HSD3B1 and Resistance to Androgen Deprivation Therapy in Prostate Cancer

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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.