Review

The association between genetic variants in *HSD3B1* and clinical management of PCa

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Abstract

Androgen is an important factor in the occurrence and progression of prostate cancer. The principal clinical strategy is androgen deprivation therapy (ADT). However, progression to castrate-resistant prostate cancer (CRPC) is almost inevitable to occur after ADT. One of the key mechanisms is the intertumoral synthesis of androgen where 3b-hydroxysteroid dehydrogenase isoenzyme-1 (3bHSD1, encoded by *HSD3B1*) catalyzes the rate-limiting step. A germline missense-encoding variant of

HSD3B1(1245A>C, rs1047303) has been focused because *HSD3B1*(1245C) works as an adrenal-permissive allele and encodes a more stable enzyme that promotes the synthesis of androgen. Several studies were performed to explore the role of *HSD3B1*(1245C) in the development to CRPC and the outcome of clinical management. Since that, we searched the published research articles using key words "prostate cancer" and "HSD3B1", in PubMed and Embase database. After review of the abstract and full articles, 16 original research articles from 45 search results were finally selected and reviewed. Based on current evidences, *HSD3B1* (1245C) is supposed to be accelerate ADT resistance and development of CRPC. It is also associated with a poorer prognosis of PCa treated with ADT. However, with a conflict among present results, the association between *HSD3B1* (1245C) and the effect of next-generation hormone therapy (i.e., Abiraterone) for patients with CRPC is not clear enough. As a result, *HSD3B1*(1245C) has its value for predicting the outcome of PCa and its potential to be involved in therapeutic decision making.

Keywords: *HSD3B1*, germline, prostate cancer, androgen deprivation therapy, castration-resistant prostate cancer, abiraterone, predictive biomarker, multienzyme complexes; patient stratification, omics

INTRODUCTION

It is widely accepted that androgen and androgen receptor (AR) play an important role in occurrence and progression of prostate cancer (PCa)[1]. Androgen deprivation therapy (ADT) via medical or surgical castration, which has been applied since 1941[2], is the principal therapeutic strategy to advanced prostate cancer. The general clinical efficiency of ADT depends on its blockage of gonadal androgen[3-5]. However, the development from castrate-sensitive prostate cancer (CSPC) to castrate-resistant prostate cancer (CRPC) is eventually inevitable[4]. One of the key mechanisms is the intertumoral synthesis of androgen, including testosterone and dihydrotestosterone (DHT), which originate from adrenal precursor steroid, such as dehydroepiandrosterone (DHEA)[6,7]. The androgen synthesis is supposed to induce the reactivation of AR. When the disease finally progresses to the state of CRPC, it becomes highly lethal. In order to solve this clinical problem, next generation

hormone therapies were introduced nearly a decade ago[8]. Since then, the PCa prognosis is noted to be largely improved by several new drugs such as docetaxel (a microtubule inhibitor), abiraterone (a selective inhibitor of cytochrome P450 17A1 [CYP17A1] which is a key enzyme in androgen synthesis), and enzalutamide (a targeted androgen receptor inhibitor)[9-11].

In terms of the intertumoral androgen synthesis, several key enzymes and genes in the synthetic process are identified as potential targets for diagnosis or treatment. One of them is 3b-hydroxysteroid dehydrogenase isoenzyme-1 (3bHSD1, encoded by *HSD3B1*), which catalyzes the rate-limiting step in the metabolic conversion from DHEA to testosterone and DHT in adrenal gland[12]. A specific germline missense-encoding variant of *HSD3B1* (1245A>C, rs1047303) leads to a divergence of enzyme level and downstream androgen synthesis. *HSD3B1* (1245A) is known as an adrenal-restrictive allele as it codes an enzyme degraded more rapidly; while *HSD3B1* (1245C), an adrenal-permissive allele, codes a stable enzyme resistant to proteasomal degradation that promote robust conversion from DHEA to DHT[13,14]. A series of studies indicated that genetic variants in *HSD3B1* are found to be associated with the progression of PCa and resistance of ADT. In this review, homozygous variant genotype was named as *HSD3B1* (CC), while heterozygous genotype and homozygous wild type was named as *HSD3B1* (AC) and *HSD3B1* (AA), respectively.

In this review, we summarized the present studies regarding the association between *HSD3B1* and the clinical management of PCa, including both states of CSPC and CRPC. We also discussed the contemporary significance of *HSD3B1* and its potential value in the therapeutic decision in PCa.

EVIDENCE SYNTHESIS

We searched the published research articles using key words “prostate cancer” and “HSD3B1”, in PubMed and Embase database. A total of 45 results were found. After review of the abstract and full articles, 16 original research articles were finally included in this review.

HSD3B1 (1245C) PROMOTES RESISTANCE TO ADT AND DEVELOPMENT TO CRPC

Recently, plenty of evidence showed that PCa patients carrying *HSD3B1* (1245C) variant were more likely to become resistant to ADT and progress to CRPC. This variant was also reported to be associated with worse survival outcome for patients with PCa treated with ADT, especially for those with low-volume diseases.

As shown in Table 1, since first reported by Ross *et al.*[15] in 2008, where it was found that SNP rs1870050 in CYP19A1 (hazard ratio [HR]: 0.60, P=0.0007), rs1856888 in *HSD3B1* (HR: 0.58, P=0.0047), and rs7737181 in HSD17B4 (HR: 0.70, P=0.0096) were related to shorter time to progression, the role of *HSD3B1* in PCa has been paid close attention by researchers, because 3βHSD1 encoded by *HSD3B1* is necessary for synthesis of non-testicular testosterone or DHT. Wu *et al.*[16] first summed up that *HSD3B1* (1245C) are more likely to progress to CRPC in 2015, according to a retrospective study involving 85 patients with AA genotype and 18 with AC genotype who were diagnosed as advanced PCa and underwent surgical castration. However, no significant disparity of overall survival time was shown related to *HSD3B1*.

Table 1 Summary of studies about the association between *HSD3B1* variants and PCa treated with ADT.

Study	Medical Management	Number of Cases	Number of Carriers	Results	Conclusions
Ross, 2008*	ADT	529	62	For TTP: HR 0.58; 95% CI 0.41-0.81; P=0.0047	The polymorphism in HSD3B1 was associated with time to progression during ADT for PCa.
Wu, 2015	ADT	103	18	For incidence of CRPC: AC vs. AA 100% vs. 64.7%; P=0.003	Variant HSD3B1 associated higher incidence of CRPC
Hearn, 2016	ADT	118	74	For PFS: CC: HR 2.4; 95% CI 1.1-5.3; P=0.029 AC: HR 1.7; 95% CI 1.0-2.9; P=0.041 For OS: CC: HR 3.3; 95% CI 1.3-8.3;	Patients carrying variant HSD3B1 are more likely to fail with ADT and to have worse survival outcome.

				P=0.013 AC: HR 2.0; 95% CI 1.1-3.7; P=0.036	
	ADT	137	60	For PFS: CC: HR 2.7; 95% CI 1.2-5.9; P=0.013 AC: HR 1.0; 95% CI 0.7-1.7; P=0.085	
	ADT	188	90	For OS: CC: HR 2.5; 95% CI 1.2-5.0; P=0.013 AC: HR 1.5; 95% CI 1.0-2.1; P=0.036	
Agarwel, 2017	ADT	102	52	For PFS: CC: HR 2.16; 95% CI 1.01-4.58; P=0.046 AC: HR 1.04; 95% CI 0.64-1.07; P=0.86	HSD3B1 genotype CC but not AC, was associated with shorter PFS
Hearn, 2018	ADT after radiotherapy	218	116	For time to metastasis: CC: HR 2.01; 95% CI 1.02-3.97; P=0.045 AC: HR 1.19; 95% CI 0.74-1.92; P=0.48 No significant differences in TTP or OS	Variant HSD3B1 was associated with shorter time to metastasis but not with death and progression risk.
Shiota, 2019	ADT	104	9	For PFS: CC/AC: HR 2.34; 95% CI 1.08-4.49; P=0.03 For OS:	Variant HSD3B1 was associated with shorter PFS but not with death risk.

				CC/AC: HR 1.36; 95% CI 0.52-2.92; P=0.50	
Hearn, 2020	ADT randomized plus docetaxel	475	270	For PFS: In low-volume disease group: CC/AC: HR 1.89; 95% CI 1.13-3.14; P=0.02 In high-volume disease group: CC/AC: HR 1.10; 95% CI 0.82-1.47; P=0.52 For OS: In low-volume disease group: CC/AC: HR 1.74; 95% CI 1.01-3.00; P=0.045 In high-volume disease group: CC/AC: HR 0.89; 95% CI 0.65-1.22; P=0.48	Variant HAD3B1 was associated with higher risk of progression and death for patients with low-volume disease, but not with high-volume.
Chen, 2020	ADT	101	42	For OS: CC/AC vs. AA 5.0yrs vs. 6.5yrs; P=0.052	Variant HSD3B1 was marginally significantly associated with shorter OS.

Hearn *et al.*[17] reported that *HSD3B1* (1245C) is significantly associated with PCa resistance to ADT. As a multi-cohort study, it enrolled 443 patients treated with ADT after prostatectomy from three cohorts, the post-prostatectomy cohort from the Cleveland Clinic registry, the post-prostatectomy validation cohort from the Mayo Clinic SPORE registry, and the metastatic validation cohort from the Mayo Clinic metastatic prostate cancer registry. The frequency of variant was 26%-36%. In primary cohort, compared with the AA genotype group, CC genotype groups (HR: 2.4, P=0.029) and AC group (HR: 1.7, P=0.041) were associated with worse

progression-free survival (PFS). However, in the other two cohorts, CC shown the same significant effect on development to CRPC, while association between AC genotype and progression of CRPC was not significant (HR: 1.1, P=0.38). In addition, variant allele was predictive to a worse overall survival.

Subsequently, a few of studies came to similar conclusions. Agarwal *et al.*[18] retrospectively analyzed 102 patients with metastatic CSPC accepting ADT. The frequency of variant was 31%. Compared with the PFS in AA genotype group, in the CC genotype group, PFS was shorter (11 vs 21 months; HR: 2.16, P=0.046), while that in AC genotype groups was similar (19 vs 21months; HR: 1.04, P=0.86). Besides, Shiota *et al.*[19] also performed an analysis in a primary ADT cohort with 104 Japanese patients of metastatic CSPC where the frequency of variant is 5%. The result turned out that patients with CC genotype and AC genotype were more possible to be resistant to ADT (HR: 2.34, P=0.03) but had no significant difference for mortality.

Hearn *et al.* furthered their studies on the basis of the original. Instead of post-prostatectomy, focusing on patients undergoing ADT post-radiotherapy, the study proved that *HSD3B1* (1245C) was also associated with rapid development of metastases[20]. Furthermore, analyses were performed in the E3805 Chemohormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) which including patients with metastatic PCa undergoing ADT with or without docetaxel. The conclusion was that *HSD3B1* (1245C) was exactly related to earlier development of CRPC (HR: 1.89, P=0.02) and shorter overall survival (HR: 1.74, P=0.045) in patients with low-volume disease but not in patients with high-volume disease[21].

These are the current clinical studies on the role of *HSD3B1* in CSPC patients treated with ADT above. With regard to the effect of *HSD3B1* (CC) for accelerating the resistance to ADT and progression to CRPC, results of current studies reached agreement. A meta-analysis of Han *et al.* confirmed this conclusion and also concluded that *HSD3B1* had no association with mortality [22]. Except the outcome in the primary cohort of the Hearn's study in 2016[17], *HSD3B1* (1245C) was noted to have no impact on mortality of CSPC. From a more fundamental level, Chen *et al.*[23] reported that *HSD3B1* was marginally significantly associated with impaired survival

outcome. Based on the study by Hearn *et al.*, effect of *HSD3B1* only existed in patients with low-volume PCa. It was difficult to derive a precise conclusion from an analysis to the overall cohort. In addition, it worth noting that the association between AC genotype and survival outcome remained unclear. The effect of AC genotype on promoting resistant to ADT was statistically significant in only one study[17]. In contrast, in the other two cohorts of Hearn's study in 2016 and the cohort in Agarwal's work, no difference in overall survival was observed between AC and AA genotype groups.

IMPACT OF *HSD3B1* (1245C) ON THE OTHER MEDICAL MANAGEMENT IS WAITING TO DEFINE

Since the function of germline variants in *HSD3B1* was confirmed to promote the development of resistance to ADT, several works focused on how it influences the outcome when coming to the state of CRPC. It was once reported that *HSD3B1* (1245C) might have negative effect to overall survival of CRPC. However, there were contradictions in the existing results about its association with response to medical management in the state of CRPC, such as abiraterone and enzalutamide.

Stangl-Kremser *et al.* and Chen *et al.* both summed up the association between *HSD3B1* (1245C) and survival outcome of patients with CRPC via genetic sequencing of prostate tissue. The former concluded that there was no relation between *HSD3B1* (1245C) and survival outcome of CRPC[24]. Similarly, the latter reported that *HSD3B1* (1245C) was related to a trend of worse prognosis for CRPC because of increased tumor expression of cell proliferation and cell cycle genes[23], but without significant difference.

It's not clear whether *HSD3B1* (1245C) induces an impaired survival outcome in the state of CRPC. It's also valuable to explore if germline *HSD3B1* is predictive for the reaction to the related medical management for CRPC. Hearn *et al.*[21] reported no relation between *HSD3B1* and response to docetaxel. In addition, as mentioned above, the key mechanism of CRPC development is intertumoral androgen synthesis and reactivation of AR. Some medical therapies aiming at blocking this process, known as AR pathway inhibitors (ARPIs) are widely accepted to be applied in the treatment of CRPC, such as AR antagonist like enzalutamide, and 17α-hydroxylase/17,20-lyase

(CYP17A1 inhibitor). Specially, CYP17A1 inhibitors includes nonsteroidal and steroidal types. Steroidal CYP17A1 inhibitor, as abiraterone, is converted by 3βHSD1 of which the downstream metabolites act as AR agonist inducing an opposite effect[25,26].

Biologically, *HSD3B1* (1245C) is supposed to invalidate both abiraterone and enzalutamide. Alyamani *et al.*[27] (Table 2) conducted a study of pharmacokinetic and metabolites of steroidal CYP17A1 inhibitor abiraterone. It concluded that *HSD3B1* might negate efficiency of abiraterone based on the results that the downstream metabolite of abiraterone, 3-keto-5α-abiraterone, an AR agonist, significantly increased with the more copies of *HSD3B1* (1245C) while the level of another metabolite, D4A, an AR antagonist, was not increase. Theoretically, other than abiraterone, enzalutamide may be also negated by *HSD3B1* (1245C). The permissive adrenal effect of *HSD3B1* (1245C) causes increase of testosterone. It was reported that increased AR natural ligand might decrease the activity of enzalutamide[28].

Table 2 Summary of studies about the association between *HSD3B1* variants and PCa treated with other medical management.

Study	Medical Management	Number of Cases	Number of Carriers	Results	Conclusions
Almassi, 2018	Ketoconazole	90	46	For duration of treatment: CC: HR 2.2; 95% CI 1.1-4.4; P=0.02 AC: HR 1.8; 95% CI 1.1-2.9; P=0.01 For disease progression: CC: HR 0.5; 95% CI 0.3-1.1; P=0.08 AC: HR 0.6; 95% CI 0.4-1.0; P=0.06	The HSD3B1 (1245C) variant allele is associated with prolonged time to disease progression among men with metastatic CRPC treated with nonsteroidal CYP17A1 inhibition.

Hahn, 2018	Abiraterone	76	34	For PFS: CC vs. AA: 6.4m vs. 7.3m; P=0.28 CA vs. AA: 6.2m vs. 7.3m; P=0.64	Variant HSD3B1 caused no difference with the response to abiraterone.
Shiota, 2019	Abiraterone	99	14	For treatment failure: AC: HR 0.35; 95% CI 0.13-0.80; P=0.01 For OS: AC: HR 0.40; 95% CI 0.13-0.94; P=0.04	Variant HSD3B1 was associated with less treatment failure and better survival outcome for CRPC treated with abiraterone
Hearn, 2020	ADT randomized plus docetaxel	475	270	Data not shown	Variant HSD3B1 did not appear to be predictive of differential benefit with docetaxel.
Khalaf, 2020	Abiraterone or enzalutamide	546	297	For TTP: CC: HR 1.31; 95% CI 1.02-1.67; P=0.032 For PSA response: CC vs. AC vs. AA: 48% vs. 62% vs. 65%; P=0.019 For TTPP: CC: HR 1.28; 95% CI 0.99-1.66; P=0.064	HSD3B1 (CC) was associated with shorter TTP and less response rate, but not with survival outcome.
Lu, 2020	Abiraterone or enzalutamide	266	123	For PSA30 response: CC vs. AC/AA: 67.7% vs. 68.4%; P>0.99	HSD3B1 (CC) was associated with shorter overall survival, but not with response to treatment.

				For duration of treatment: CC: HR 1.25; 95% CI 0.79-1.97; P=0.34 For OS: CC: HR 1.78; 95% CI 1.03-3.07; P=0.04

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval; CRPC, castrate-resistant prostate cancer; PFS, progression-free survival; OS, overall survival; TTP, time to progression; PSA, prostate specific antigen.

A series of clinical studies were performed to identify the role of *HSD3B1*. Almassi *et al.*[29] focused on the relation between *HSD3B1* and curative effect of nonsteroidal CYP17A1 inhibitor ketoconazole among patients with metastatic CRPC. The conclusion was that *HSD3B1* (1245C) marginally significantly prolonged time of progression. Compared with AA genotype group, HR of AC genotype group for disease progression was 0.6 (P=0.06) and HR of CC genotype group was 0.5 (P=0.08). While Hahn *et al.*[30] focused on the predictive effect of *HSD3B1* (1245C) for patients with CRPC treated with abiraterone as first-line therapy, which turned out that there were no significant association.

Works of both Lu *et al.* and Khalaf *et al.* were interested in the association between *HSD3B1* and abiraterone/enzalutamide. In the work of Khalaf *et al.*[31], 547 patients from two cohorts were involved. For patients with metastatic CRPC treated with abiraterone/enzalutamide, CC genotype had worse time to progression (HR: 1.31, P=0.032) and a nonsignificant trend to worse in terms of time to PSA progression (HR: 1.28; P=0.064). Also, CC genotype was less likely to achieve a PSA response according to PSA response rates (48% for CC, 62 for AC and 65% for AA, P=0.019). However, no association was shown between *HSD3B1* (1245C) and overall survival. In contrast, Lu *et al.*[32] proposed that *HSD3B1* (CC) was related to worse survival outcome (HR: 1.78, P=0.04) and had no association with response to management in patients with mCRPC treated with abiraterone/enzalutamide according to the analysis in cohort of 266 patients.

It was noteworthy that Shiota *et al.*[19] reported a completely opposite conclusion based on a cohort of 99 Japanese patients with CRPC using abiraterone. Patients carrying variant genotypes (CC or AC) had significantly lower progression risk (HR: 0.32, P=0.006) and lower all-cause mortality risk (HR: 0.40, P=0.04) compared with others carrying AA genotype. Furthermore, Shiota *et al.*[33] also studied the combinational use of *HSD3B1* and 5α-reductase (encoding by *SRD5A2*), a key enzyme for conversion of testosterone into DHT. The conclusion showed that *HSD3B1* (AA) with variant genotype of *SRD5A2* led to the worst response to abiraterone in the state of CRPC.

In summary, germline variants at *HSD3B1* influence the therapeutic effects of patients with CRPC, especially for abiraterone and enzalutamide. But there exists a contradiction with regard to the exact function. Further studies are necessary to figure out the role of *HSD3B1*.

POTENTIAL ROLE OF THE *HSD3B1* IN THE CLINICAL MANAGEMENT OF PCA

Based on the current studies, the role of germline *HSD3B1* (1245C) in PCa is summarized as follows: 1) in the state of CSPC, *HSD3B1* (1245C) accelerates resistance to ADT, especially for patients with low-volume diseases; 2) for the survival outcome of patients with CSPC undergoing ADT, evidence of the impact of *HSD3B1* (1245C) is not sufficient; 3) in the state of CRPC, *HSD3B1* (1245C) affects the efficiency of clinical management but cannot be a reliable biomarker because of conflicts in the current results; 4) for the survival outcome of patients with CRPC, *HSD3B1* (1245C) probably has negative effect.

Although how *HSD3B1* functions is still not clear, *HSD3B1* genotype can still provide some advices for clinical management. For patients with advanced PCa receiving ADT, *HSD3B1* variant genotypes can remind physicians of paying more attention to the progression of resistance to ADT. When choosing other medical therapies, germline variants at *HSD3B1* can act as a reference according to current studies.

Additionally, further studies are worth performing to demonstrate the effect of

HSD3B1 variants on clinical management of PCa. In theory, *HSD3B1* (1245C), as an adrenal-permissive allele, is supposed to induce a switch to a reduced tumor dependence on gonadal androgens and augmented dependence on extragonadal androgens. According to the study by Khalaf *et al.*, treatment effect and survival outcome were more favorable in the cohort where ARPIs were used as first-line therapy than other cohorts where previous first-line therapies were allowed[31]. These two facts suggest that using ARPIs in the state of CSPC might benefit patients carrying *HSD3B1* variants. In recent years, abiraterone with ADT was also shown to improve the prognosis of CSPC[34,35]. As a result, predictive role of *HSD3B1* variants for abiraterone used in the state of CSPC is a potential topic of further research.

Besides, some points provide potential directions for future study in order to identify the association between *HSD3B1* and clinical management of PCa. First, *HSD3B1* variants presents a significant inter-ethnic disparity. For example, frequency of *HSD3B1* (1245C) is 34% for European, 20% for American, 16% for South Asian, 9% for African, and 8% for East Asian[36]. Inter-ethnic disparity may be one of the explanations to the opposite outcomes about the effect of *HSD3B1* (1245C) on abiraterone. Second, loss of heterozygosity (LOH) is presented in the *HSD3B1* gene. Hearn *et al.*[17] observed that three of eleven (27%) patients with *HSD3B1* (AC) had developed CRPC with LOH of the wild-type allele, whereas none had lost the variant allele. This observation might explain better treatment outcome when ARPIs were used as first-line therapy. Third, Hearn *et al.*[21] concluded that influence of *HSD3B1* depends on the tumor burden (the extent of metastatic disease), which might be worth in-depth study. At last, it remains to be studied whether *HSD3B1* can be treated as a therapeutic target for PCa, about which no work has been reported up to now. However, the therapeutic potential of targeting *HSD3B1* was reported in triple-negative breast cancer based on an *in vitro* study[37].

CONCLUSION

HSD3B1 (1245C) was found to be associated with ADT resistance and poorer prognosis. Its association with next generation hormone therapy is still unclear (i.e., Abiraterone). Very few commercial genetic profiling products have included this variant in routine testing. However, its clinical impact as well as its high cost-effectiveness (single variant testing should be at a very low price) should not be

underestimated. Based on the review of current evidence, clinicians should probably consider a more aggressive treatment or follow-up strategy for patients with *HSD3B1* (1245C) variants who were undergoing ADT.

DECLARATIONS

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Authors' contributions

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Consent for publication

All authors contributed to the article and approved the final version.

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