DISPARITIES WITHIN LUMINAL BREAST CANCER:
CLINICAL AND MOLECULAR FEATURES OF AFRICAN AMERICAN AND NON-HISPANIC WHITE PATIENTS

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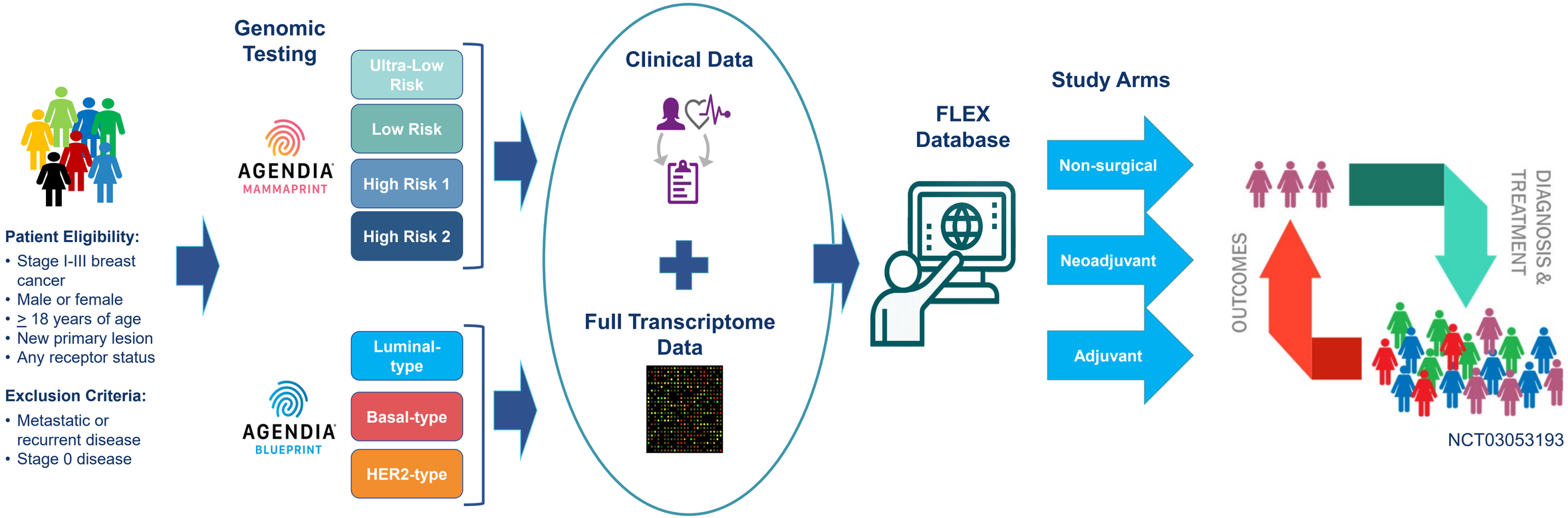
Background

- African American (AA) breast cancer patients are diagnosed younger, have more high-risk features, and have poorer clinical outcomes than non-Hispanic White patients (NHW).[1]
- The racial disparity in survival from hormone receptor (HR)-positive breast cancer persists after adjustment for AJCC stage and treatment,[2-5] suggesting disproportionately aggressive biology in tumors arising in AA women.
- We previously reported differentially expressed genes (DEGs) associated with tumor aggressiveness in Basal tumors from AA compared with NHW patients (Sharma et al., 2020).[3]
- In the current study, we compare DEGs in Luminal tumors between AA and NHW women enrolled in the multicenter FLEX study.

1. Daly B, Olopade O. 2015. *CA Cancer J Clin*
2. Rauscher GH, et al. 2017. *Breast Cancer Res Treat*
3. John EM, et al. 2021 Cancer Epidemiol Biomarkers Prev
4. Hoskins KF, et al. 2021 *JAMA Oncology*
5. Schneider BP, et al. 2017 JCO Precis Oncol
6. Sharma et al. 2020 *SABCS20-PS7-68*

FLEX Study Overview

FLEX is an adaptable real world evidence trial designed to support investigator-initiated breast cancer research through the curation of paired full transcriptome and clinical data



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Methods

Whole genome microarray data (44k) of 913 patients

Differential expression analysis

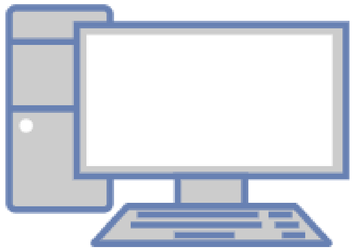
Empirical bayes test between:

1. Luminal	412 AA	vs	412 NHW
2. Luminal A	172 AA	vs	172 NHW
3. Luminal B	240 AA	vs	240 NHW
4. Luminal A Obese	50 AA	vs	50 NHW
5. Luminal B Obese	84 AA	vs	84 NHW

Differential expressed genes (DEGs)

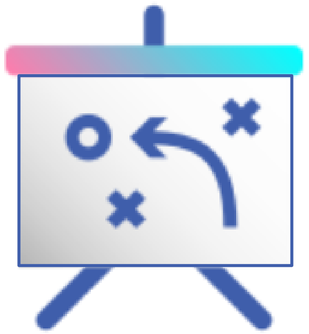
DEG defined as a gene with adjusted p-value <0.05

(Benjamini-Hochberg multiple test correction)



Gene set enrichment analysis (GSEA)

KEGG pathways and Hallmark gene sets using the same adjusted p-value threshold as used for the DEGs



Clinical Data

	All Luminal (age-matched)		
MammaPrint Risk	**AA (n=412)**	**NHW (n=412)**	***p*-value**
Low Risk (Luminal A)	172 (42%)	215 (52%)	**0.003**
High Risk (Luminal B)	240 (58%)	197 (48%)	

- Tumors from AA patients were more often MP High Risk, regardless of age-matching
- BMI, T2DM, and LN involvement were significantly different in AA vs. NHW patients
- In an all-obese subset analysis, T2DM rate trended higher in Luminal A AA (37%) than NHW (17%) patients but similar in Luminal B patients

	MP Low Risk (age-matched)			MP High Risk (age-matched)		
Patient Characteristics *(*unknowns excluded)*	**AA (n=172)**	**NHW (n=172)**	***p*-value**	**AA (n=240)**	**NHW (n=240)**	***p*-value**
Menopausal Status						
Pre/Peri	34 (21%)	32 (19%)	0.68	56 (25%)	61 (27%)	0.83
Post	126 (79%)	134 (81%)		165 (75%)	168 (73%)	
BMI Category						
Lean/Normal weight (<24.5)	20 (12%)	50 (31%)	**<0.0001**	19 (9%)	69 (30%)	**<0.0001**
Overweight (24.5-29.9)	47 (29%)	53 (32%)		58 (26%)	72 (31%)	
Obese (≥30.0)	95 (59%)	60 (37%)		143 (65%)	92 (39%)	
Diabetes Status						
No evidence	110 (72%)	142 (89%)	**0.0002**	155 (71%)	197 (88%)	**<0.0001**
Type 2 DM	43 (28%)	18 (11%)		64 (29%)	27 (12%)	
Grade						
G1	71 (47%)	69 (45%)	0.913	30 (14%)	37 (17%)	0.662
G2	74 (49%)	78 (51%)		121 (57%)	123 (57%)	
G3	6 (4%)	7 (4%)		61 (29%)	57 (26%)	
T stage						
cT1	77 (75%)	64 (71%)	0.310	70 (51%)	84 (62%)	0.130
cT2	24 (24%)	22 (24%)		54 (40%)	45 (33%)	
cT3 / cT4	1 (1%)	4 (5%)		12 (9%)	6 (5%)	
N stage						
cN0	76 (84%)	79 (92%)	0.113	83 (67%)	104 (81%)	**0.034**
cN1	13 (14%)	7 (8%)		33 (27%)	23 (18%)	
cN2/cN3	2 (2%)	0		7 (6%)	2 (1%)	
Tumor Type						
IDC	107 (67%)	128 (78%)	0.064	179 (81%)	177 (77%)	0.249
ILC	34 (21%)	26 (16%)		26 (12%)	26 (11%)	
Mixed or Other Type	20 (12%)	11 (6%)		15 (7%)	26 (12%)	

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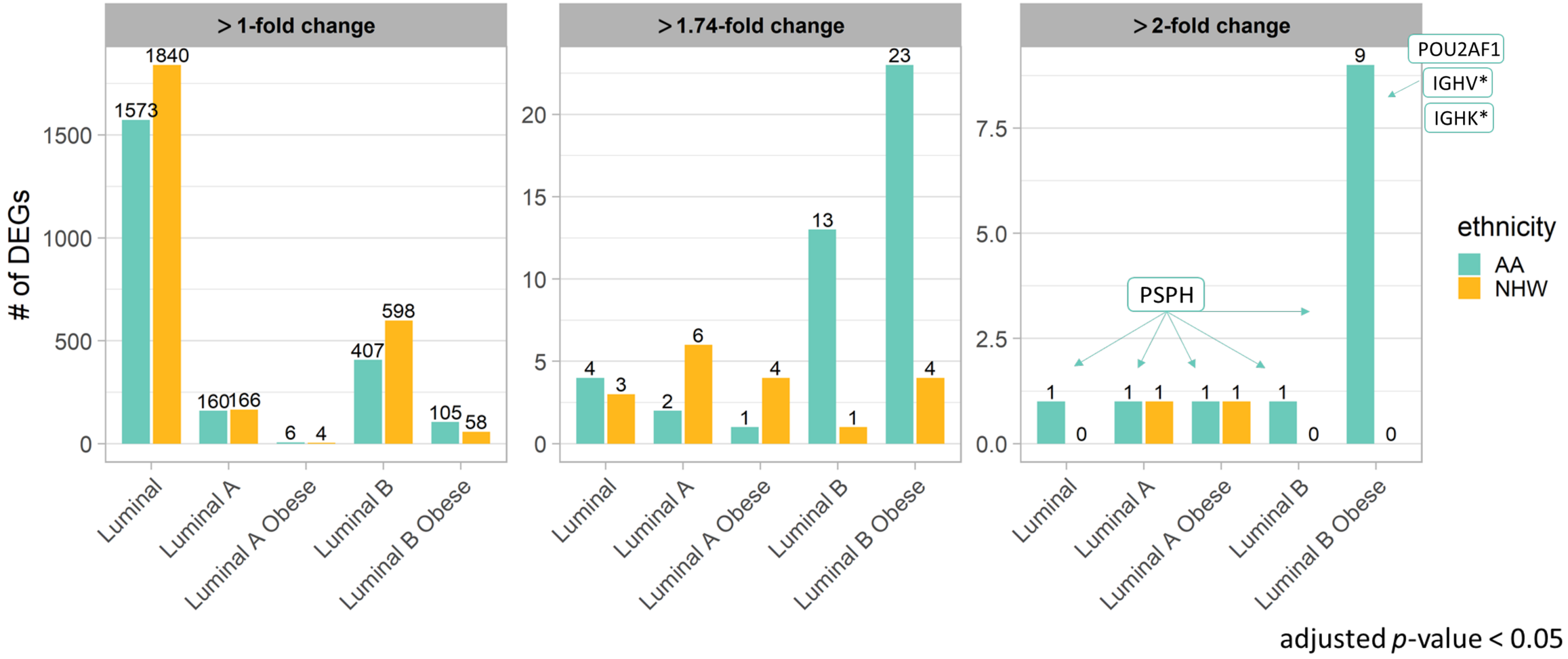
Significant transcriptomic differences were observed between Luminal tumors from African American and Non-Hispanic White patients



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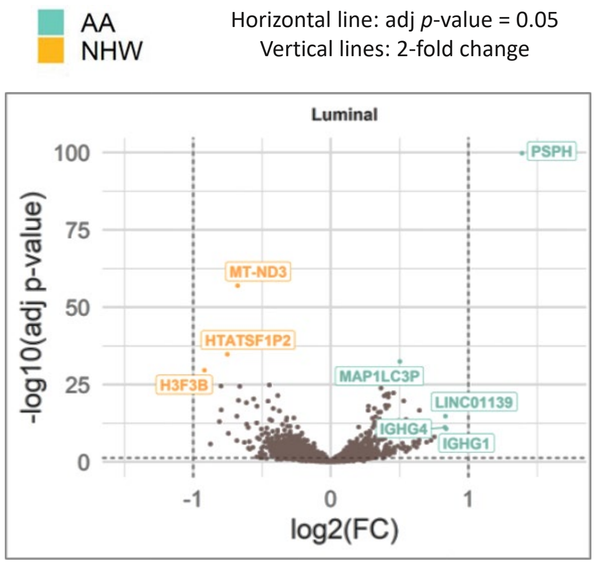

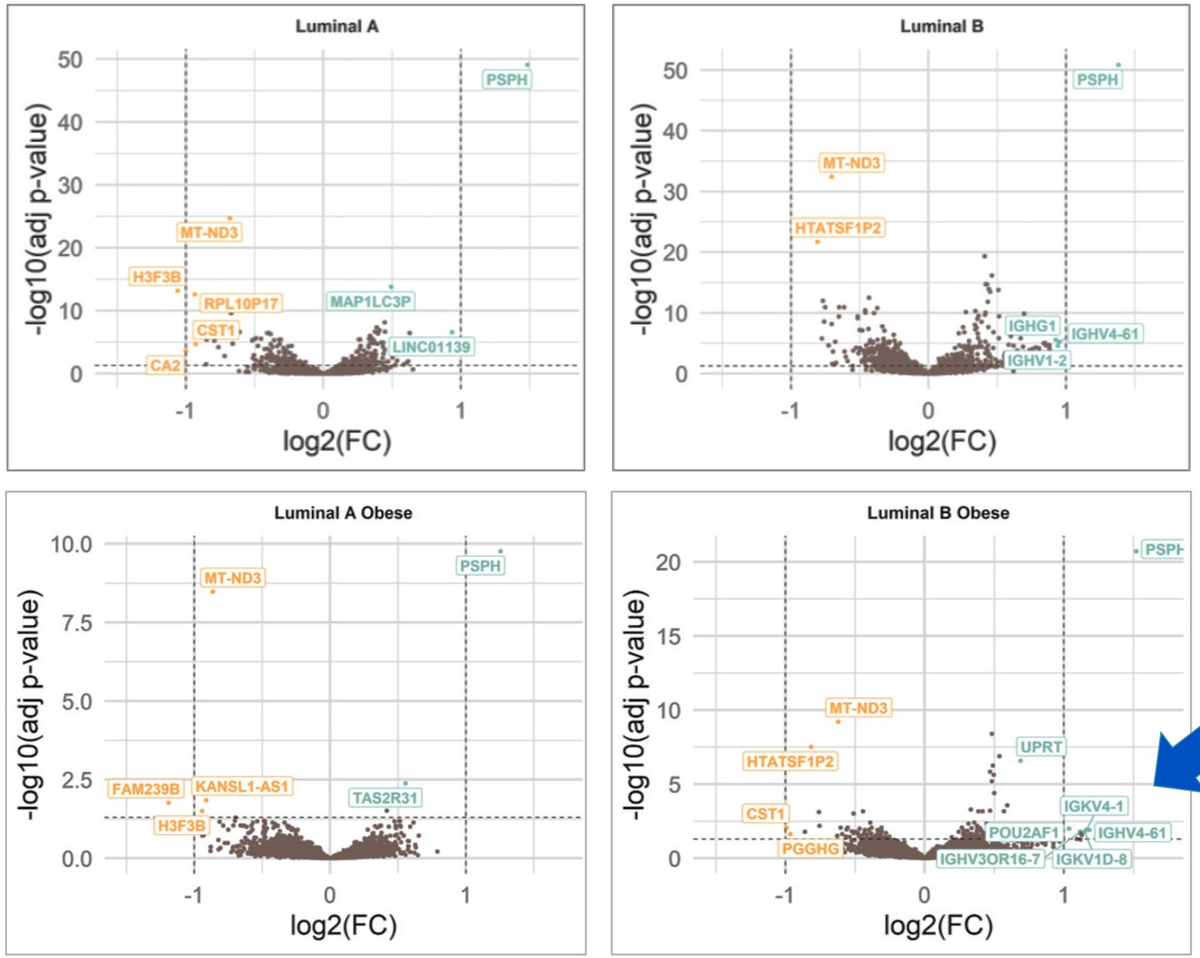

- The highest number of upregulated genes were found in Luminal B tumors of obese patients (**blue arrow**)
- AA DEGs such as *PSPH and MAP1LC3P* from previous AA Basal tumor studies[4] (*Nunes et al. 2019*) were also identified in this analysis

4. Nunes et al. 2019 *SABCS19-P2-10-08*

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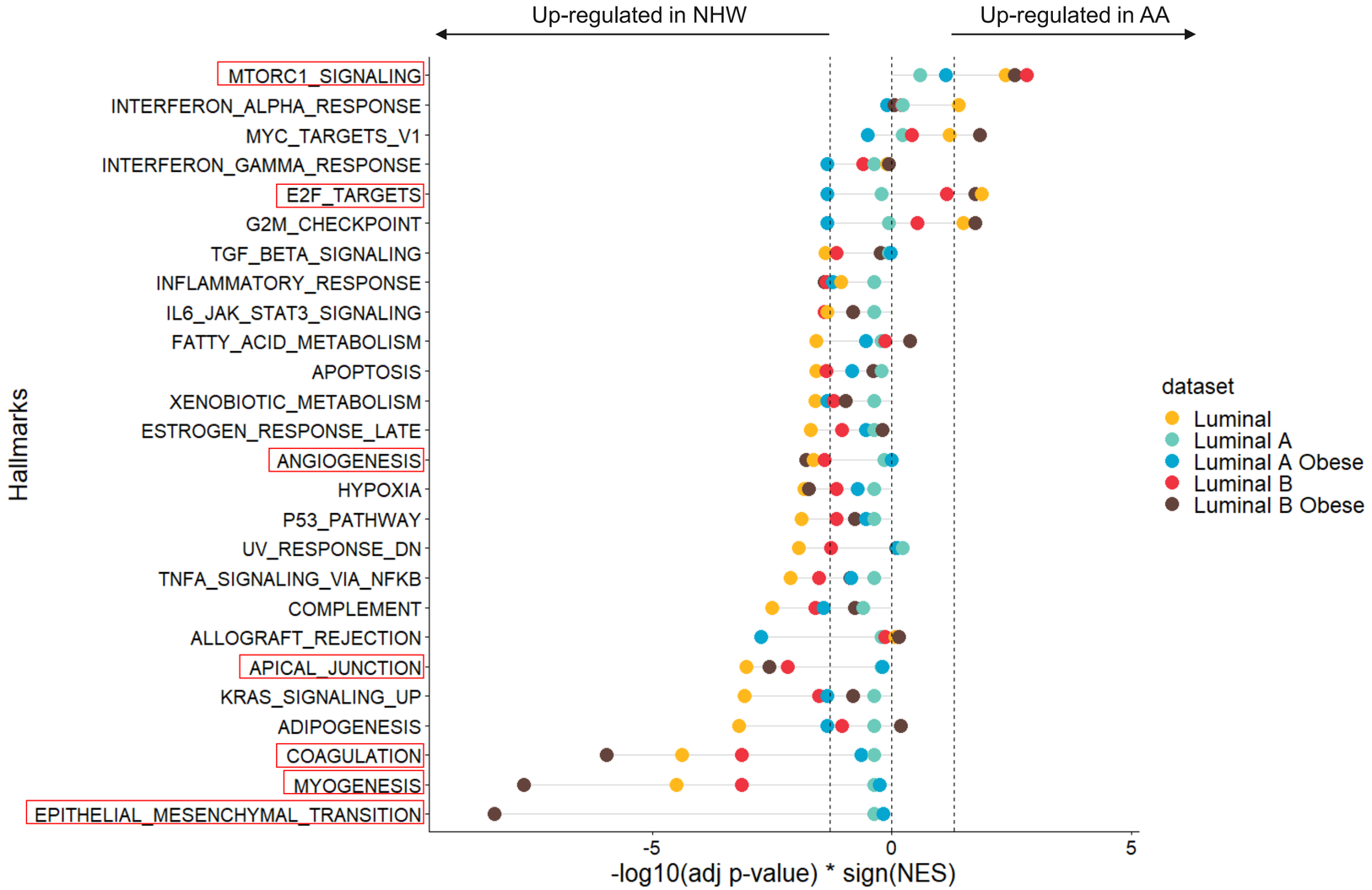
Gene set enrichment analysis revealed altered pathway signaling in AA versus NHW Luminal B tumors

- Gene set enrichment analysis revealed altered pathway signaling in AA Luminal B tumors consistent with AA Basal tumors (*Sharma et al., 2020*)

- Differentially expressed genes (red boxes) in AA tumors were associated with:
  - metabolism
  - proliferation
  - translation
  - cellular stress response pathways



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Conclusions

- We found significant transcriptomic differences between Luminal tumors from African American and Non-Hispanic White patients when controlling for age, BMI, and genomic classification of the tumor.
- A subset of DEGs in Luminal B tumors were consistent with those in Basal tumors, suggesting that similar race-associated factors drive DEGs regardless of tumor subtype.
- Gene expression changes that may be unique to Luminal tumors arising in African American women were also identified.

This study suggests biological differences in luminal breast tumors from AA women may have clinically-relevant implications which warrant further study. Our data underscores the need for inclusion of diverse patient groups in real world evidence cohorts and clinical trials.

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