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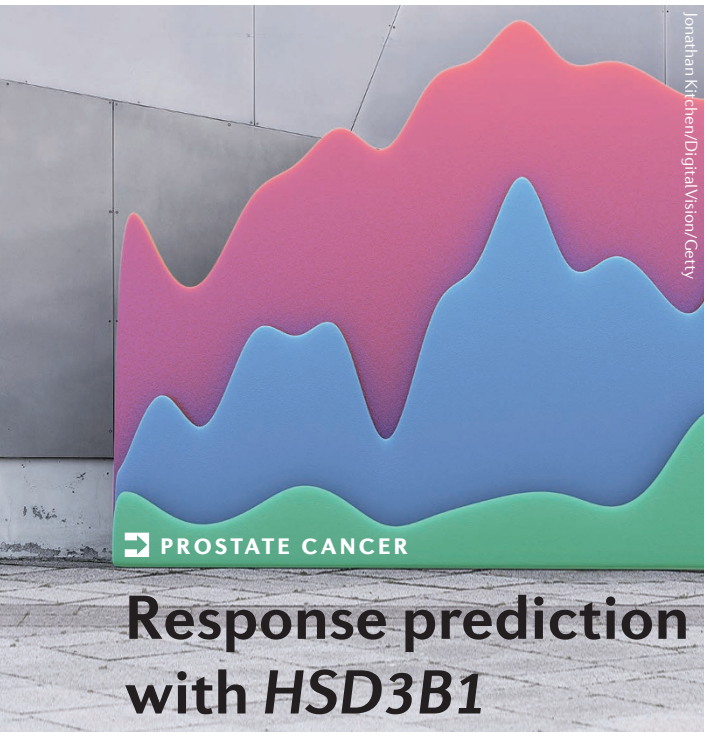

Response prediction with *HSD3B1*

> the *HSD3B1* variant could be a useful biomarker for response prediction to ADT

Two new papers published in *JAMA Oncology* corroborate the predictive relevance of inheritance of a 3β-HSD1 (encoded by *HSD3B1*) variant in men with prostate cancer. Harbouring the *HSD3B1* 1245A>C variant results in worse outcomes, probably owing to increased tumoural androgen synthesis from extragonadal precursor steroids. In addition, tumours with the *HSD3B1* variant seem to respond better to inhibition of extragonadal androgen synthesis, suggesting a specific therapeutic sensitivity conferred by inheritance of this variant.

"We previously discovered that a common germline variant of *HSD3B1* encodes a gain-of-function in 3β-HSD1 that essentially increases the rate-limiting step of dihydrotestosterone synthesis from extragonadal precursor steroids," explains Nima Sharifi from the Cleveland Clinic, Ohio, USA, senior author of both studies. "We also previously showed that patients harbouring this variant have worse outcomes than those who do not when receiving androgen deprivation therapy [(ADT)] for PSA recurrence after prostatectomy or metastatic disease."

In the first of the two new studies, the researchers investigated associations between *HSD3B1* genotype and outcomes in men who had PSA recurrence after definitive radiotherapy for localized prostate cancer treated with ADT, as effects of the *HSD3B1* variant in these patients were unknown.

Of 213 men who were retrospectively genotyped, 46% were homozygous for wild-type *HSD3B1*, 45% were heterozygous, and 9% were homozygous for the *HSD3B1* variant. At a median follow-up time of 7.9 years, no significant association between the number of variant alleles and time to progression (TTP) or overall survival was observed. Median TTP was 2.3 years for men with no or one variant allele and 1.4 years for those with two variant alleles ($P = 0.68$). Median overall survival was 7.7, 6.9, and 7.2 years in men with no, one, and two variant alleles, respectively ($P = 0.31$). However, inheritance of the variant gene was predictive of time to metastasis (TTM). Median TTM decreased as the number of variant alleles increased: TTM was 7.4, 5.8, and 4.4 months in men with no, one, and two variant alleles, respectively ($P = 0.03$). The number of variant alleles remained predictive of TTM in multivariate analysis using zero variant alleles as the reference (HR 1.19, $P = 0.48$; and HR 2.01, $P = 0.045$, for one and two variant alleles, respectively).

In the second of the two studies, researchers investigated whether inheritance of the *HSD3B1* variant was associated with response to extragonadal androgen ablation with ketoconazole, a nonsteroidal inhibitor of steroid 17-α-hydroxylase/17,20 lyase (CYP17A1), in men with metastatic castration-resistant prostate cancer (CRPC).

Median ketoconazole treatment duration (KTD; n = 88) and median progression-free survival (PFS; n = 81) increased with the number of inherited variant *HSD3B1* alleles: KTD was 5.0, 7.5, and 12.3 months ($P = 0.01$) and PFS was 5.4, 9.7, and 15.2 months ($P = 0.03$) for no, one, and two variant alleles, respectively. Compared with men who had no variant alleles, the hazard ratios for disease progression were 0.6 (95% CI 0.4–1.0, $P = 0.06$) and 0.5 (95% CI 0.3–1.1, $P = 0.08$) for men with one and two variant alleles, respectively.

"Inheritance of the *HSD3B1* variant is associated with worse outcomes in patients treated with ADT after radiotherapy and PSA recurrence, consistent with previous studies in men after prostatectomy or those with metastasis," summarizes Sharifi. "Furthermore, the *HSD3B1* variant is associated with better outcomes in patients with CRPC treated with ketoconazole, suggesting that patients that have tumours with a genetically conferred ability to synthesise dihydrotestosterone from extragonadal precursors are more likely to have improved responses to nonsteroidal CYP17A1 inhibition."

These data show that the *HSD3B1* variant could be a useful biomarker for response prediction to ADT and for selecting patients who are particularly responsive to nonsteroidal inhibitors of androgen synthesis or signalling. "We are now specifically examining what this genetic effect on steroid biochemistry means for patients treated with the steroidal CYP17A1 inhibitor abiraterone," Sharifi concludes.

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ORIGINAL ARTICLES Almassi, N. *et al. HSD3B1* and response to a nonsteroidal CYP17A1 inhibitor in castration-resistant prostate cancer. *JAMA Oncol.* http://dx.doi.org/10.1001/jamaoncol.2017.3159 (2017) | Hearn, J. W. *et al.* Association of HSD3B1 genotype with response to androgen-deprivation therapy for biochemical recurrence after radiotherapy for localized prostate cancer. *JAMA Oncol.* http://dx.doi.org/10.1001/jamaoncol.2017.3164 (2017)
FURTHER READING Stuchbery, R. *et al.* Androgen synthesis in prostate cancer: do all roads lead to Rome? *Nat. Rev. Urol.* **14**, 49–58 (2017)