Racial disparities within Basal-type breast cancer: clinical and molecular features of African American and Caucasian obese patients

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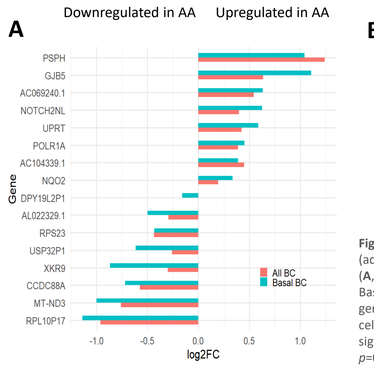
BACKGROUND

African American breast cancer (BC) patients (AA) are diagnosed at a younger age and present more frequently with triple-negative/Basal tumors than Caucasian American patients (CA) (1). High prevalence of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome in AA (2) may confound attempts to evaluate the influence of ancestry on gene expression patterns in BC. Previously we showed that differentially expressed genes (DEGs) between Basal subtype tumors of AA and CA were related to metabolism, translation, and cell signaling pathways (3). However, AA had higher rates of obesity and T2DM than CA, and we were unable to distinguish between the influence of metabolic factors and race/ancestry. In the current analysis, we aim to better understand these factors by comparing clinical and molecular features of Basal subtype breast tumors in obese AA and CA.



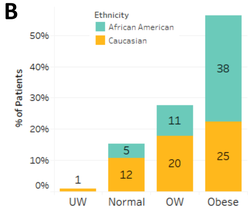


Figure 1.* Significant differentially expressed genes (adj. $p \leq 0.05$) in AA patients relative to CA patients (**A**, pink, all patients, regardless of subtype) and in Basal tumors of AA relative to CA (**A**, green). These genes play a role in metabolism, translation, and cell signaling. BMI category distribution was significantly different between Basal AA and CA (**B**, $p=0.02$) and DEGs were not stratified by obesity/T2DM status. **Presented previously at SABCS (3)*

METHODS

The prospective, observational FLEX Study (NCT03053193) includes stage I, II, and III breast cancer patients who receive 70-gene signature (MammaPrint, MP)/80-gene signature (BluePrint, BP) testing and consent to full transcriptome and clinical data collection. This interim sub-study included 50 AA and 96 CA (n=146), enrolled from 2017 to present, all obese by body mass index (BMI, ≥30) and whose tumors were MP High Risk and BP Basal subtype. AA were significantly younger (mean, 55 years) than CA (mean, 60 years, $p=0.02$); thus, an age distribution–matched subset (n=49 AA, n=49 CA) was added for comparison. Gene expression data were quantile normalized using R limma package; DEGs were compared between tumors in the following groups: (1) all AA (n=50) and CA (n=96), (2) AA and 3 random selections (RS) of CA (n=50 pairs), and (3) age-matched AA and CA (n=49 pairs).

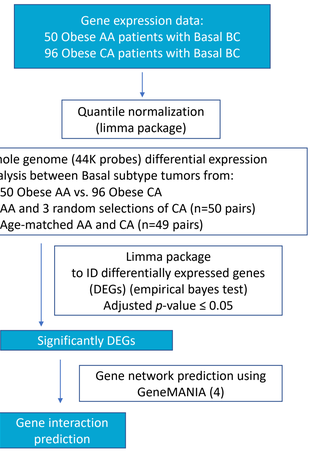
CLINICAL CHARACTERISTICS

Table 1	Patient Characteristics *(*unknowns excluded)*			
Patient Group	**Age, Mean**	**Age, Median**	**Pre/Peri-Menopausal**	**Post-Menopausal**
AA (n=50)	55.0	55	15 (36%)	27 (64%)
All CA (n=96)	60.4	63	13 (14%)	77 (86%)
p-value	**0.024**		**0.011**	
CA RS-1 (n=50)	59.4	59	7 (16%)	38 (84%)
p-value	0.08		**0.047**	
CA RS-2 (n=50)	60.8	61	5 (10%)	43 (90%)
p-value	**0.025**		**0.005**	
CA RS-3 (n=50)	60.6	60	7 (15%)	40 (85%)
p-value	**0.029**		**0.028**	

Tables 1-2. Compared with CA, AA with BluePrint Basal subtype tumors were significantly younger and more frequently pre/peri-menopausal in all patients and in three random selections (RS1-3) ($p<0.05$, **Table 1**). After adjusting for age, clinical-pathological factors, including tumor grade, tumor stage, ER status, nodal stage, and frequency of T2DM were not significantly different between AA and CA (**Table 2**).

Table 2	Age Group Match		
Patient Characteristics *(*unknowns excluded)*	**AA (n=49)**	**CA (n=49)**	***p*-value**
Age, Mean	55	55	0.988
Age, Median	55	57	
Menopausal Status			
Pre/Peri	15 (36%)	10 (22%)	0.164
Post	27 (64%)	36 (78%)	
Grade			
G1	1 (2%)	1 (2%)	0.381
G2	2 (4%)	5 (10%)	
G3	43 (94%)	34 (72%)	
GX	0	7 (15%)	
T stage			
T1	13 (45%)	12 (35%)	0.673
T2	11 (38%)	18 (53%)	
T3	3 (10%)	2 (6%)	
T4	2 (7%)	2 (6%)	
N stage			
N0	24 (77%)	23 (68%)	0.169
N1	5 (16%)	9 (26%)	
N2	0	2 (6%)	
N3	2 (6%)	0	
ER status (IHC)			
Positive	15 (32%)	22 (46%)	0.208
Negative	32 (68%)	26 (54%)	
Diabetes			
No evidence	36 (72%)	38 (76%)	1.00
Type 2 DM	10 (20%)	10 (20%)	
Unknown	4 (8%)	2 (4%)	

DEGs IN BASAL-TYPE TUMORS FROM OBESE AA AND CA



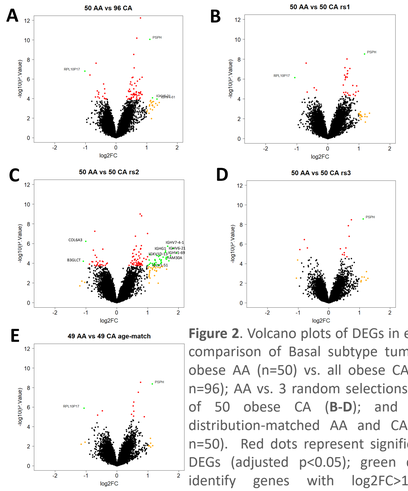


Figure 2. Volcano plots of DEGs in each comparison of Basal subtype tumors: obese AA (n=50) vs. all obese CA (**A**, n=96); AA vs. 3 random selections (rs) of 50 obese CA (**B-D**); and age distribution-matched AA and CA (**E**, n=50). Red dots represent significant DEGs (adjusted p<0.05); green dots identify genes with log2FC>1 + adjusted $p<0.05$; yellow dots signify genes with log2FC>1, but not statistically significant. Gene names are shown only for selected green dots.

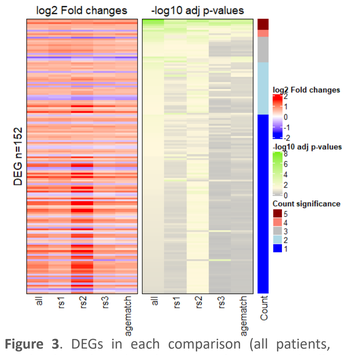


Figure 3. DEGs in each comparison (all patients, randomly selected subsets, and age-matched). There were 152 DEGs considering all comparisons together (115 gene upregulated in AA, 37 genes upregulated in CA).

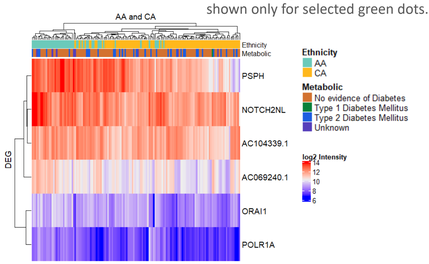


Figure 4. Across all comparisons, 6 genes were consistently more highly expressed in tumors of AA: *PSPH*, *NOTCH2NL*, *POLR1A*, AC069240.1 (MAP1LC3B pseudogene), *ORAI1*, and AC104339.1 (RPS26 pseudogene). These genes suggest upregulation of Notch-associated aggressiveness, which may be particularly relevant under hypoxic conditions (e.g., obesity) (5), and pathways associated with stemness, metastasis, and chemotherapy resistance (5-7).

MOLECULAR INTERACTION NETWORKS AMONG UPREGULATED GENES IN AA

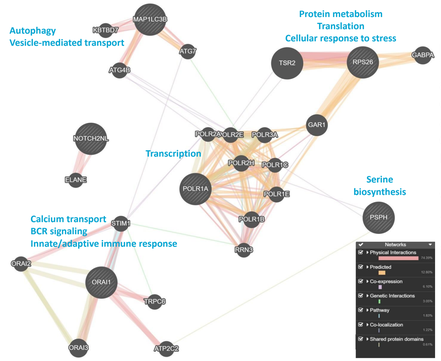


Figure 5. Network interactions among the 6 common DEGs in all comparisons. Of the 6 common DEGs (represented by the large nodes with gray lines) upregulated in Basal subtype tumors of AA patients, 5 were shown to be connected at the molecular level.

CONCLUSIONS

The current study aimed to distinguish between the influence of ancestry and obesity on breast tumor DEGs by matching clinical features. ***The results suggest disparities in AA breast cancer patients beyond those attributable to clinical and social factors prevalent within this population.***

- When controlling for clinical factors, including age and obesity, there were significant transcriptomic differences between AA and CA tumors, suggesting that ancestry contributes to these differences.
- These data demonstrate the need for greater representation of minority populations in BC clinical trials to inform treatment strategies and improve prognosis.
  - Most (66%) AA patients in this analysis were enrolled in Texas, Florida, and Georgia, all states with the highest AA populations in the US (9). This illustrates the diverse, real world BC population represented in the ongoing, prospective FLEX trial.

FUTURE DIRECTIONS

- The elucidation of ancestry-related biological heterogeneity is particularly important for patient subsets with clinical outcome disparities, such as AA BC patients. Further exploration of DEGs in the current study may help to identify novel therapeutic targets and improved treatment strategies specific for this patient population.
- Future studies in collaboration with the Center for Metabolism and Obesity Research at Johns Hopkins University School of Medicine will explore the biological pathways and molecular networks that may contribute to racial disparities in AA BC patients.

References

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