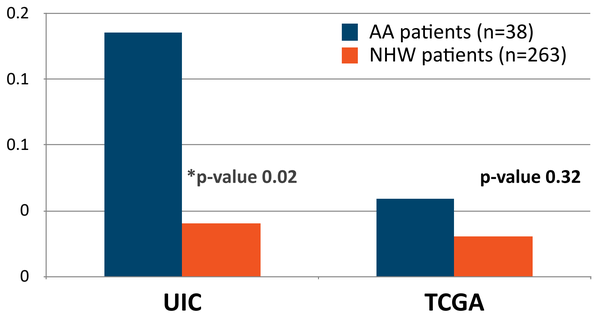
Gene	AA patients (n=72)	NHW patients (n=56)	Odds ratio (95% CI)	P-value
ARID1A (SNV)	16.7%	3.6%	5.4 (1.24-24.9)	**0.02**
ATM (SNV)	12.5%	1.8%	7.9 (1.19-87.6)	**0.04**
CCND1 (CNV)	15.3%	16.7%	0.94 (0.36-2.3)	> 0.99
ERBB2 (SNV)	12.5%	5.4%	2.5 (0.7-8.9)	0.22
PIK3CA (SNV)	51%	71%	0.42 (0.20-0.90)	**0.03**
TP53 (SNV)	9.7%	25.0%	0.32 (0.13-0.83)	**0.03**

Table 1. Frequency of driver gene alterations according to race.

Results

- In total, 128 primary tumors were evaluated (Black, n=72; non-Black, n=56). Results for the most prevalent alterations are presented Table 1.
- Inactivating SNVs and indels in ARID1A and ATM were more common in tumors from Black patients.
- Results of analyses for associations between neighborhood- and individual-level indicators of disadvantage and tumor genomic profile, and validation is demonstrated via comparison with TCGA data as seen in Graph 1.

Graph 1: ARID1A alteration frequency comparison between UIC and TCGA data.



Discussion

- Inactivation of ARID1A (a key component of the SWI/SNF chromatin remodeling complex) in HR+ breast cancer cells leads to loss of luminal identity, switch to an estrogen-independent basal-like phenotype, and resistance to endocrine therapy[3].
- Enrichment of ARID1A somatic driver mutations in HR+/HER2- tumors from Black patients with EBC provides a mechanistic explanation for the higher rate of HR+ basal tumors in that population.
- This finding along with the higher rate of ATM alterations can inform development of targeted therapeutic strategies designed to mitigate racial disparity in EBC survival.

Future Directions

- This preliminary study demonstrates promising targets which essential in HR-positive early breast cancer in AA women. Larger cohort studies will be needed to validate these findings.
- We further aim to look into indicators of neighborhood disadvantage through geocoding residential addresses and linking to census tract measures of the social and environmental context to examine associations between tumor genomic profile and neighborhood contextual factors.

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