

Association Between CYP17A1, CYB5A Polymorphisms and Efficacy of Abiraterone Acetate/Prednisone Treatment in Castration-Resistant Prostate Cancer Patients

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine

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Purpose: The purpose of this study was to investigate the association between single nucleotide polymorphisms (SNPs) of CYP17A1, CYB5A and the efficacy of abiraterone acetate treatment in patients with castration-resistant prostate cancer (CRPC).

Patients and Methods: Data were collected from 58 CRPC patients who had been treated with abiraterone acetate/prednisone (AA/P). The SNPs rs743572 and rs10883783 on CYP17A1 and SNPs rs1790834 and rs1790858 on CYB5A were assayed, and their relationship with prostate-specific antigen (PSA) response in patients after AA/P treatment, overall survival (OS) and progression-free survival (PFS) were analyzed by logistic regression, Cox regression, Kaplan–Meier and Log rank analyses.

Results: The SNP rs1790834 on CYB5A showed significant association with PSA response in CRPC patients treated with AA/P ($P < 0.05$), but rs743572, rs10883783 and rs1790858 did not. The rs1790834 variant significantly decreased both PFS and OS ($P < 0.05$).

Conclusion: The CYB5A rs790834 genotype is a novel SNP related to CRPC and may be used as a biomarker for CRPC treatment.

Keywords: abiraterone, androgens, castration-resistant prostate cancer, CYP17A1, CYB5A

Introduction

Prostate cancer (PCa) is one of the most common malignancy, which caused approximately 29,430 deaths in the United States in 2018.¹ In China, the incidence of PCa is much lower than that in Western countries, but is increasing linearly every year due to unhealthy lifestyles. The growth of PCa requires androgens, which are detected by androgen receptor (AR). At early stage, PCa could be treated by radical prostatectomy, brachytherapy and radiotherapy. When PCa recurs, the androgen deprivation therapy (ADT), which inhibits the function of AR, displays good efficacy in most PCa patients. However, increased production of androgen in tumor cells, overexpression and mutation of AR, changes in coregulatory molecules and alteration of factors indirectly activating AR would invalidate ADT.^{2–4} Proliferation of cancer cells was then stimulated, causing castration-resistant prostate cancer (CRPC)⁵ and finally leading to a lethal outcome.⁶

Many studies suggest that recurrent PCa patients are neither hormone refractory nor androgen independent, but maintain a clinically reliance on the AR signaling axis.^{7–9} Due to high sensitivity to the residual level of exogenous prostaglandins,

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the AR signaling axis is vital to the understanding of steroid synthesis signaling pathways in PCa and is a promising target pathway for the treatment of CRPC. PCa studies have focused on candidate genes based on biological pathways relevant to prostate carcinogenesis, including cytochrome P450 17A1 (CYP17A1), 17 β -hydroxysteroid dehydrogenase (HSD17B) family and 5 α reductase (SRD5A).^{10–15} Some new drugs targeting on the AR signaling axis have been reported to successfully slow-down CRPC progression and improve survival. For example, abiraterone is an inhibitor of CYP17A1, presumably through blockade of multiple steroidogenic enzymes and antagonism of AR.¹⁶ Recent studies showed that abiraterone acetate and prednisone (AA/P) significantly increased overall survival (OS) in patients at castration-resistant stage.^{3,14,16}

Androsterone is synthesized by the sequential action of several enzymes, particularly CYP17A1 and heme-containing protein cytochrome b5 (CYB5A). CYB5A is a membrane-bound cytochrome that reduces methemoglobin to ferrous hemoglobin and stimulates CYP17A1 activity.^{17,18} Since CYP17A1 and CYB5A are directly or indirectly involved in the biosynthesis of androgen, genetic variation of these two genes may affect prostate growth, development of PCa and its sensitivity to chemical treatment.^{19–21} Single nucleotide polymorphism (SNP) represents a difference in a single nucleotide in DNA sequence. It is the most common genetic variation in human. Binder et al²² reported that the SNP rs26486758 on CYP17A1 was associated with lower odds of experiencing a biochemical response and a shorter time to biochemical progression in CRPC patients. Besides, Wang et al²⁰ revealed significant associations between rs619824, rs2486758 polymorphisms and PCa risk, as well as a significant association between rs743572 polymorphism and PCa risk in Black population but not in Caucasian or Asian populations. Salvi et al¹⁴ highlighted no significant associations between rs743572, rs10883783, rs17115100, rs284849 polymorphisms on CYP17A1 and clinical outcome of CRPC. However, individuals with the most common TT genotype for rs10883783 had a 3 months' longer progression-free survival (PFS) than individuals with the TA + AA genotype.¹⁴ Wright et al²³ found that men with the variant A allele in rs10883783 had a 56% risk reduction in PCa-specific mortality. Obviously, studies on the relationship between prostate cancer outcomes and CYP17 gene rs743572, rs10883783 variants showed conflicting results. More investigations

are still required. In CYB5A, both rs1790834 and rs1790858 were associated with rheumatoid arthritis.²⁴ Furthermore, the SNP rs1790834 may help to maintain androgen levels in women.²⁵ However, their relationship with PCa risk has not been reported to the best of our knowledge.

In the present study, to clarify the association between CYB5A rs1790834, rs1790858 variants and responses to AA/P, as well as to validate the association between CYP17A1 rs743572, rs10883783 variants and responses to AA/P, 58 CRPC patients were examined. Moreover, the relationship between clinical efficacy of AA/P and these SNPs were also investigated. These results may contribute more information for the clinical treatment of CRPC.

Patients and Methods

Patients

This study was approved by the Ethics Committee of the Fujian Provincial Hospital. As a retrospective survey, preparation of informed consent was exempted by the Ethics Committee. The study was conducted according to the principles of the Declaration of Helsinki (2013). Records and/or information of all patients were anonymized and de-identified before analyses.

From January 2015 to December 2018, approximately 80 participants diagnosed as hormone-refractory prostate cancer (HRPC) and treated with AA/P without chemotherapy or second-line treatment were collected from the Fujian Provincial Hospital and the First Hospital of Peking University. The HRPC criteria as follows: (1) Androgen deprivation with serum testosterone <50 ng/dL; (2) Rising prostate-specific antigen (PSA) defined as three rises of PSA two weeks apart; (3) Anti-androgen withdrawal therapy for more than four weeks; (4) Progression of PSA during second-line treatment; (5) Progression of bone or soft tissue metastatic. Finally, 58 patients diagnosed as CRPC were included in the present study.

SNP Sequencing

Two SNPs on CYP17A1 (rs743572 and rs10883783) and two SNPs on CYB5A (rs1790834 and rs1790858) were included in the present study. Genomic DNA was isolated from whole blood using Biospin Whole Blood Genomic DNA Extraction Kit (Bioer, Hangzhou) and then stored at -20°C . Purified DNA was amplified for detection of the CYP17A1 and CYB5A variants using the TaqMan real-time quantitative polymerase chain reaction (RT-qPCR) assay.²⁶ Primer

Table 1 Primer Sequences and TaqMan Probes of rs743572, rs10883783, rs1790834 and rs1790858

Genes	Primer Sequences	TaqMan Probes
rs743572	Forward 5'-TTGGGCCAAAACAATAAGC-3' Reverse 5'-GGGCTCCAGGAGAATCTTTC-3'	5'-CGGTGGAGTAGAAGAG-3'
rs10883783	Forward 5'-CTATGGCAGGATGAGGGTGT-3' Reverse 5'-TGAGTTTGCTGTGGACAAGG-3'	5'-TGGAGCCAAGAGTTT-3'
rs1790834	Forward 5'-ATACGGACTGACCCCATCTG-3' Reverse 5'-CCAGTCCACCAGGACATTCT-3'	5'-TGGAGCCAAGAGTTT-3'
rs1790858	Forward 5'-CGAACTGCTGGACTCAAG-3' Reverse 5'-GATTATCTTCTTGGCTCTGTAG-3'	5'-GAGGGGACACGCGAGAGA-3'

sequences and TaqMan probes are shown in Table 1. For each 25 μ L of PCR reaction, 5 μ L extracted DNA was used. The reaction was initially carried out at 95 °C for 10 min, followed by 40 cycles of denaturation at 94 °C for 30 s, annealing at 42 °C for 90 s, and extension at 72 °C for 30 s, with a final extension at 72 °C for 5 min. All DNA samples were analyzed in duplicate using a TaqMan PCR Master Mix on a 7500 real-time PCR cyclers according to the manufacturer's instructions.

Clinical Data

Treatment consisted of 28-day cycles of 1000 mg of abiraterone acetate daily on an empty stomach with 5 mg of prednisone twice per day. Treatment continued until there was evidence of disease progression and/or unacceptable toxicity. Before commencement of treatment, blood samples were collected from all patients to measure the level of PSA, and all patients underwent a computed tomography (CT) scan of the chest and abdomen. Patients were evaluated monthly to check the change of PSA level and to monitor any hepatic and renal toxicity. CT scan was performed every 3 months during treatment with abiraterone. Disease progression was defined according to the Prostate Cancer Working Group 2 (PCWG2) criteria.²⁷ Compared with the PSA level before treatment, a 50% decline of PSA level, which could be repeatedly confirmed after at least three weeks, was considered as non-progression. Progression was defined as the increase in PSA. After therapy by AA/P, the data of PSA level, testosterone level, age, tumor node metastasis (TNM) stages, Gleason score and Eastern Cooperative Oncology Group (ECOG) for each patient were recorded.

Statistical Analysis

Tests for Hardy–Weinberg equilibrium were performed for each SNP. Fisher's exact test and Chi-square test were used to compare biochemical responses to AA/P between various

SNP groups. PFS was defined as the time from the starting date of abiraterone treatment to the first observation of progression, relapse or death (whichever came first). OS was defined as the time from the starting date of abiraterone treatment to the date of death resulted from any cause. The Kaplan–Meier method was used to estimate PFS and OS. The Log-rank test was carried out to compare the PFS and OS curves between different genotypes. Logistic regression was used for association analyses. Odds ratios (OR) and 95% confidential intervals (CI) were calculated. Cox proportional hazards regression was used to assess the association between genetic variation and time to biochemical progression. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 23.0.

Results

The clinical and pathological characteristics of the 58 patients included in the present study are shown in Table 2. At the time of initial PCa diagnosis, the median age, PSA level and testosterone level of patients were 69 years, 4.75 ng/mL and 0.95 nmol/L, respectively. Forty-eight patients (83%) had Gleason score of ≥ 8 .

All studied SNP polymorphisms were in Hard-Weinberg equilibrium (HWE). PSA level decreased for 50% was defined as effective PSA response. Statistical analyses showed a significant association between rs1790834 and PSA response (AA vs GG, $P = 0.02$; AG + AA vs GG, $P = 0.047$), but no significant association between rs743572, rs10883783, rs1790858 and PSA response (Tables 3 and 4).

Based on the data of all CRPC patients, treatment with AA/P revealed the median PFS of 12 months (95% CI: 10.794–13.206) and the median OS of 28 months (95% CI: 24.526–31.474) (Figure 1). For rs1790834, significant

Table 2 Clinical Characteristics of the 58 Patients Involved in the Present Study. Demographics Were the Values at the Time of Initial Diagnosis

Indices	Values
Demographics	
Median age (years)	69 (50–82)
Median prostate-specific antigen (ng/mL)	4.75 (1–67.8)
Median testosterone level (nmol/L)	0.95 (0.3–7)
Stage	
T1–T2b	0 (0%)
T2c	1 (2%)
T3+	57 (98%)
N+	27 (47%)
M+	58 (100%)
Gleason Grade	
5–6	0 (0%)
7	10 (17%)
8–10	48 (83%)
Chemotherapy	25 (43%)
ECOG Score	
0–1	57 (98%)
2	1 (2%)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

differences in either PFS or OS were detected between patients with GG and AG + AA ($P < 0.001$). The PFS of patients with GG variant (14 months) was 4 months longer than those with AG+AA genotype (10 months) (Figure 2).

The results of Cox proportional hazards analyses for PFS and OS are shown in Table 5. Cox regression analysis with adjustment for age, Gleason score and tumor stage at diagnosis showed that rs1790834 variation significantly affected PFS and OS of CRPC patients. The hazard ratios of AG genotype and AA genotype were greatly higher than those of GG genotype for both PFS and OS.

Discussion

Endogenous hormones, especially androgens, are required for essential prostate functions, and affect the proliferation

Table 3 Association of CYP17A1 and CYB5A Gene Polymorphisms with PSA Response. PSA Response Was Defined as 50% Reduction of PSA Level After Treatment with AA/P

Genotype	Case Number (%)	P value	OR (95% Confidential Interval)
rs1790834 (G>A)			
GG ^a	27 (46.6)		1.000 (reference)
AG	26 (44.8)	0.110	–
AA	5 (8.6)	0.020 ^b	–
AG+AA	31 (53.4)	0.047	–
rs1790858 (C>T)			
CC ^a	25 (43.1)		1.000 (reference)
CT	27 (46.6)	1.000	1.091 (0.199–5.981)
TT	6 (10.3)	1.000 ^b	–
CT+TT	33 (56.9)	1.000	1.364 (0.251–7.407)
rs10883783 (T>A)			
TT ^a	2 (3.4)		1.000 (reference)
AT	27 (46.6)	0.200 ^b	0.080 (0.004–1.818)
AA	29 (50)	0.245 ^b	0.115 (0.006–2.361)
AT+AA	56 (96.6)	0.198 ^b	10.2 (0.55–189.125)
rs743572 (A>G/A>T)			
AA ^a	14 (24.1)		1.000 (reference)
AG/AT	33 (56.9)	1.000	0.558 (0.057–5.490)
GG/TT	11 (19.0)	1.000 ^b	0.769 (0.043–13.866)
AG+GG/AT+TT	44 (75.9)	1.000	0.600 (0.064–5.619)

Notes: ^aReference group. ^bFisher's exact test.

Abbreviation: PSA, prostate-specific antigen.

and differentiation of luminal epithelia.¹² Since endogenous factors affecting the functional genome may differ among different populations, it is important to define the polymorphic spectrum of genes that are implicated in cancer causation. The biosynthesis of androgens depends on two key enzymes, 17 α -hydroxylase and 17.20-lyase. Both of them link to CYP17A,²⁸ and 17.20-lyase activity requires additional participation of P450 oxidoreductase and CYB5A.²⁹ In addition, CYB5A is also involved in a number of other processes such as drug metabolism and fatty acid desaturation.³⁰ Thus, CYP17A and CYB5A are greatly important to androgen synthesis and may influence prostatic carcinogenesis and its sensitivity to chemotherapy.

Table 4 Logistic Regression Analyses Between rs1790834 Variants and PSA Response

Model	rs1790834	rs1790858	rs10883783	rs743572
Unadjusted	OR (NA), $P = 0.025$	OR (NA), $P = 0.748$	3.54 (0.051–247.277), $P = 0.276$	0.688 (0.047–10.103), $P = 0.799$
Age-adjusted	OR (NA), $P = 0.025$	OR (NA), $P = 0.755$	4.29 (0.069–266.691), $P = 0.288$	0.688 (0.047–10.093), $P = 0.791$
TNM-adjusted	OR (NA), $P = 0.020$	OR (NA), P (NA)	OR (NA), $P = 0.430$	OR (NA), P (NA)

Abbreviations: PSA, prostate-specific antigen; OR, odds ratio; NA, not available; TNM, tumor node metastasis.

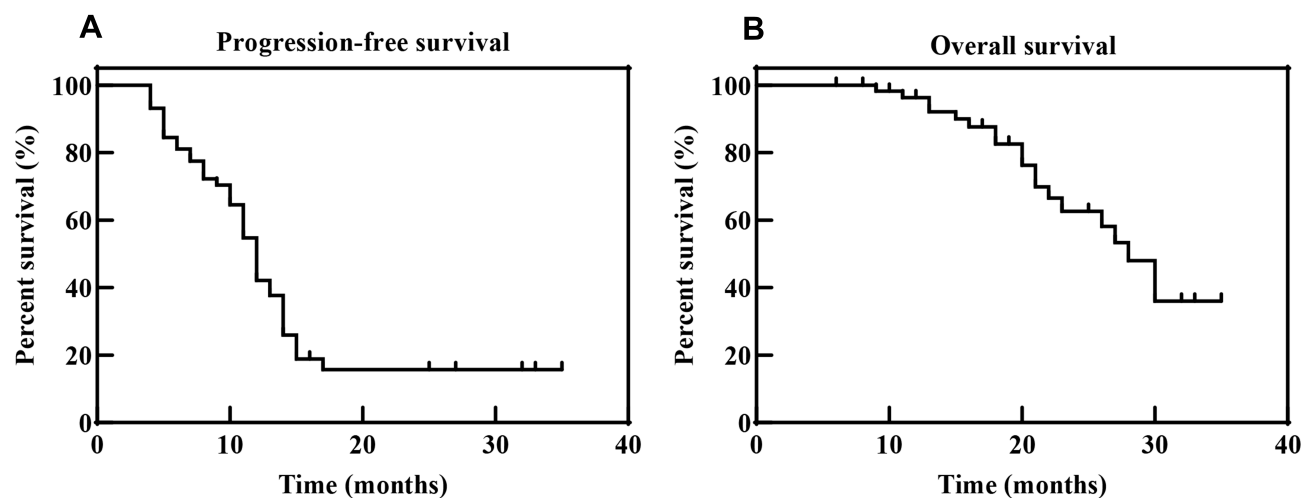


Figure 1 Kaplan-Meier curves of progression-free survival (A) and overall survival (B) for all 58 patients.

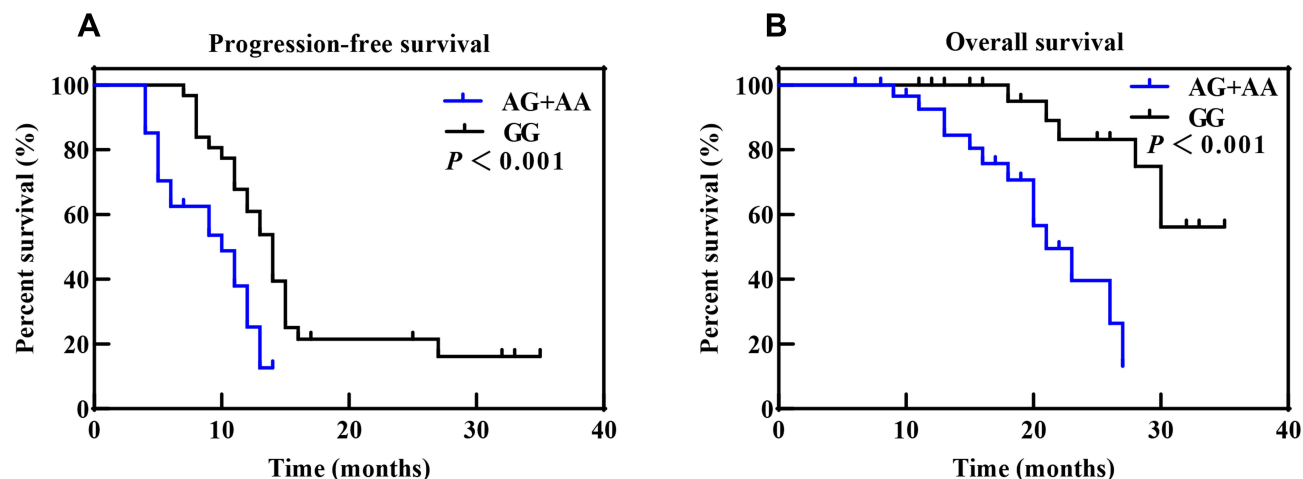


Figure 2 Kaplan-Meier curves of progression-free survival (A) and overall survival (B) for patients with different CYP17A1 rs1790834 genotypes.

In previous studies, the rs743572 and rs10883783 polymorphism of CYP17A1 showed no significant association with PCa risk.^{31–34} A meta-analysis between 2404 PCa patients and 2755 health persons concluded that the rs743572 polymorphism was unlikely to alter PCa risk.³⁵ In the present study, rs10883783 and rs743572 on CYP17A1 did not show significant association with PSA response, suggesting that mutation on these two sites might not contribute to efficacy and AA/P treatment in Chinese patients. These results were consistent with the results provided by Wang et al,²⁰ Salvi et al,¹⁴ Han et al¹² and Severi et al,³¹ but conflicted with the results from African-American and Japanese men.^{23,36,37} Salvi et al¹⁴ revealed that patients with TT genotype on rs10883783 showed better survival than TA + AA genotype, but Wright et al²³ found that the variant A allele had a lower risk of PCa-specific mortality. In

the present study, our data cannot support or deny these two conclusions, due to insufficient sample size. Only two patients had TT variant on rs10883783 in the present study. More samples are still required to test this hypothesis on Chinese population in future.

Compared with CYP17A1, association between efficacy of AA/P treatment and SNPs on CYP5A was less investigated. In the present study, two SNPs (rs1790858 and rs1790834) were investigated. SNPs rs1790858 showed no significant association with PSA response. However, rs1790834 was significantly correlated with PSA response. More importantly, the variant AG+AA showed significantly lower PFS and OS than GG, respectively. These results indicated that patients with AG + AA might be less effective to AA/P treatment than GG, which could be useful for selection of therapeutic plan. To the

Table 5 Cox Proportional Hazards Model of Biochemical Progression for CRPC Patients

Genes rs1790834	Progression-Free Survival	Overall Survival
GG ^a	HR 1.000 (reference), P < 0.001	HR 1.000 (reference), P < 0.001
AG	HR 2.752 (1.415–5.354), P = 0.003	HR 9.248 (2.253–37.959), P = 0.002
AA	HR 10.624 (3.012–37.47), P < 0.001	HR 42.492 (7.074–255.253), P < 0.001
rs1790858		
CC ^a	HR 1.000 (reference), P = 0.883	HR 1.000 (reference), P = 0.393
CT	HR 1.132 (0.570–2.250), P = 0.723	HR 0.730 (0.240–2.224), P = 0.580
TT	HR 0.893 (0.309–2.576), P = 0.834	HR 2.099 (0.543–8.111), P = 0.282
rs10883783		
TT ^a	HR 1.000 (reference), P = 0.719	HR 1.000 (reference), P = 0.892
AT	HR 0.576 (0.108–3.081), P = 0.519	HR 1.581 (0.131–19.027), P = 0.718
AA	HR 0.715 (0.137–3.717), P = 0.690	HR 1.774 (0.157–20.037), P = 0.643
rs743572		
AA ^a	HR 1.000 (reference), P = 0.917	HR 1.000 (reference), P = 0.366
AG/AT	HR 1.025 (0.451–2.326), P = 0.954	HR 0.897 (0.277–2.912), P = 0.857
GG/TT	HR 1.222 (0.408–3.657), P = 0.721	HR 2.373 (0.466–12.081), P = 0.298

Note: ^aReference group.

Abbreviations: CRPC, castration-resistant prostate cancer; HR, hazard ratio.

best of our knowledges, this is the first report for the relationship between rs1790834 and efficacy of AA/P treatment in PCa patients.

In humans, CYP17A1 catalyzes the 17 α -hydroxylase and 17,20-lyase reactions to convert pregnenolone to 17 α -hydroxypregnenolone and dehydroepiandrosterone (DHEA), and also catalyzes the 17,20 lyase reaction to produce androstenedione.^{38,39} DHEA and androstenedione are the precursors of androgen and testosterone.⁴⁰ Meanwhile, CYB5A promotes the 17,20-lyase reaction by CYP17A1. Peacock et al⁴¹ identified a rare polymorphism on the pig CYB5A gene just upstream of the translational start site, which decreased levels of CYB5A and synthesis of androstenedione. Similarly, the SNP rs1790834 is localized to the intron 1 of the CYB5A gene in

humans. Genotype dependent gene expression in synovial fibroblasts, a cell type potentially responsible for androgen biosynthesis in the joint, showed an association between the rare allele of rs1790834 and increased CYB5A expression,^{24,25} which then should promote the biosynthesis of androgen. A high level of androgen would negatively affect the efficacy of ADT and then increase the risk of CRPC.

Associations between four SNPs and efficacy of ADT were analyzed in the present study. The results showed that the SNP rs1790834 might be a promising biomarker for selection of the best treatment method for CRPC patients. However, the present study only investigated 58 patients and all the patients were from the mainland of China. Investigations on more patients are still required to test the conclusions in different populations. Moreover, the present study demonstrated that CYB5A was an important gene for CRPC patients. The pharmacokinetics and pharmacodynamics of abiraterone on patients with different CYB5A genotypes should be further investigated.

Conclusion

This study found that the SNP rs1790834 is associated with the efficacy of AA/P in CRPC patients and decreases the sensitivity of patients to ADT. No associations were found between the SNPs rs743572, rs10883783, 1790858 and PSA response. There is a promising approach of primary genotyping to select the best treatment method in prostate cancer patients.

Acknowledgments

The authors thank all the staff of Fujian Provincial Hospital and all patients that were associated with this study. This work was supported by the Youth Innovation Project of Fujian Natural Science Foundation (No. 2018J05123) and the Young and Middle-aged Key Talents Training Project of Fujian Provincial Health Commission (No. 2017-ZQN-2).

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflict of interests to declare.

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