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Germline Predictors of Androgen Deprivation Therapy Response in Advanced Prostate Cancer

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Abstract

Objective: To evaluate whether germline variations in genes involved in sex steroid biosynthesis and metabolic pathways predict time to treatment failure for patients with advanced prostate cancer undergoing androgen deprivation therapy (ADT), because there are few known clinical predictors of response.

Patients and Methods: In a cohort of 304 patients with advanced prostate cancer undergoing ADT, we genotyped 746 single-nucleotide polymorphisms (SNPs) from 72 genes from germline DNA (680 tagSNPs from 58 genes and 66 candidate SNPs from 20 genes [6 genes common in both]). Association with the primary end point of time to ADT failure was assessed using proportional hazards regression models at the gene level (for genes with tagging SNPs) and at the SNP level. False discovery rates (FDRs) of 0.10 or less were considered noteworthy to account for multiple testing.

Results: At the gene level, *TRMT11* showed the strongest association with time to ADT failure ($P<.001$; FDR=0.008). Two of 4 *TRMT11* tagSNPs were associated with time to ADT failure. Median time to ADT failure for rs1268121 (A>G) was 3.05 years for the AA, 4.27 years for the AG, and 6.22 years for the GG genotypes ($P=.002$), and for rs6900796 (G>A), it was 2.42 years for the GG, 3.52 years for the AG, and 4.18 years for the AA genotypes ($P<.001$). No other gene level or SNP level tests had an FDR of 0.10 or less.

Conclusion: Genetic variation in *TRMT11* was associated with time to ADT failure. Confirmation of these preliminary findings in an independent cohort is needed.

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Prostate cancer is a leading cause of cancer-related mortality in the United States,[1] with an estimated 32,050 deaths in 2010. Mortality from prostate cancer occurs primarily in patients with advanced-stage disease, for which the initial treatment for hormone-sensitive prostate cancer is androgen deprivation therapy (ADT). Although not curative,[2] ADT enhances the duration of disease control and offers significant palliation of symptoms, although it is almost universally followed by progression to a hormone-resistant state. The durability of response to ADT is heterogeneous and can vary from a few months to several years, with a median time ranging from 18 to 30 months.[3-6] Gleason score and prostate-specific antigen (PSA) levels have been evaluated as predictors of response durability,[7] but results are mixed and these factors are not used in the clinical management of patients for predicting response to ADT. Because the number of patients with prostate cancer treated each year with ADT is a major public health burden, with an estimated one-third of the prostate cancer patient population (prevalence, 2.276 million patients in 2007 in the United States[8]) undergoing ADT at some time during their cancer care, identifying patient profiles associated with therapy success, failure, or both is a high priority.

The paucity of predictive factors for ADT response has led to investigation of a role for germline variation to predict durability of response, but results of single-nucleotide polymorphisms (SNPs) with significant associations to response have been limited.[9-11] Recently, genetic variants in 2 androgen transporter genes, *SLCO2B1* and *SLCO1B3*, have been reported to be associated with time to progression in patients receiving ADT.[12] Because the clinical outcome of time to ADT failure may have multiple genetic determinants associated with the phenotype, we evaluated the genetic variation in genes implicated in sex steroid hormonal biosynthetic and metabolic pathways in 2 prostate cancer patient cohorts receiving ADT and report results of this candidate gene association study.

PATIENTS AND METHODS

Study Population

Patients for this analysis were derived from 2 clinical databases of patients with advanced, nonlocalized

prostate cancer in whom ADT failed at Mayo Clinic, Rochester, MN, and the University of Rochester, Rochester, NY. Both clinical databases have been reviewed and approved for conducting research by the institutional review boards.

At Mayo Clinic, patients with prostate cancer have been prospectively enrolled in a registry since 2003 through the Mayo Clinic Prostate Cancer Specialized Program of Research Excellence (SPORE) Clinical Research Core. The registry collects peripheral blood samples, and DNA is extracted from one of the tubes. To be included in this study, patients had to be receiving failing ADT for advanced, nonlocalized, hormone-sensitive prostate cancer and have an adequate DNA specimen.

The other cohort of patients was obtained from a registry in collaboration with the investigators at the University of Rochester. Patients were prospectively enrolled from 2005 to 2008, and peripheral blood specimens (including extracted DNA) were banked. This registry included a similar population of patients with advanced, nonlocalized prostate cancer to the Mayo Clinic SPORE registry.

Clinical Data and Outcome Collection

Patients in the 2 study cohorts had clinical and follow-up data abstracted from medical records for prostate cancer outcome. Clinical variables collected included demographic information; age at the time of DNA specimen collection; initial cancer diagnosis date; Gleason score at the time of initial diagnosis; time between primary prostate treatment and initiation of castration for nonlocalized, advanced disease; date of castration; date of progression while receiving ADT for nonlocalized, advanced disease; modality of castration (surgical or medical); PSA level at the time of disease progression while receiving ADT; and whether disease progression was biochemical progression alone (serially increasing PSA levels) or based on imaging criteria with the development of new metastases, or both. In addition, we also collected relevant clinical information before ADT, including stage at the time of initial cancer diagnosis and primary prostate treatments received previously. The follow-up and care of all individuals in the registry after initiating ADT was performed as per the standard of care for patients with advanced prostate cancer by the treating physicians at both tertiary-level institutions.

The primary end point of the study was time to ADT failure, defined as time from initiation of castration to progression of disease while receiving continuous ADT. Disease progression while receiving ADT was defined by the first occurrence of either 2 serially increasing PSA levels measured at least 4 weeks apart without evidence of new radiographic criteria of progression (biochemical progression) or the development of new image-based metastasis with or without serially increasing PSA levels or a change in treatment for disease progression, including addition of a peripheral antiandrogen to ADT monotherapy or withholding ongoing antiandrogen treatments during combined ADT for the purpose of eliciting an antiandrogen "withdrawal syndrome." Source documentation from medical records was used to confirm the date of progression during ADT for all study participants in the final analysis. A total of 338 patients with nonlocalized, advanced prostate cancer that progressed while the patients were receiving ADT and who had DNA specimens and all clinical data available were identified in the 2 registries.

Selection of Candidate Genes and Candidate SNPs for Genotyping

We tagged 58 candidate genes belonging to sex steroid biosynthesis and metabolic pathways, including the C21–steroid hormone pathway (conversion from cholesterol to pregnenolone), the delta-4 pathway (conversion of progesterone, a 4-en-3-oxo-steroid to androstenedione), the delta-5 pathway (conversion of pregnenolone, a 5-ene-3β-hydroxy-steroid to dehydroepiandrosterone to androstenedione), and the so-called backdoor alternate pathway (the key feature of this alternate pathway for synthesis of dihydrotestosterone is the presence of 5α-reductase in the steroidogenic tissue, which allows 21-carbon steroids, such as 17-hydroxy progesterone, to be 5α-reduced to its product, 5α-pregnane-3α,17α-diol-20-one, which is an excellent substrate for the 17,20-lyase activity of CYP17A1, yielding the 5α-reduced androgen androsterone).[13,14] Reference genotype data of the SNPs residing within $\pm$5000 base pairs (bp) of the candidate genes (RefSeq 29, Build 36, dbSNP129) were obtained from the International HapMap Phase II (http://www.hapmap.org), Seattle SNPs (http://pga.mbt.washington.edu/), and National Institute of Environmental Health Sciences SNPs (http://egp.gs.washington.edu/projects) for European populations. We selected tagSNPs for each gene using a pairwise tagging approach with a minor allele frequency of 5% or higher and an r^2 of 0.9 using SNPPicker.[15] For genes with more than 1 genotype source, the one with more linkage disequilibrium bins was used, giving priority to HapMap in case of an equal number of bins. HapMap was chosen as the best source for 57 genes and the National Institute of Environmental Health Sciences for 1 gene. SNPPicker picks the best tagSNP for each bin, allowing optimization to be performed according to assay score, functional relevance, and the 60 bp between 2 tagSNPs constraint in the Illumina GoldenGate platform. To reduce the probability of failure in larger bins, we picked 2 and 3 tagSNPs for bins with 10

or more and 30 or more SNPs, respectively. All chosen tagSNPs met the minimum Illumina design score of 0.4. A total of 755 tagSNPs in the 58 candidate genes were selected for genotyping.

In addition, we genotyped 69 targeted candidate SNPs from 20 candidate genes also in sex steroid biosynthesis and metabolism genes of which 6 genes were already included in the tagged set, but none of the SNPs overlapped. These candidate SNPs were selected based on previous published data from single patient cohorts, suggesting either a potential functionality for the SNP or a potential significant association with response to ADT.[9,10]

The selection process for all the tagSNPs allowed for SNPs to tag more than 1 gene. After applying the SNP to gene annotation, the 680 unique tagSNPs increased to 956 nonunique tagSNPs (Supplemental Table 1A, available online at http://www.mayoclinicproceedings.org), of which 622 tagSNPs were mapped to single unique genes, whereas 58 tagSNPs mapped to multiple sets of genes (12 tagSNPs mapped to 2 genes, 5 tagSNPs to 3 genes, 2 tagSNPs to 4 genes, 10 tagSNPs to 5 genes, 4 tagSNPs to 6 genes, 5 tagSNPS to 7 genes, 2 tagSNPs to 8 genes, and 18 tagSNPs to 9 genes).

Genotyping

All 824 SNPs (755 tagSNPs belonging to candidate genes plus 69 selected tagSNPs) were genotyped at the Mayo Genotyping Shared Facility using the Illumina GoldenGate multiplex assay. Genotypes were generated on samples from 338 patients with prostate cancer and 3 Centre d'Etude du Polymorphisme Humain (CEPH) patients. For quality assurance, 8 of the 338 prostate cancer samples were duplicated twice within the same plates, whereas the CEPH samples were genotyped multiple times within and across plates. All pairwise replicate sample comparisons showed 100% genotype concordance. Duplicated samples with lower call rate, together with the CEPH samples, were eliminated from the subsequent statistical analysis. Of the remaining 338 samples, 8 generated no genotypes and were therefore excluded. Evaluation of paired identity by state of the genotypes revealed 5 related pairs of samples. We were able to confirm independently in the clinical databases that these paired samples came from different blood draws of the same individuals. Only the sample with the higher call rate was retained for each of the 5 patients.

We excluded 78 SNPs because of the following reasons: 15 SNPs with failed assays, 1 X-linked SNP with excessive heterozygosity, 48 SNPs with minor allele frequency less than 5%, 12 SNPs with a call rate less than 98%, and 2 SNPs that deviated from Hardy-Weinberg equilibrium (χ^2 test, $P<.001$) and verified with poor clustering quality. After discarding 2 samples with call rates less than 98% and 19 samples with unconfirmed clinical data for time to ADT failure, a final data set composed of 746 SNPs from a cohort of 304 patients was used for subsequent analysis.

Statistical Analyses

The primary end point was time to ADT failure. Because all patients were enrolled at time of ADT failure, no censored observations were available with regard to time to ADT failure. For all genes, we calculated a global gene-level test using the principal components to create uncorrelated components that were linear combinations of the SNPs from a gene. The global gene test allowed tagSNPs to be analyzed multiple times according to the SNP to gene annotation. These components were then ranked according to the amount of the total SNP variance explained. The resulting smallest subset of components that accounted for at least 90% of the variability among the SNPs was included in a Cox proportional hazards model, and overall gene significance was determined using the likelihood ratio test.[16] For genes with 1 SNP and for the selected single SNPs, we used the Cox proportional hazards model. Finally, these models were explored with and without adjusting for the effect of Gleason score on the outcome. To control for false-positive results at the gene analysis, we calculated the false discovery rate (FDR) by the method of Benjamini and Hochberg.[17] The FDRs of 0.10 or less were considered noteworthy. For genes meeting the FDR, we evaluated individual SNPs, summarizing the distribution of time to ADT failure as a median with the corresponding interquartile range (IQR), and associations with individual SNPs were based on Spearman correlation.

RESULTS

Table 1 summarizes the demographic and disease characteristics of the patients included in the analysis. The median time from ADT initiation to failure was 3.21 years (IQR, 1.54-6.20 years). Supplemental Tables 1A and B (available online at http://www.mayoclinicproceedings.org) list the gene and SNP-level Cox proportional hazards *P* values and FDRs for all candidate gene tagSNPs and candidate tagSNPs, respectively.

At the gene-level analysis, statistical significance ($P<.05$) was observed for 3 genes (*TRMT11, HSD17B12,* and *PRMT3*) with time to ADT failure after adjusting for Gleason score (Table 2), with a suggestive trend ($P\leq.07$ and a corresponding FDR of 0.80) for an additional gene, *WBSCR22* (eTable 1A). Of these, *TRMT11* was the most significant gene ($P<.001$; FDR=0.008). Two of the 4 *TRMT11* tag-

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SNPs (rs1268121 and rs6900796) were found to be highly significant for time to ADT failure (Table 3). An overall protective effect was observed in the presence of 0, 1, or 2 minor alleles for these 2 SNPs in the *TRMT11* gene, with ADT time to failure ranging from 2.42 to 6.22 years. The effect of variation in *TRMT11* SNPs with time to ADT failure was detected to be prolonged with an increasing number of minor alleles for each tagSNP when accounting for the number of minor alleles present in the other tagSNP (Figure). In Hapmap (CEU phase II), these 2 SNPs were not in linkage disequilibrium (r^2=0.19).

The 2 other genes were significant at $P<.05$, although the FDRs were greater than 0.10. *HSD17B12* (gene-level $P=.02$) had 2 of 30 tagSNPs at $P<.05$: rs11037589 was positively associated with ADT response ($P=.02$), and rs11037662 was inversely associated with ADT response ($P=.001$). *PRMT3* (gene-level $P=.05$) had 2 of 23 SNPs at $P<.05$: rs7396037 was positively associated with ADT response ($P=.05$), and rs12420525 was inversely associated with ADT response ($P=.03$).

Among the nontagged candidate SNPs, 4 showed a significant association ($P<.05$) with ADT response (Table 4). Two of the SNPs (rs10478424 and rs11749784) were from *HSD17B4,* whereas the other SNPs were from *CYP19A1* (rs2124872) and *SREBF2* (rs11702960). However, none of these associations was confirmed with an FDR of less than 0.10.

TABLE 1. Demographic and Disease Characteristics of 304 Patients in Whom Androgen Deprivation Therapy Failed

Clinical characteristic	Value
Race	
White	301 (99)
Others	3 (1)
Age, median (IQR) (y)	72 (47-91)
PSA at the time of ADT failure, median (range) (ng/mL)	11.5 (4-46)
Clinical T stage at first diagnosis	
T1	18 (6)
T2	127 (42)
T3+4	16 (5)
T4	41 (13)
TX (unverifiable)	102 (34)
N0	37 (12)
N1	4 (1)
NX	263 (87)
Patients with no metastatic disease at diagnosis (M0)	279 (92)
Patients with metastatic disease at diagnosis (M1)	23 (8)
Mx (unverifiable)	2 (1)
Time from diagnosis to ADT initiation (y)	
For initially nonmetastatic patients (M0), median (IQR)	1.5 years (19 days to 5 years)
For initially metastatic patients (M1), median (IQR)	16 days (0-31 days)
Biopsy Gleason score at initial diagnosis	
<6	65 (21)
7	90 (30)
>8	121 (40)
Unknown	28 (9)
Definitive local therapy	
None	85 (28)
Radical prostatectomy	131 (43)
Radiation therapy	88 (29)
Type of ADT	
LHRH analogue	210 (69)
Orchiectomy	94 (31)

Data are presented as No. (percentage) of patients unless indicated otherwise. ADT = androgen deprivation therapy; IQR = interquartile range; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen.

DISCUSSION

Knowledge of predictive factors for ADT has become increasingly pertinent to the treatment of patients with prostate cancer. There is now recognition that many patients treated with ADT carry a major burden of long-term treatment-related adverse effects, which include an increased risk of diabetes mellitus, coronary artery disease, loss of libido, osteoporosis, and metabolic syndrome.[18,19] At the very least, predictive biomarkers of ADT efficacy may further help identify subsets of patients destined for long-term responses who may be chosen to undergo an intermittent ADT schedule, thereby mitigating some of these chronic adverse effects associated with continuous ADT administration, because intermittent ADT administration, although not widely accepted in clinical practice, appears to be as efficacious as continuous ADT.[20,21] Conversely, 6% to 14% of all patients with advanced prostate cancer treated with ADT are known to have a minimal response duration lasting for a few weeks to months.[22] Predictive biomarkers for ADT response may also help identify this subset who may benefit from a more aggressive initial treatment strategy than ADT alone, including combinations with novel drugs targeting the testosterone-androgen receptor axis.[23-26] Future selection of drug combinations with these emerging novel agents may be enhanced with the development of adjunctive pharmacogenetic-based predictive biomarkers that allow rational drug design and combinations, which is in line with a movement toward individualizing prostate cancer therapeutics.

TABLE 2. TagSNP Gene-Level Association Results for the Top 3 Genes

Gene symbol	No. of tagSNPs: Total (N=58)	No. of tagSNPs: With $P<.05$	No. of tagSNPs: Modeled via principal component analysis	Principal component analysis: P value	Principal component analysis: Gleason score–adjusted P value	False discovery rate (q value)
TRMT11	4	2	2	<.001	.008	.008
HSD17B12	30	2	9	.02	.25	.47
PRMT3	23	2	5	.05	.06	.81

SNP = single-nucleotide polymorphism.

We evaluated the potential of novel pharmacogenetic markers of androgen biosynthesis and metabolism as markers of ADT response. We hypothesized that SNPs in candidate sex hormone–regulating genes and pathways will be associated with treatment outcomes in ADT. Results from our association study identified a strong association of time to ADT failure with *TRMT11*, and although significant associations of time to failure with variation in *HSD17B12* and *PRMT3* were also observed, the FDRs for both these genes were greater than 0.10. TagSNPs in the *TRMT11* gene were most significantly associated with time to failure, suggesting a role for variation in this previously unknown methyltransferase gene as a germline predictive marker of ADT failure. The *TRMT11* gene is highly conserved across species, but its function is unknown. It was included in our candidate set of genes because it appears listed in a class of hormone-associated genes (class E.C; identification No. 2.1.1; http://enzyme.expasy.org/), which includes other methyltransferases, such as the *COMT* gene. Variation in *COMT* has been reported to be associated with the metabolism of estrogens and breast cancer risk and outcomes.[27,28] Although speculative, our results raise the possibility of germline variation in related methyltransferases with ADT outcomes in prostate cancer as well, which will need clinical validation and a more rigorous functional assessment in future studies to understand its exact role.

In the present study, we relied mainly on using a "discovery" tagSNP candidate gene approach to evaluate for genetic variation in sex steroid–related genes, which was complemented by the inclusion of previously evaluated tagSNPs from 2 published studies on ADT response based on germline variation in a similar patient population. The first study evaluated the association of 43 tagSNPs in the androgen and estrogen receptor genes with ADT response in a hospital-based cohort study[10] but found no significant associations, and our results are consistent with their findings. In the second report, 529 men were genotyped for 129 SNPs from 20 genes involved in androgen metabolism.[9] Three tagSNPs (from *CYP19A1*, *HSD3B1*, and *HSD17B4*) were significantly associated ($P<.01$) with the intermediate end point of biochemical relapse during ADT (increasing PSA levels). Our study included 1 of the 3 SNPs in the analysis performed by Ross et al.[9] This SNP, in the *CYP19A1* gene (rs1870050), was associated with a trend to response with ADT duration (biochemical relapse) (hazard ratio, 1.383; 95% confidence interval, 0.998-1.916; $P=.05$). We also note that recently, germline variation in 2 androgen transporter genes (*SLCO2B1* and *SLCO1B3*) has been reported to be associated with time to progression in patients receiving ADT,[12] and a role for gene-gene interaction was suggested, underlying the clinical observations. We did not include these variants in our candidate approach because these results

TABLE 3. Analysis of the *TRMT11* Gene and Its Corresponding SNPs in Relation to Time to ADT Failure in 304 Study Patients

TRMT11 SNP marker	Time to ADT failure, median (IQR) (y): Minor allele=0	Time to ADT failure, median (IQR) (y): Minor allele=1	Time to ADT failure, median (IQR) (y): Minor allele=2	P value (Spearman correlation coefficient)
rs1268121	3.05 (1.42-5.02)	4.27 (1.75-9.49)	6.22 (3.62-13.17)	.002 (0.18)
rs2326215	3.01 (1.41-5.87)	3.56 (1.64-6.29)	3.85 (2.26-7.02)	.09 (0.09)
rs6569442	3.01 (1.41-5.87)	3.56 (1.64-6.29)	3.85 (2.26-7.02)	.09 (0.09)
rs6900796	2.42 (1.36-4.26)	3.52 (1.51-6.48)	4.18 (2.33-7.33)	<.001 (0.20)

ADT = androgen deprivation therapy; IQR = interquartile range; SNP = single-nucleotide polymorphism.

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were not available at the time of our study. In addition, in a separate study, an association of a single polymorphism in the *SLCO1B3* gene (334 T>G) with time to development of androgen independence[11] was detected in a relatively small cohort of 68 white patients. This cohort of patients undergoing ADT was further divided into 2 smaller subcohorts of men, and an association of the T allele of the *SLCO1B3* gene with a shorter time to androgen independence was observed (P=.11 and P=.18). The limited size of the cohort with marginal significance observed for the associations prevented incorporation for further study in the candidate approach we pursued. Nevertheless, we recognize that there are likely to be multiple genetic variants in hormone-related genes potentially associated with durability of ADT response, which will need validation in larger cohorts.

We recognize the limitations of our study, particularly that these results are limited to white patients. Apart from a lack of a validation set, the retrospective nature of the cohort can introduce a selection bias. Specimens in this study were collected at the time of developing castration recurrence, which results in no patient with prolonged ADT response being censored. However, the overall follow-up period for our study cohort from the time of ADT initiation to failure of ADT was 5 years (IQR, 3-9 years). Because ADT for nonlocalized, advanced disease is noncurative, with a median time to progression to a castration-recurrent stage of 18 to 30 months,[3-6] it is unlikely that the lack of censoring for patients with prolonged responses would have affected these results because more than 95% of patients undergoing ADT would have progressed to castration recurrence in this period. Nevertheless, validation of these results is needed to confirm the preliminary nature of these observations.

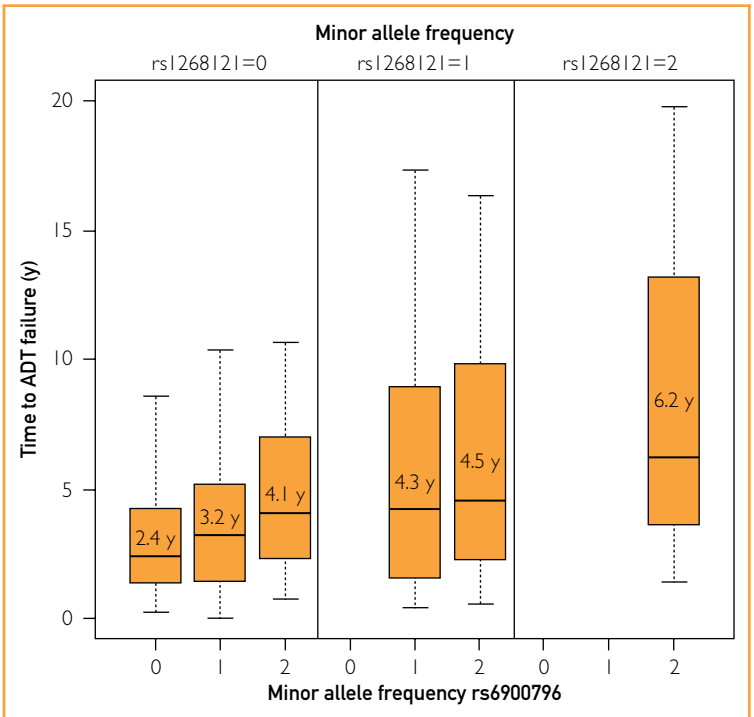

FIGURE. Independent association of the 2 most significant *TRMT11* tag single-nucleotide polymorphisms (SNPs), rs1268121 and rs6900796, with time to androgen deprivation therapy (ADT) failure. The time to ADT failure is prolonged with an increasing number of minor alleles for each tagSNP in the presence of 0, 1, and 2 minor alleles for the other tagSNP. Under the additive allele model, the adjusted hazard ratio for rs1268121 (ie, controlling for the minor allele frequency of rs6900796) was 0.76 (95% confidence interval, 0.58-0.99; P=.04). Similarly, the adjusted hazard ratio for rs6900796 (ie, controlling for the minor allele frequency of rs1268121) was 0.81 (95% confidence interval, 0.68-0.97; P=.02).

CONCLUSION

Variation in *TRMT11* in a cohort of patients with advanced prostate cancer was observed to be associated with time to ADT failure. Confirmation of these findings in an independent cohort of patients with advanced prostate cancer undergoing ADT and a determination of a functional role for this gene in defining efficacy of androgen ablation treatments is needed in future studies.

TABLE 4. Candidate SNP-Level Association Results for the Top 4 of 66 SNPs Tested

		Principal component analysis		
rs	Gene symbol	*P* value	Gleason score–adjusted *P* value	False discovery rate (*q* value)
rs10478424	*HSD17B4*	.02	.02	.83
rs2124872	*CYP19A1*	.04	.31	.83
rs11702960	*SREBF2*	.04	.22	.83
rs11749784	*HSD17B4*	.05	.06	.83

SNP = single-nucleotide polymorphism.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

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