**HSD3B1 and Resistance to Androgen Deprivation Therapy in Prostate Cancer**

**Authors:** Jason W.D. Hearn, M.D.,1,2* Ghada AbuAli, Ph.D.,3* Chad A. Reichard, MD,4 Chandana A. Reddy, M.S.,2 Cristina Magi-Galluzzi, M.D., Ph.D,1 Kai-Hsiung Chang, Ph.D.,3 Rachel Carlson, B.A.,6 Laureano Rangel, M.S.,6 Kevin Reagan, B.S.,7 Brian J. Davis, M.D., Ph.D.,8 R. Jeffrey Karnes, M.D.,9 Manish Kohli, M.D.,10 Donald Tindall, Ph.D.,7 Eric A. Klein, M.D.,3 Nima Sharifi, M.D.2,3,11

**Affiliations:** Department of Radiation Oncology, University of Michigan, Ann Arbor, MI.1 Depts. of Radiation Oncology,2 Cancer Biology,3 Urology,4 Pathology,5 and Hematology & Oncology,11 Cleveland Clinic, Cleveland, OH. Depts. of Health Sciences Research,6 Biochemistry & Molecular Biology,7 Radiation Oncology,8 Urology,9 and Oncology,10 Mayo Clinic, Rochester, MN. *These authors contributed equally.

**Background**

HSD3B1(1245A>C) has been mechanistically linked to castration-resistant prostate cancer by encoding an altered enzyme that augments dihydrotestosterone synthesis. We hypothesized that men inheriting the HSD3B1(1245C) allele would exhibit resistance to androgen deprivation therapy (ADT).

**Methods**

We determined HSD3B1 genotype retrospectively in men treated with ADT for post-prostatectomy biochemical failure and correlated genotype with long-term clinical outcomes. Patients who received postoperative radiotherapy were eligible, provided they had residual active disease as reflected by continued increase in their PSA after treatment. We analyzed progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) according to HSD3B1 genotype. Multivariable analyses were performed to assess the independent predictive value of HSD3B1 genotype on outcomes. Results were externally validated in two additional cohorts, including a second post-prostatectomy biochemical failure cohort as well as a metastatic cohort.

**Results**

The study included 443 patients: 118 in the primary cohort, 137 in the post-prostatectomy validation cohort, and 188 in the metastatic validation cohort. In the primary study cohort, median PFS diminished as a function of the number of variant alleles inherited: 6.6 years in homozygous wild-type men (95% CI, 3.8 to not reached); 4.1 years in heterozygotes (95% CI, 3.0 to 5.5); and 2.5 years in homozygous variant men (95% CI, 0.7 to not reached); P=0.011. Median DMFS likewise decreased according to the number of variant alleles inherited: 9.1 years (95% CI, 7.4 to not reached); 6.8 years (95% CI, 4.3 to 7.4); and 3.6 years (95% CI, 1.0 to 7.3), respectively; P=0.014. Finally, OS diminished with the number of variant alleles inherited: 5-year and 10-year OS 82% (95% CI, 69 to 94) and 55% (95% CI, 35 to 75) in homozygous wild-type men; 74% (95% CI, 62 to 85) and 35% (95% CI, 21 to 49) in heterozygotes; and 58% (95% CI, 30 to 86) and 0% in homozygous variant men; P=0.0064. On multivariable analysis, the hazard ratio (HR) for progression was 1.6 for men with at least one variant allele (95% CI, 1.0 to 2.7; P=0.074), which compared favorably with Gleason score (HR 1.3 for Gleason score 8-10 vs. 6-7; 95% CI 0.8 to 2.0; P=0.31), though neither factor reached statistical significance with the small sample size. The impact of homozygous variant genotype on metastasis (HR 2.8; 95% CI, 1.1 to 6.7; P=0.025) and death (HR 3.5; 95% CI 1.3 to 9.5; P=0.013) was maintained on multivariable analysis. Findings in the external cohorts independently validated the impact of HSD3B1(1245C) on outcomes, including survival.

**Conclusions**

Inheritance of the HSD3B1(1245C) allele that enhances dihydrotestosterone synthesis predicts innate resistance to ADT in prostate cancer. Future studies should stratify by HSD3B1 genotype in light of the profound differences in outcomes according to the number of variant alleles present.

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**Conflict of Interest**

A patent for 3β-hydroxysteroid dehydrogenase in steroid-dependent disease has been filed by Cleveland Clinic. All grant support and other funding is listed in the Funding Acknowledgments section.