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Adrenal-Permissive HSD3B1 Genotype-An Invisible Stimulator of Prostate Cancer Mortality

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Prostate cancer progression is dependent on androgen receptor signaling, which is activated by the circulating gonadal androgen testosterone and its more potent metabolite, 5α-dihydrotestosterone (DHT) generated from testosterone in the prostate. Androgen deprivation therapy (ADT) leading to the loss of gonadal testosterone exploits this dependency on androgen receptor activity. However, resistance to ADT is promoted by the metabolic ability of prostate cancer cells to locally synthesize active androgens from circulating, inactive precursors produced by the adrenal gland, leading to the development of castration-resistant prostate cancer (CRPC)[1].

The first and rate-limiting step of the metabolic pathway is catalyzed by the enzyme 3β-hydroxysteroid dehydrogenase type 1 (3β-HSD1), which converts adrenal-derived dehydroepiandrosterone to androstenedione. Androstenedione is then converted to testosterone and DHT in only one or two additional metabolic steps, respectively[1]. 3β-HSD1 activity thus represents a clinical obstacle.

3β-HSD1 is encoded by the *HSD3B1* gene, which has a common germline variation [rs1047303, *HSD3B1*(1245A/C)] that introduces an amino acid change (N367T) in the 3β-HSD1 protein, rendering it resistant to ubiquitination and degradation, thereby promoting the production of bioactive androgens[2]. Since our mechanistic discovery in 2013 that this 'adrenal-permissive' *HSD3B1*(1245C) allele stimulates local production of active androgens in prostate cancer compared to the 'adrenal-restrictive' *HSD3B1*(1245A) allele[2], several studies have independently demonstrated that the inheritance of the adrenal-permissive *HSD3B1* allele in men with prostate cancer is associated with more rapid development of CRPC and worse clinical outcomes. The most consistent clinical findings are in men with non-metastatic or low-volume metastatic prostate cancer who are treated with ADT. In these men, CRPC-associated outcomes are progressively worse with increasing copy number of adrenal-permissive *HSD3B1* alleles in the germline (0 vs. 1 vs. 2)[3]. These clinical data are in line with the function of 3β-HSD1 in extragonadal androgen biosynthesis and a greater contribution of *HSD3B1* inheritance with lower tumor burden and less genomically complex prostate cancer. However, these studies were limited by sample sizes of at most a few

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hundred men, making it challenging to definitively determine genotype-associated prostate cancer-specific mortality (PCSM).

The current study by McKay, *et al.*, is a major leap forward that builds upon the previously established biochemical mechanisms and CRPC-associated clinical outcomes for the adrenal-permissive *HSD3B1* allele[4]. This study is from the Million Veterans Program, one of the world's largest research studies designed to link genetics with health and disease outcomes. McKay *et al.* analyzed the impact of *HSD3B1* germline inheritance on outcomes in a racially diverse cohort of 5,287 men with prostate cancer. They found an increase in the 5-year cumulative incidence of PCSM after prostate cancer diagnosis for homozygous adrenal-permissive inheritance (1.9%, 2.1% and 4.0% for men with 0, 1 and 2 alleles, respectively; p=0.02). The cumulative incidence of PCSM for homozygous adrenal-permissive inheritance was elevated for men who developed metastatic prostate cancer at any time (18.5%, 17.9% and 36.0% for men with 0, 1 and 2 alleles, respectively; p=0.01) and for men with non-metastatic prostate cancer at diagnosis (0.6%, 0.9% and 1.8% for men with 0, 1 and 2 alleles; p=0.04). Men with homozygous adrenal-permissive inheritance who developed metastatic disease at any time have a hazard ratio (HR) of 2.48 (p=0.004) for PCSM from time of metastases. Despite the associations with prostate cancer mortality, homozygous adrenal-permissive inheritance is not associated with prostate cancer Gleason category, PSA at diagnosis or the incidence of metastases. Together, these data are in line with *HSD3B1* acting outside the realm of traditional oncogenic pathways (e.g., DNA damage, genomic instability, cellular dedifferentiation, etc.), and instead, specifically revealing its effects after the initiation of hormonal therapy and hastening the development of hormone therapy resistance and lethality.

To better understand the overall significance of *HSD3B1* germline variation for prostate cancer outcomes, a comparison to the impact of other germline genetic variants that are associated with PCSM in non-metastatic prostate cancer is helpful. For example, highly penetrant and commonly studied germline mutations associated with an increased risk of prostate cancer and more aggressive prostate cancer (including adverse pathology and incidence of metastatic disease) occur in homologous recombination repair genes, such as *BRCA1* and *BRCA2*. The HR for PCSM in *BRCA2* carriers, which occur in about 3% of men with non-metastatic prostate cancer, is about 3.2 or 1.9 when accounting for other prognostic factors[5]. This is a similar magnitude as the impact of homozygosity for the adrenal-permissive *HSD3B1* in the current study. Given the population prevalence of adrenal-permissive *HSD3B1* homozygosity (7.6% in the present study and up to 10% in certain populations), it seems likely that germline *HSD3B1* inheritance is a significant contributor to prostate cancer mortality. Overall, the frequency of the adrenal-permissive *HSD3B1* allele is highest in people of European genetic ancestry[3].

Why is *HSD3B1* an "invisible" driver of prostate cancer mortality? *HSD3B1* inheritance is not reflected in any intermediate clinical indicators, such as pathology or incidence of metastases[4]. This is in contrast to the example of *BRCA2*. Instead, the *HSD3B1*-inherited androgen metabolism characteristics of the tumor are not made clinically apparent until the initiation of hormonal therapy and, as now shown by the study of McKay, *et al*, have a clear consequence for prostate cancer mortality. As such, any germline panel assessment

for non-metastatic prostate cancer should now include *HSD3B1*. An increase in PCSM in 7%-10% of the population is too common to ignore. Detection of homozygosity can impact disease management because it identifies men with more lethal prostate cancer that is not otherwise captured by current clinical prognostic factors and provides an opportunity to treat at the time of localized disease prior to tumor dissemination and need for hormonal therapy. Further, these men might benefit from intensified hormonal therapy approaches that ablate or block non-gonadal androgens at the time of localized disease[6] or even an approach that directly targets the 3β-HSD1 enzyme[7]. Although prior studies consistently show increased risk of CRPC on hormonal therapy with heterozygous inheritance, no association with PCSM was detected in the current study. The reasons for this are not clear and could be due to a lower effect size with heterozygous inheritance, the absence of an effect on mortality, or an interplay that includes other factors, including the differential effects of subsequent therapies.

Finally, it is notable that the discovery and functional understanding of *HSD3B1* as a driver of prostate cancer mortality originated as a fundamental biochemical finding in the laboratory rather than by genome-wide or large-scale approaches. All the subsequent clinical work, including association studies, was hypothesis-driven, with a mechanistic and physiological rationale. This illustrates the value of mechanism-driven research in an era dominated by big data and large-scale untargeted approaches. Discovery of fundamental mechanisms of biology has the power to make the invisible actionable.

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