Racial disparities in breast cancer: identifying predisposing clinical and molecular features associated with African American patients

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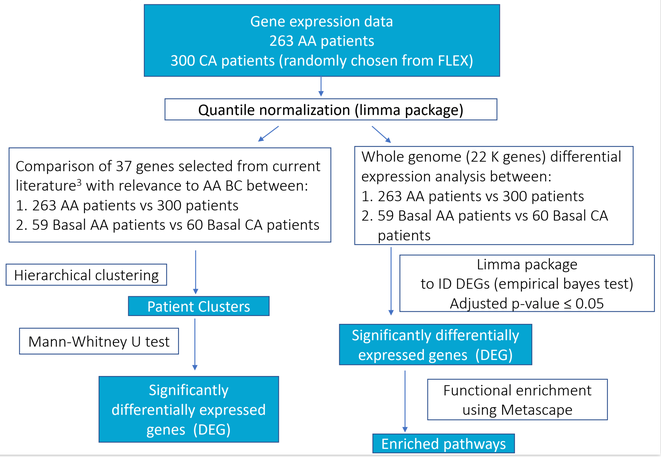
Background

Breast cancer (BC) mortality is higher in African-American women (AA) than in Caucasian women (CA)[1]. AA are also diagnosed at a younger age, have more aggressive subtypes, and greater incidence of metabolic dysfunction, such as obesity and diabetes[2]. These disparities have been attributed to a confluence of socioeconomic, genetic, and epigenetic factors[2]. However, the distinctive tumor biology of AA BC is not yet fully elucidated, as AA remain underrepresented in breast cancer studies and databases. Here, we compared clinical and molecular BC features of AA and CA patients for insights into mechanisms associated with these racial disparities.

Methods

The FLEX Registry Trial (NCT03053193) is an ongoing, prospective study evaluating primary tumor specimens collected from patients with stage I, II, or III BC who have consented to receive MammaPrint (MP) risk of recurrence and BluePrint (BP) molecular subtyping assays and clinically annotated full genome (FG) data. FLEX subset analyses investigate new gene expression profiles that may be relevant to BC biology. This sub-study includes 263 AA and 300 CA patients (n=563) enrolled since September 2017. As expected from variation in demographics, AA patients were primarily enrolled in the Southeast, Texas, and mid-Atlantic states. CA patients were selected in a random, unbiased manner using R software. Additionally, AA patients with basal-type tumors (n=59) were compared with randomly selected CA patients with basal-type tumors (n=60). Clinical characteristics used in the analysis include age, menopausal status, metabolic factors, tumor and nodal stage, histopathologic grade, and IHC results.



Clinical Characteristics

Clinical Characteristics (unknowns excluded)	Patient Ethnicity			
	AA (n=263)	CA (n=300)	Basal AA (n=59)	Basal CA (n=60)
Age, years				
Median	61	61	59	59
Mean	58.7	60.5	56.9	59.5
Menopausal Status				
Pre or Peri	56 (24%)	42 (15%)	10 (21%)	12 (21%)
Post	182 (76%)	232 (85%)	38 (79%)	45 (79%)
Tumor Stage				
T1	90 (55%)	121 (67%)	19 (49%)	18 (43%)
T2	58 (36%)	50 (28%)	17 (44%)	20 (48%)
T3	8 (5%)	6 (3%)	1 (3%)	4 (10%)
T4	6 (4%)	3 (2%)	2 (5%)	0 (0%)
Nodal Stage				
N0	113 (72%)	143 (81%)	31 (79%)	29 (69%)
N1	32 (21%)	28 (16%)	5 (13%)	10 (24%)
N2	8 (5%)	3 (2%)	1 (3%)	2 (5%)
N3	3 (2%)	2 (1%)	2 (5%)	1 (2%)
Grade				
G1	62 (25%)	92 (33%)	3 (5%)	2 (4%)
G2	96 (39%)	136 (48%)	3 (5%)	14 (26%)
G3	90 (36%)	53 (19%)	51 (89%)	37 (70%)
Tumor Type				
IDC	184 (71%)	226 (78%)	52 (88%)	54 (92%)
ILC	36 (14%)	32 (11%)	0	1 (2%)
Mixed IDC/ILC	10 (4%)	13 (5%)	1 (2%)	0
Other	29 (11%)	20 (7%)	6 (10%)	4 (6%)
ER status (IHC)				
Positive	219 (82%)	262 (93%)	21 (36%)	18 (32%)
Negative	48 (18%)	20 (7%)	37 (64%)	39 (68%)

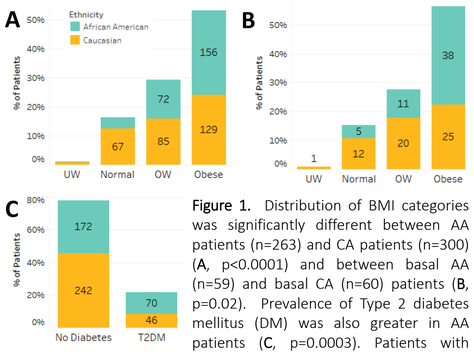
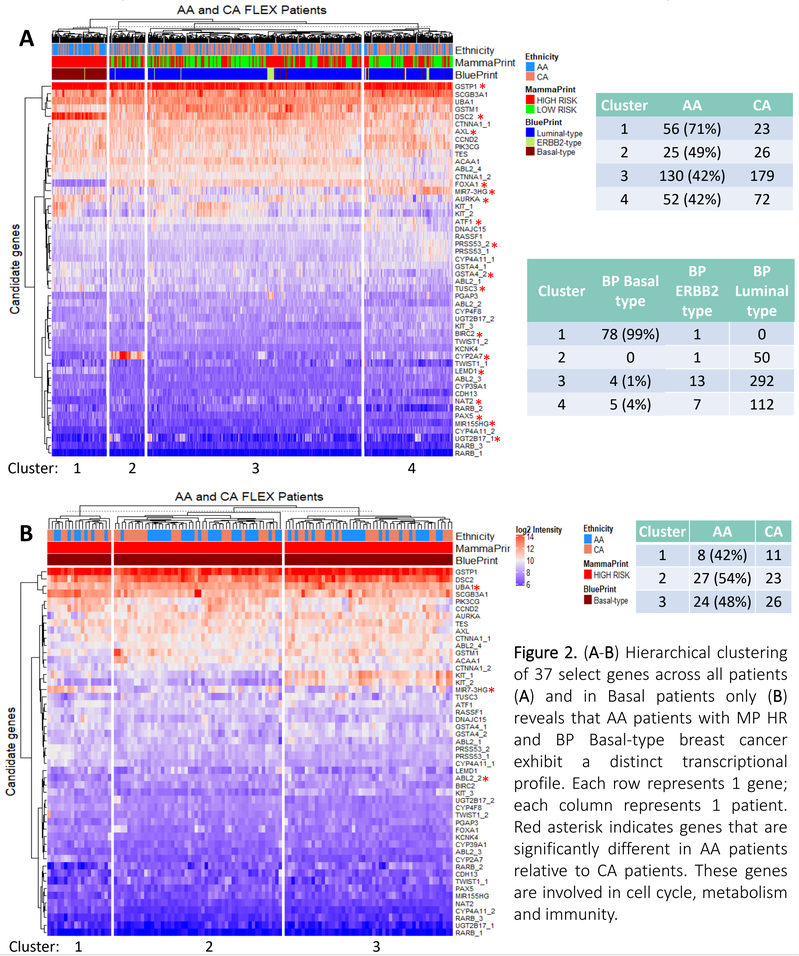


Figure 1. Distribution of BMI categories was significantly different between AA patients (n=263) and CA patients (n=300) (**A**, p<0.0001) and between basal AA (n=59) and basal CA (n=60) patients (**B**, p=0.02). Prevalence of Type 2 diabetes mellitus (DM) was also greater in AA patients (**C**, p=0.0003). Patients with unknown factors were excluded.

Gene expression differences between AA and CA patients



Cluster	AA	CA
1	56 (71%)	23
2	25 (49%)	26
3	130 (42%)	179
4	52 (42%)	72

Cluster	BP Basal type	BP ERBB2 type	BP Luminal type
1	78 (99%)	1	0
2	0	1	50
3	4 (1%)	13	292
4	5 (4%)	7	112

Cluster	AA	CA
1	8 (42%)	11
2	27 (54%)	23
3	24 (48%)	26

Figure 2. (**A**-**B**) Hierarchical clustering of 37 select genes across all patients (**A**) and in Basal patients only (**B**) reveals that AA patients with MP HR and BP Basal-type breast cancer exhibit a distinct transcriptional profile. Each row represents 1 gene; each column represents 1 patient. Red asterisk indicates genes that are significantly different in AA patients relative to CA patients. These genes are involved in cell cycle, metabolism and immunity.

Whole genome differential expression analysis in Basal AA vs Basal CA

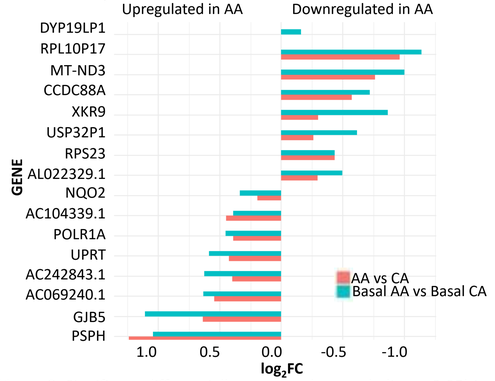


Figure 3. Significant differentially expressed genes (adj. p ≤ 0.05) in AA patients relative to CA patients (pink) and in Basal AA patients relative to Basal CA patients (green). These genes play a role in metabolism, translation, and cell signaling.

Conclusions

- AA BC patients were predominantly MP HR and BP Basal-type
- AA BC exhibits a distinct transcriptional profile compared to CA BC, which is characterized by dysregulation of cell proliferation and metabolism
- DEGs in Basal AA relative to Basal CA suggest ethnicity and/or other clinical characteristics, such as metabolic factors, play a role in BC progression in AA in addition to molecular subtype
- These data highlight how inclusion in genomic research can provide needed information on BC patients with AA ancestry. The majority (60%) of AA BC patients in this analysis were enrolled in Texas, Florida, and Georgia, which are also among those states with the highest AA populations[4]. This indicates that the prospective FLEX Registry is enrolling a diverse, real-world BC patient population
- This study identifies candidate genes for further study in elucidating the molecular biology of breast cancer in AA

References

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2. Siddharth and Sharma 2018. *Cancers*
3. Ahmad et al. 2017 *Biochim Biophys Acta*
4. Rastogi et al. 2011 US Census Bureau

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