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Review

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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 3β-hydroxysteroid dehydrogenase isoenzyme-1 (3βHSD1, encoded by HSD3B1) catalyzes the rate-limiting step. A germline missense-encoding variant of HSD3B1(1245A>C, rs1047303) has been the focus of research 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 of CRPC and the outcome of clinical management. Thus, we searched the published research articles using the keywords "prostate cancer" and "HSD3B1", in PubMed and Embase database. After reviewing the abstracts and full articles, 16 original research articles from 45 search results were finally selected and reviewed. Based on the current evidence, HSD3B1(1245C) is proposed to accelerate ADT resistance and the development of CRPC. It is also associated with a poorer prognosis of PCa treated with ADT. However, due to conflicting 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. In conclusion, HSD3B1(1245C) has value for predicting the outcome of PCa and 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 the 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 steroids, such as dehydroepiandrosterone (DHEA)[6,7]. The androgen synthesis is considered to induce the reactivation of AR. When the disease finally progresses to the state of CRPC, it becomes highly lethal. 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 3β-hydroxysteroid dehydrogenase isoenzyme-1 (3βHSD1, encoded by HSD3B1), which catalyzes the rate-limiting step in the metabolic conversion from DHEA to testosterone and DHT in the 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 that is degraded more rapidly, while HSD3B1(1245C), an adrenal-permissive allele, codes a stable enzyme resistant to proteasomal degradation that promotes robust conversion from DHEA to DHT[13,14]. A series of studies indicated that genetic variants in HSD3B1 are associated with the progression of PCa and resistance of ADT. In this review, the homozygous variant genotype is referred to as HSD3B1 (CC), while the heterozygous genotype and homozygous wild type are referred to as HSD3B1 (AC) and HSD3B1 (AA), respectively.

In this review, we summarize the published studies regarding the association between HSD3B1 and the clinical management of PCa, including both CSPC and CRPC. We also discuss the contemporary significance of HSD3B1 and its potential value in the therapeutic decision in PCa.

EVIDENCE SYNTHESIS

We searched the published research articles using the keywords "prostate cancer" and "HSD3B1", in PubMed and Embase database. In total, 45 results were found. After review of the abstracts 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 shows 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 Ross *et al.*[15] first reported in 2008 that SNPs 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 the synthesis of non-testicular testosterone or DHT. Wu *et al.*[16] in 2015 first summarized that HSD3B1(1245C) PCa is more likely to progress to CRPC, 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.

Hearn *et al.*[17] reported that HSD3B1(1245C) is significantly associated with PCa resistance to ADT. As a multi-cohort study, they 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 the primary cohort, compared with the AA genotype group, the CC genotype groups (HR = 2.4; P = 0.029) and the AC group (HR = 1.7; P = 0.041) were associated with worse progression-free survival (PFS). However, in the other two cohorts, CC showed the same significant effect on development to CRPC, while the association between the AC genotype and the progression of CRPC was not significant (HR = 1.1; P = 0.38). In addition, the variant allele was predictive to a worse overall survival.

Subsequently, a few 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 the AA genotype group, in the CC genotype group, PFS was shorter (11 months *vs.* 21 months; HR = 2.16; P = 0.046), while that in the AC genotype groups was similar (19 months *vs.* 21 months; HR = 1.04; P = 0.86). Shiota *et al.*[19] also performed an analysis on a primary ADT cohort with 104 Japanese patients of metastatic CSPC where the frequency of variant was 5%. The results shown that patients with the CC genotype and the AC genotype were more likely to be resistant to ADT (HR = 2.34; P = 0.03) but had no significant difference for mortality.

Hearn *et al.*[20] furthered their studies on the basis of their original report. 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. Furthermore, analyses were performed on the E3805 Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer cohort which included patients with metastatic PCa undergoing ADT with or without docetaxel. They concluded that HSD3B1(1245C) was 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].

The current clinical studies on the role of HSD3B1 in CSPC patients treated with ADT are discussed above. With regard to the effect of HSD3B1 (CC) for accelerating the resistance to ADT and progression to CRPC, the results of current studies are in agreement. A meta-analysis by Han *et al.*[22] confirmed this conclusion and also concluded that HSD3B1 had no association with mortality. Except the outcome in the primary cohort of the Hearn's study in 2016[17], HSD3B1(1245C) was noted to have no impact on the mortality of CSPC. At 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.*[21], the effect of HSD3B1 was only found in patients with low-volume PCa. It was difficult to derive a precise conclusion from the analysis for the overall cohort. In addition, it is worth noting that the association between the AC genotype and

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

Study	Medical management	No. of Cases	No. of Carriers	Results	Conclusions
Ross *et al.*[15], 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 *et al.*[16], 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 *et al.*[17], 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; *P* = 0.013 AC: HR = 2.0; 95%CI: 1.1-3.7; *P* = 0.036	Patients carrying variant HSD3B1 are more likely to fail with ADT and to have worse survival outcome
	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	
Agarwal *et al.*[18], 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 *et al.*[20], 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 *et al.*[19], 2019	ADT	104	9	For PFS: CC/AC: HR = 2.34; 95%CI: 1.08-4.49; *P* = 0.03 For OS: CC/AC: HR = 1.36; 95%CI: 0.52-2.92; *P* = 0.50	Variant HSD3B1 was associated with shorter PFS but not with death risk
Hearn *et al.*[21], 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 *et al.*[23], 2020	ADT	101	42	For OS: CC/AC *vs.* AA: 5.0 years vs. 6.5 years; *P* = 0.052	Variant HSD3B1 was marginally significantly associated with shorter OS

*Except for the study by Ross *et al.*[15] (rs1856888), all other studies investigated the variant rs1047303. ADT: Androgen deprivation therapy; TTP: time to progression; HR: hazard ratio; 95%CI: 95% confidence interval; CRPC: castrate-resistant prostate cancer; PFS: progression-free survival; OS: overall survival.

survival outcome remains unclear. The effect of the AC genotype on promoting resistance 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 study, no difference in overall survival was observed between the 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 has been reported that HSD3B1(1245C) might have a negative effect on the overall survival of CRPC. However, there are contradictions in the existing results about its association with the response to medical management, such as abiraterone and enzalutamide, in the state of CRPC.

Stangl-Kremser *et al.*[24] and Chen *et al.*[23] both summarized 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 is not clear whether HSD3B1(1245C) induces an impaired survival outcome in the state of CRPC. It would also be 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 antagonists including enzalutamide and CYP17A1 inhibitors including 17α-hydroxylase/17,20-lyase. In addition, CYP17A1 inhibitors include nonsteroidal and steroidal types. Steroidal CYP17A1 inhibitors, such as abiraterone, are converted by 3βHSD1, the downstream metabolites of which act as AR agonists, 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 on the pharmacokinetics and metabolites of the steroidal CYP17A1 inhibitor abiraterone. They concluded that HSD3B1 might negate the efficiency of abiraterone based on the results that the downstream metabolite of abiraterone, 3-keto-5α-abiraterone, which is an AR agonist, significantly increased with more copies of HSD3B1(1245C), while the level of another metabolite, D4A, which is an AR antagonist, did not increase. Theoretically, in addition to abiraterone, enzalutamide may also be negated by HSD3B1(1245C). The permissive adrenal effect of HSD3B1(1245C) causes an increase of testosterone. It has been reported that increased the AR natural ligand might decrease the activity of enzalutamide[28].

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

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

Study	Medical management	No. of Cases	No. of Carriers	Results	Conclusions
Almassi *et al.*[29], 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, *et al.*[30], 2018	Abiraterone	76	34	For PFS: CC *vs.* AA: 6.4 m *vs.* 7.3 m; *P* = 0.28 CA *vs.* AA: 6.2 m *vs.* 7.3 m; *P* = 0.64	Variant HSD3B1 caused no difference with the response to abiraterone
Shiota *et al.*[19], 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 *et al.*[21], 2020	ADT randomized plus docetaxel	475	270	Data not shown	Variant HSD3B1 did not appear to be predictive of differential benefit with docetaxel
Khalaf *et al.*[31], 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 *et al.*[32], 2020	Abiraterone or enzalutamide	266	123	For PSA30 response: CC *vs.* AC/AA: 67.7% *vs.* 68.4%; *P* > 0.99 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	HSD3B1 (CC) was associated with shorter overall survival, but not with response to treatment

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.

Both Khalaf *et al.*[31] and Lu *et al.*[32] investigated 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, the CC genotype had worse time to progression (HR = 1.31; *P* = 0.032) and a nonsignificant trend to shorter time to PSA progression (HR = 1.28; *P* = 0.064). In addition, the CC genotype was less likely to achieve a PSA response according to the 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 of a cohort of 266 patients.

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 the 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. They 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 of HSD3B1 influence the therapeutic effects of patients with CRPC, especially for abiraterone and enzalutamide. However, 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 published 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 conflicting results; and (4) for the survival outcome of patients with CRPC, HSD3B1(1245C) probably has a negative effect.

Although how HSD3B1 functions is still not clear, the HSD3B1 genotype can still provide some advice for clinical management. For patients with advanced PCa receiving ADT, HSD3B1 variant genotypes can remind physicians to pay more attention to the progression of resistance to ADT. When choosing other medical therapies, germline variants of 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 considered 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.*[31], the 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. 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, a 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 the clinical management of PCa. First, HSD3B1 variants present a significant inter-ethnic disparity. For example, the frequency of HSD3B1(1245C) is 34% for European, 20% for American, 16% for South Asian, 9% for African, and 8% for East Asian patients[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 3 of 11 (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 the better treatment outcome when ARPIs were used as first-line therapy. Third, Hearn *et al.*[21] concluded that the 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) has been 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 is usually inexpensive) should not be underestimated. Based on the review of the current evidence, clinicians should consider a more aggressive treatment or follow-up strategy for patients with HSD3B1(1245C) variants who are undergoing ADT.

DECLARATIONS

Authors' contributions

Conception and design: Na R, Huang D, Huang J
Literature review: Huang J, Huang D
Manuscript writing: Na R, Huang D, Huang J
All authors contributed to the article and approved the final version.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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