Genomic and transcriptomic comparison between breast cancer patients of African and European ancestries demonstrates potential for biomarker-informed therapies

Abstract #: 766

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INTRODUCTION

Therapies for breast cancer (BC) are informed by tumor subtypes and molecular heterogeneity. While patients of African ancestry (AA) exhibit a high mortality rate compared with patients of European ancestry (EA), the biological underpinnings of this disparity are not entirely understood.

Here, we present a genomic and transcriptomic comparison between BC tumors from AA and EA patients stratified by BC subtype and clinical stage in a real-world cohort.

METHODS

- De-identified records from AA (n=623) and EA (n=2810) patients with BC were selected from the Tempus Database (**Table 1**). All tumors underwent sequencing with the Tempus xT or xE assay, including targeted-panel DNA and/or full-transcriptome RNA-seq.
- Ancestry was estimated from DNA-seq data.
- Mutational prevalence, gene expression, and gene set enrichment (hallmark and oncogenic signature sets) were compared between EA and AA groups.
- All comparisons were stratified by stage and BC subtype, HR+/HER2- and triple-negative breast cancer (TNBC).

Characteristic	African Ancestry Samples (N=623)	European Ancestry Samples (N=2810)
Median Age (years)	53.74	56.01
Stage, n (%)		
0	0 (0.00)	1 (0.04)
I	11 (1.77)	92 (3.27)
II	48 (7.70)	152 (5.41)
III	45 (7.22)	193 (6.87)
IV	519 (83.31)	2372 (84.41)
Subtype, n (%)		
HR+/HER2-	221 (35.47)	1281 (45.59)
Triple-Negative	143 (22.95)	400 (14.23)
Other	259 (41.57)	1129 (40.18)
Tumor Grade, n (%)		
Low	163 (26.16)	980 (34.88)
High	354 (56.82)	1198 (42.63)
Unknown	106 (17.01)	632 (22.49)

Table 1. Demographics and clinical characteristics of the cohort.

SUMMARY

In HR+/HER2- and triple-negative breast cancers, we observed significant differences in mutational spectrums and gene expression between genetically determined African and European ancestries. Gene sets were differentially enriched by ancestry in HR+/HER2- but not triple-negative breast cancers. These findings may support future biomarker-informed research and, ultimately, precision cancer care.

RESULTS

Prevalence of BC-Related Mutations Differ Between AA and EA Patients

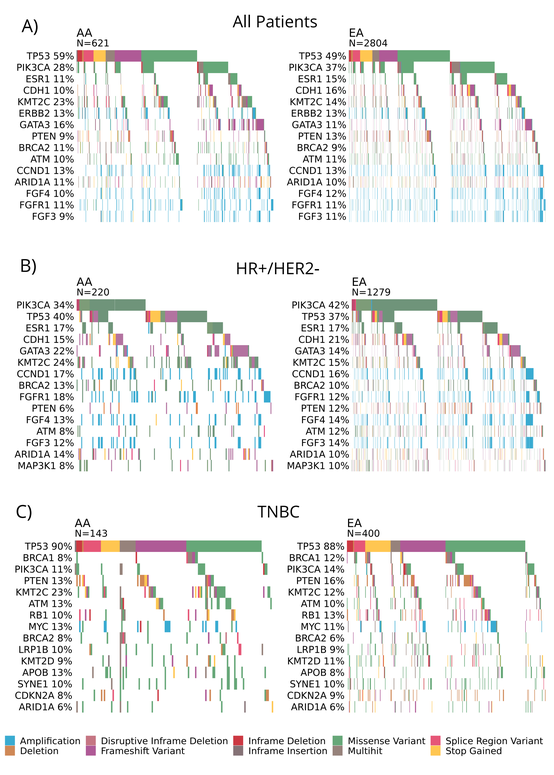

Figure 1. Mutational landscape separated by AA or EA and subtypes. Oncoplots show the top 15 pathogenic mutations in A) all patients (AA n=621, EA n=2,804), B) patients with HR+/HER2- disease (AA n=220, EA n=1279), and C) patients with TNBC (AA n=143, EA n=400).

- *TP53* was most commonly mutated and was significantly more prevalent in AA (60%) than EA (49%) patients (*P*=2.37e-06).
- *PIK3CA* was the second most prevalent and significantly more frequent in EA (37%) vs. AA (28%) patients *(P*=2.08e-05*)*.
- *KMT2C* occurred at significantly higher rates in AA (23%) vs. EA (14%) patients (*P*=1.65e-08).

BC-Related Genes are Differentially Expressed Between AA and EA Patients

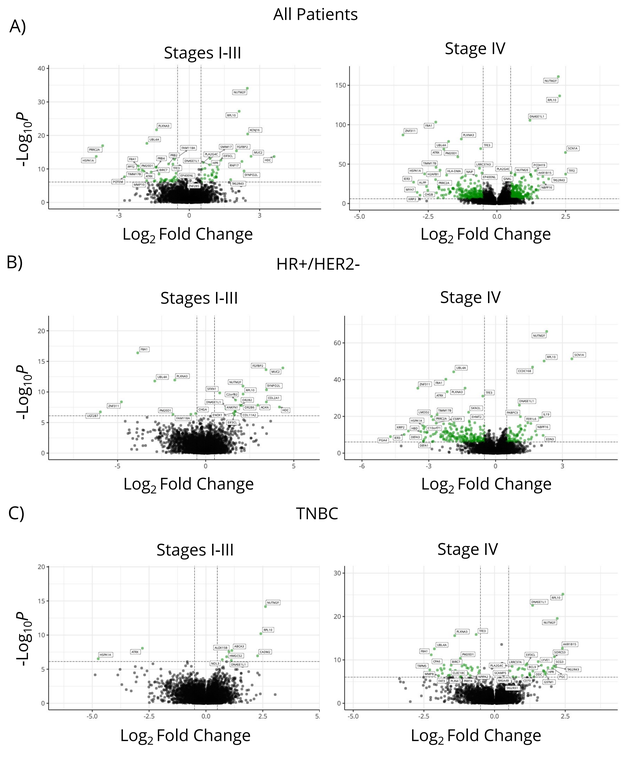

Figure 2. Differentially expressed genes between AA and EA for A) all patients (n=3,433), B) patients with HR+/HER2- disease (n=1,502), and C) patients with TNBC (n=543), stratified by stage. Genes are plotted by log fold changes in expression and meta *P*-values, with the EA population taken as a reference for fold changes. Bonferroni *P*-value cutoffs are *P*=1e-06 for all plots. Genes with significantly different enrichment are highlighted in green.

- Over 8,000 genes with significantly different expression between the two ancestral groups were identified.
- *RPL10* and *NUTM2F* were expressed higher in AA patients throughout every subtype and stage, whereas *HSPA1A* and *ATRX* were significantly lower in AA patients for both HR+/HER2- and TNBC.

BC-Related Gene Sets are Differentially Enriched between AA and EA patients in HR+/HER2-

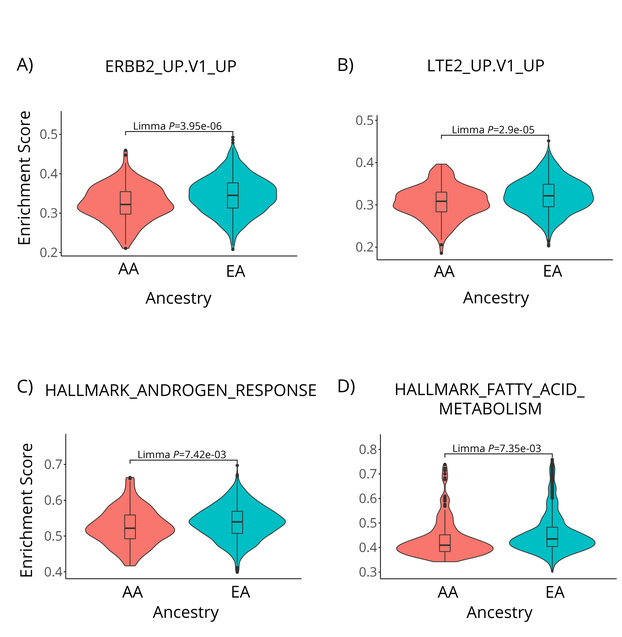

Figure 3. Among 64 differentially enriched gene sets between AA and EA patients with stage IV HR+/HER2- BC, four were considered particularly relevant to BC and are displayed above: A) ERBB2_UP.V1_UP, B) LTE2_UP.V1_UP, C) HALLMARK_ANDROGEN_RESPONSE, and D) HALLMARK_FATTY_ACID_METABOLISM. All data displayed are from stage IV, HR+/HER2- patient records (n=1,287).

- There were no significant differences between ancestral groups for stage III HR+/HER2- or any stage of TNBC (data not shown).

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