HSD3B1 (c.1100) genotype is associated with distinct tumoral and clinical outcomes in breast and endometrial cancers

Justin Hwang[1,2], Shayan S. Nazari[3], Andrew Elliott[3], Ari VanderWalde[3], Melissa Geller[1,2], Carol Lange[1,2], Charles J Ryan[1,2], Nima Sharifi[4], Emmanuel S. Antonarakis[1,2]

[1]Masonic Cancer Center, Minneapolis, MN, 55455, [2]Department of Medicine, University of Minnesota, MN, 55455, [3]Medical Affairs, Caris Life Sciences, Irving, TX 85040, [4]Desai Sethi Urology Institute, Sylvester Comprehensive Cancer Center, University of Miami, FL 33136, USA

Abstract

Background: A germline single-nucleotide polymorphism in the *HSD3B1* gene results in adrenal-permissive (c.1100 C) and adrenal-restrictive (c.1100 A) phenotypes with respect to androgen synthesis. In pre- and post-menopausal patients with breast cancer (n=3548 and 7871, respectively) and endometrial cancer (n=1588 and 8439, respectively), we annotated samples as *HSD3B1* adrenal permissive (CC/AC) or restrictive (AA) based on *HSD3B1* variant status and then examined tumoral characteristics and clinical outcomes.

Methods: We utilized the Caris Life Sciences Precision Oncology Alliance (Caris POA) database to infer germline *HSD3B1* c.1100 genotype in breast and endometrial cancers using variant allele frequencies (VAFs) derived from tumor DNA sequencing: c.1100 C VAF of 0% defined the AA genotype, VAF of 40-60% defined the AC genotype, and VAF of 100% defined the CC genotype. We explored associations of the permissive and restrictive *HSD3B1* genotypes with other genomic (WES) and transcriptomic (RNA-seq) features, as well as with survival outcomes. We performed separate analyses according to menopausal status, which was defined using the patient's age at the time of biopsy (>55 indicating post-menopausal).

Results: In both breast cancer (BC) and endometrial cancer (EC), the permissive *HSD3B1* genotype was associated with increased estrogen receptor (*ESR1*) mRNA expression, particularly in the BC post-menopausal cohort (q-value <0.0001). In post-menopausal ECs, the permissive genotype was associated with increased alterations in the PI-3-kinase pathway (*PTEN*, *PIK3CA*, *PIK3R1*) and in *KRAS* (q-value <0.0001). Post-menopausal clear-cell ECs with the restrictive genotype exhibited worse survival (HR=1.60, 95% CI 1.07-2.38, p=0.03) and were 3 times less likely to be TMB-high (q-value =0.55) or MSI-high (q-value =0.41). In pre-menopausal HER2+ BCs, the restrictive genotype was associated with inferior survival (HR=1.40, 95% CI 1.05-1.85, p=0.027) and exhibited increases in hallmark GSEA signatures including epithelial-to-mesenchymal transition (EMT).

Conclusion: Breast and endometrial cancers can be classified as adrenal-permissive or -restrictive based on germline *HSD3B1* c.1100 genotype. This classification informs clinical outcomes and tumoral features, particularly when stratifying by menopausal status. Importantly, these genotypes may be differentially associated with druggable pathways (PI-3-kinase) and markers of immune sensitivity (TMB, MSI).

Restrictive and Permissive *HSD3B1* Genotypes in BC and EC

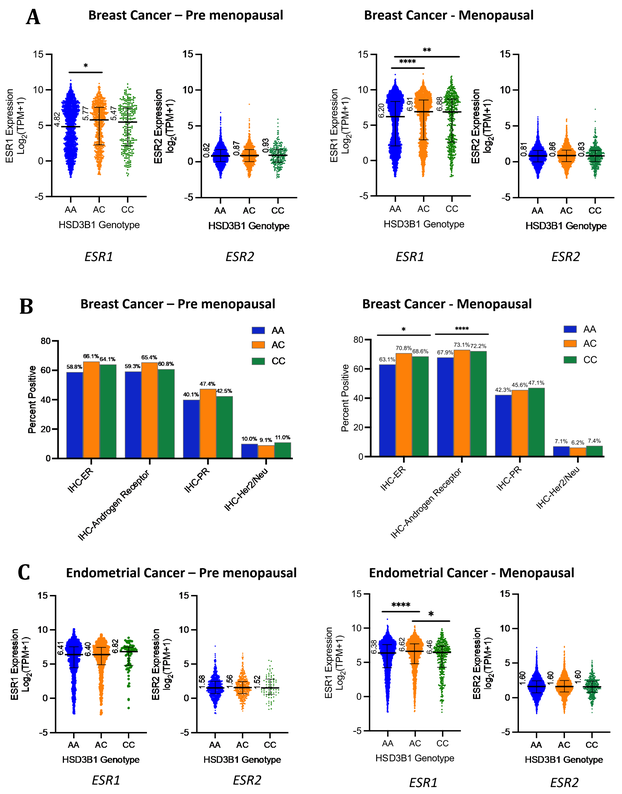
Breast Cancer and Subtypes

	Pre-menopausal				Menopausal			
	AA	AC	CC	N/A	AA	AC	CC	N/A
Luminal A	235 (51.0%)	155 (33.6%)	36 (7.8%)	35 (7.6%)	791 (52.3%)	445 (29.4%)	123 (8.1%)	153 (10.1%)
Luminal B	728 (55.9%)	322 (24.7%)	106 (8.1%)	147 (11.3%)	1626	807	244	472
Basal	708 (58.5%)	238 (19.7%)	92 (7.6%)	172 (14.2%)	1053 (60.5%)	313 (18.0%)	115 (6.6%)	260 (14.9%)
Her2	311 59.1%)	105 (20.0%)	40 (7.6%)	70 (13.3%)	755 (55.3%)	336 (24.6%)	85 (6.2%)	190 (13.9%)

Endometrial Cancer and Subtypes

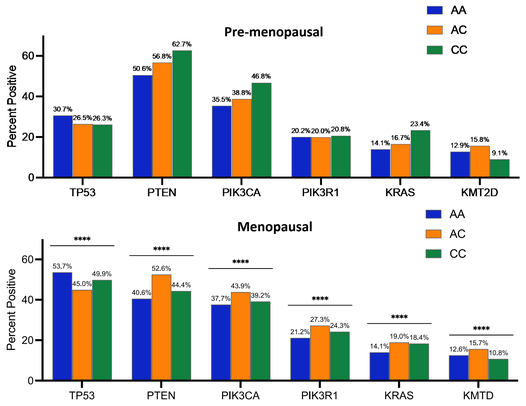
	Pre-menopausal				Menopausal			
	AA	AC	CC	N/A	AA	AC	CC	N/A
Endometrioid	399 (58.6%)	216 (31.7%)	40 (5.9%)	26 (3.8%)	1477 (53.7%)	1014 (36.8%)	157 5.7%)	105 (3.8%)
Serous	53 (73.6%)	12 (16.7%)	2 (2.8%)	5 (6.9%)	1270 (59.6%_	571 (26.8%)	107 (5.0%)	183 (8.6%)
Clear Cell	18 (75%)	5 (20.8%)	1 (4.2%)	0 (0.0%)	153 (57.1%)	76 28.4%)	16 (6.0%)	23 (8.6%)
Carcinosarcoma	15 (60.0%)	9 (36.0%)	0 (0.0%)	1 (4.0%)	114 (62.0%)	32 (17.4)	13 (7.1%)	25 (13.6%)

Permissive *HSD3B1* genotype is associated with increased *ESR1* / ER in menopausal BC and EC



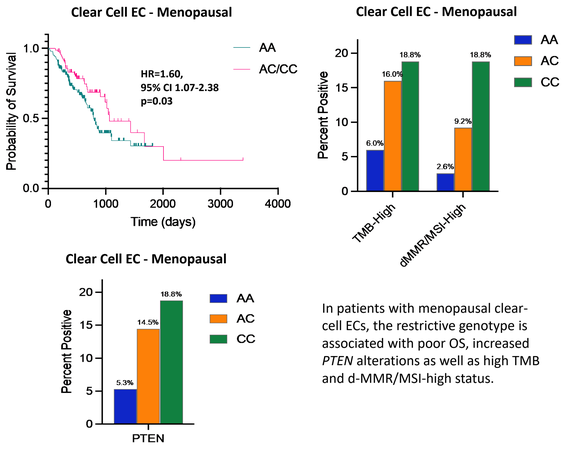
A. RNA expression of *ESR1* / *ESR2* is shown in BC samples based on menopausal status, Pre-menopausal: (*ESR1*, AA: 4.82, AC: 5.77, CC:5.47, q-value <0.05; *ESR2*, AA:0.82, AC: 0.87. CC: 0.93, q-value=0.75). In menopausal: (*ESR1*, AA: 6.20, AC:6.91, CC:6.88, q-value <0.05; *ESR2*, AA:0.81, AC: 0.86, CC:0.83, q-value=0.44). All expression units for *ESR1/ESR2* are log_2(TPM+1). TPM= Transcript Per Million.
B. IHC for hormone receptors (ER, AR, PR) as well as HER2 status in BC based on menopause status
C. RNA expression of *ESR1* / *ESR2* is shown in BC samples based on menopausal status, Pre-menopausal: (*ESR1*, AA: 6.41, AC: 6.40, CC: 6.82, q-value=0.88; *ESR2*, AA:1.58, AC: 1.56, CC: 1.52 (q-value=0.88)). In menopausal: (*ESR1*, AA:6.38, AC:6.62, CC:6.46 (q-value<0.05); *ESR2*, AA:1.60, AC: 1.60, CC: 1.60, q-value=0.09). All expression units for *ESR1/ESR2* are log_2(TPM+1). TPM= Transcript Per Million.

Post menopausal endometrial cancers are associated with increased kinase alterations



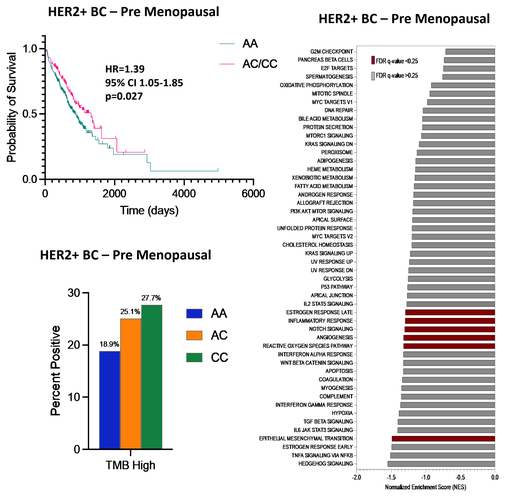
Somatic alterations in the PI-3-kinase pathway and in *KRAS* are associated with the permissive *HSD3B1* genotype in post-menopausal EC patients.

The restrictive genotype in menopausal clear-cell EC



In patients with menopausal clear-cell ECs, the restrictive genotype is associated with poor OS, increased *PTEN* alterations as well as high TMB and d-MMR/MSI-high status.

The restrictive genotype has inferior OS and reduced TMB in pre menopausal HER2+ BC



In pre-menopausal HER2+ BCs, the restrictive genotype is associated with poor OS, increased TMB and significant changes in GSEA pathways including Hallmark EMT as well as reactive oxygen species and angiogenesis.

Conclusions

The germline adrenal-permissive *HSD3B1* variant (c.1100 CC) is associated with various somatic alterations in breast and endometrial cancers including increases in *ESR1* expression, PI-3-kinase pathway and *KRAS* alterations, reduced TMB, and improved OS. These changes are dependent on menopausal status and histologic tumor subtype, relevant clinical features that should be evaluated along with *HSD3B1* status.

Justin Hwang, Ph.D. jhwang@umn.edu
Emmanuel Antonarakis, M.D. anton401@umn.edu
Twitter @EAntonarakis

ASCO 2024