

Short Communication

Association Studies of Serum Prostate-specific Antigen Levels and the Genetic Polymorphisms at the Androgen Receptor and Prostate-specific Antigen Genes¹

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Abstract

Testing for serum prostate-specific antigen (PSA) levels has been widely used to screen for prostate cancer. However, PSA testing has low specificity and sensitivity because PSA is not prostate cancer-specific. PSA is encoded by the *APS* gene, and the expression of this gene is regulated by androgens. W. Xue *et al.* *Cancer Res.*, 60: 839–841, 2000 reported recently that serum PSA levels are associated with a G/A polymorphism at androgen responsive element 1 (ARE1) of *APS* and/or the CAG repeats in exon 1 of the androgen receptor (*AR*) gene. This result, if confirmed, may significantly increase the specificity and sensitivity of PSA testing by incorporating genotype-specific thresholds. In this study, we tested for the association between serum PSA levels and these single nucleotide polymorphisms (SNPs) in a large sample of 518 men. For the *AR* gene, we observed slightly (but not statistically significant) higher mean serum PSA levels in men with shorter CAG repeats (≤ 21) or shorter GGC repeats (≤ 16). For the ARE1 of the *APS*, we found slightly (but not statistically significant) lower PSA levels in men with the AA genotype. It is worth noting that this observation is opposite to the findings of W. Xue *et al.* *Cancer Res.*, 60: 839–841, 2000. We hypothesize that the effects of ARE1 and *AR* genotypes on mean PSA levels may reflect the effect of other causal polymorphisms in these genes, which are in linkage disequilibrium with these polymorphisms. A systematic approach is required to identify sequence variants in these genes and other related genes, and to test for an association between these variants and PSA levels in large samples.

Introduction

PSA³ is a glycoprotein produced mainly by epithelial cells in the prostate gland. Prostatic diseases such as prostate cancer may have high serum PSA levels because of enhanced production of PSA and/or architectural distortions in the gland that allow PSA greater access to the circulation. Thus, testing for serum PSA levels is widely used to screen for prostate cancer, resulting in the detection of prostate cancer, on average, 5 years earlier than would be possible otherwise (1). The early detection of prostate cancer is at least partially responsible for the recent decrease in prostate cancer mortality rates in the United States (2).

However, PSA testing has relatively low sensitivity and specificity. For men with normal DREs, the probabilities of prostate cancer are 12–23%, 25%, and >50%, respectively, when PSA levels are 2.5–4 ng/ml, 4.1–10 ng/ml, and ≥ 10 ng/ml (3–8). The low specificity of PSA testing is because PSA is not prostate cancer-specific. Any prostatic disease that increases the volume of the prostate or disrupts the prostatic architecture, including benign prostatic hyperplasia and prostatitis, can elevate serum PSA levels. Other factors such as age and race are also associated with PSA levels, and these may indirectly reflect differences in prostate sizes. Mean PSA levels (ng/ml) of 10-year age groups differ significantly between each group (age 40–49, 0.83; 50–59, 1.23; 60–69, 1.83; and 70–79, 2.31). Blacks have significantly higher PSA levels, followed by Asians, whites, and Latinos (9).

Recently, genetic polymorphisms in two genes that are potentially important in regulating PSA [*AR* and *PSA* gene (*APS*)] have been reported to be associated with PSA levels. PSA is encoded by *APS*, which was mapped to *19q13* (10). There are several variant *APS* cDNAs, caused by intron retention and alternative splicing of the primary transcript (11). PSA expression can be regulated by androgens. At least three AREs have been identified in the *APS* promoter region (12, 13). *AR*, which maps to *Xq11–12*, binds to the AREs and regulates *APS* expression. Xue *et al.* (14) reported that serum PSA levels in healthy men are associated with a G/A polymorphism (*NheI*) at ARE1 of *APS* (at position –158) and/or the number of CAG repeats in exon 1 of the *AR* gene. The same polymorphisms were also reported to be associated with prostate cancer risk and severity (15). These results, if confirmed, are potentially important because they may help us to understand the variation of PSA levels in populations, and significantly increase the sensitivity and specificity of PSA testing by incorporating the genotyping information at the two genes. The goal of this study is to evaluate the findings of association between serum PSA

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³ The abbreviations used are: PSA, prostate-specific antigen; DRE, digital rectal examination; *AR*, androgen receptor; ARE, androgen receptor element; HWE, Hardy-Weinberg Equilibrium; LD, linkage disequilibrium.

Table 1 Characteristics of study subjects

	Whites	Blacks	Total
Number of subjects	469	49	518
Number with prostate cancer	27	3	30
Number with positive family history	43	7	50
Age, nonprostate cancer			
<i>n</i>	439	46	485
Mean (SD)	63.7 (9.1)	59.8 (10.8) ^a	63.3 (9.4)
Median (range)	64 (34–93)	59.5 (39–81)	63 (34–93)
log ₁₀ (PSA), nonprostate cancer			
<i>n</i>	437	46	483
Mean (SD)	0.04 (0.40)	0.12 (0.37) ^b	0.04 (0.40)
Median	0	0.08	0.02
Range	–1.70, 1.31	–0.62, 0.89	–1.70 1.31
PSA			
Median	1.01	1.20	1.05
Range	0.02, 20.70	0.24, 7.70	0.02, 20.70

^a The difference in the mean age between the whites and blacks was statistically significant ($P = 0.008$).

^b The difference in the mean log₁₀ PSA between the whites and blacks was statistically significant, after adjusting for age ($P = 0.03$).

levels and the genetic polymorphisms at both exon 1 of the *AR* gene (CAG and GGC) and ARE1 of the *APS* (*NheI*), in a large collection of 518 men unselected for prostate cancer status.

Materials and Methods

Subjects. The study subjects are a subset of a large population study where asbestos-exposed workers were recruited to study the impact of genetic and environmental factors on the development of asbestos-induced lung diseases. In this subset of the workers ($n = 518$), serum PSA levels were measured to determine whether exposure to asbestos increased the risk for prostate cancer. Participants worked as painters, pipefitters, plumbers, operators, and electricians. Physical examination was performed. Complete medical, family, and occupational histories were elicited from each worker at the time of physical examination. Approximately 30 cc of whole blood was obtained from each of the 518 men to isolate DNA and measure serum PSA levels. The research protocol was reviewed and approved by the St. Louis University Institutional Review Board.

Serum PSA Levels. Serum PSA concentrations were determined by immunometric assay with kits (Tandem-R) obtained from Hybritech. We used the normal range recommended by the manufacturer (0–3.9 $\mu\text{g/liter}$).

Genotyping. Two microsatellite repeats (CAG and GGC) in exon 1 of the *AR* gene and a *G/A* polymorphism (*NheI*) at ARE1 of the *APS* (at position –158) were genotyped. For the microsatellite repeats, multiplex PCR using fluorescently labeled primers was performed. The primers used to amplify the CAG repeats were AR-CAG-F (5'-TCCAGAATCTGTTCCAGAGCGTGC-3') and AR-CAG-R (5'-GCTGTGAAGGTTGCTGTTCCTCAT-3'). The primers used to amplify the GGC repeats were AR-GGC-F (5'-TCCTGGCACACTCTCTTAC-3') and AR-GGC-R (5'-GCCAGGTTACCACACATCAGGT-3'). The resulting PCR fragments were separated in an ABI 3700 sequencer, and the genotypes were scored using ABI software (Genotyper). Nested PCR was used to amplify an 862-bp region of the *APS* gene from positions –529 to +333 relative to the transcription start site. The first set of PCR primers were F (5'-TAGAGGATCTGTGGACCA-3') and R (5'-TTCCCCTTAGTAAAGCAGTGGG-3'). The second set of PCR primers were F (5'-TGACAGTAGCAATGTATCTGTGG-3') and (5'-GGGAGCTGGCTGGCAATGGGG-3'). The PCR product

was digested with *NheI* (New England Biolabs, Beverly, MA), and the digested products were separated on an agarose gel.

Statistical Methods. The HWE test for the *G/A* polymorphism of ARE1 and a pair-wise LD test between CAG and GGC of *AR* were performed using the Genetic Data Analysis (GDA) computer program (16). The HWE test was based on an exact test, where many of the possible arrays were generated by permuting the alleles among genotypes and calculating the proportion of these permuted genotypic arrays that have a smaller conditional probability than the original data. The LD test was based on an exact test assuming multinomial probability of the multilocus genotype, conditional on the single-locus genotype (17). A Monte Carlo simulation was used to assess the significance by permuting the single-locus genotypes among individuals in the sample to simulate the null distribution. The empirical P s of both the HWE and LD tests were based on 10,000 replicate samples.

The number of CAG repeats was examined as a quantitative variable ($\leq 17, 18, 19, 20, 21, 22, 23, 24, 25, 26$, and ≥ 27), as well as a qualitative variable (CAG ≤ 21 versus CAG ≥ 22), based on the median value of CAG repeats in the sample. Because the majority of men had 16 or 17 GGC repeats, this repeat was examined as a qualitative variable (GGN ≤ 16 versus GGN ≥ 17). Because the distribution of serum PSA levels deviates significantly from a normal distribution (Kolmogorov D statistic = 0.24; $P < 0.01$), PSA levels were log₁₀ transformed. After the transformation, the distribution approached normality but remained significantly different from a normal distribution ($D = 0.09$; $P < 0.01$). Multiple regression models were fit to estimate the effects of the genotype of CAG (qualitative or quantitative), GGC, and combined genotypes of both *AR* and ARE1 on age-adjusted log serum PSA levels. ANOVA tests were performed to test for differences in mean log PSA levels among men with the genotype AA, AG, or GG at ARE1, and the combined genotypes at *AR* (CAG and GGC) and *APS* (ARE1). To decrease the potential population stratification, all of the hypothesis tests were performed in whites because they comprised the majority of the study subjects. All of the P s were two-sided.

Results

Characteristics of the study subjects are presented in Table 1. There were a total of 518 men included in this study. The racial

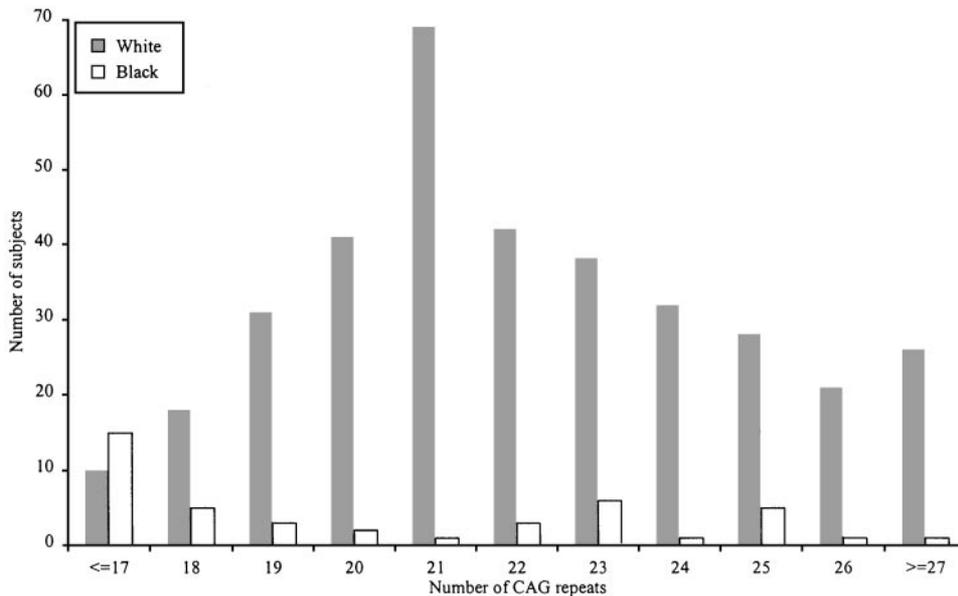


Fig. 1. The distribution of CAG repeats in the 469 white men, as indicated by solid bar, and in 49 black men, as indicated by cross-hatched bar.

distribution of the subjects was 91% white and 9% black. A diagnosis of prostate cancer was reported by 5.8% ($n = 30$) of men, and this rate was similar in both whites (5.8%; $n = 27$) and blacks (6.1%; $n = 3$). Because we are primarily interested in the PSA levels in the men without prostate cancer, the 30 subjects who reported a diagnosis of prostate cancer were excluded from all of the following analyses. The mean age of the study subjects at examination was 63.3 years. The whites had a significantly higher mean age (63.7 years) than the blacks (59.8 years), $P = 0.008$. The median PSA level was 1.05 ng/ml in the total of 483 men with measured PSA levels and was higher in blacks (1.20 ng/ml) than in whites (1.01 ng/ml). The difference in the age-adjusted mean $\log_{10}(\text{PSA})$ levels between the blacks and whites was statistically significant ($P = 0.03$). The $\log_{10}(\text{PSA})$ levels increased significantly with age (year) in the whites ($P < 0.0001$) and blacks ($P = 0.049$). Among the subjects without a self-reported diagnosis of prostate cancer, there were 43 men (38 whites and 5 blacks) with PSA levels ≥ 4 ng/ml.

The G/A polymorphism at ARE1 was in HWE in whites and blacks. The two microsatellite repeats of AR (CAG and GGC) were in strong LD ($P < 0.0001$). The distribution of CAG repeats was significantly different among the whites and blacks (Fisher's exact test $P < 0.0001$). On average, the blacks had shorter CAG repeats than the whites, with the repeat number ≤ 17 and 21 being the most frequent allele in the blacks and whites, respectively (Fig. 1). For the GGC repeats, 76% of the blacks had ≤ 16 repeats compared with 61% of the whites, although this difference was not statistically significant ($P = 0.12$). There was no statistical difference in the distribution of ARE1 genotypes in the whites and blacks ($P = 0.053$).

The association between PSA levels and the polymorphisms in the AR gene and APS was tested in whites. The mean \log_{10} PSA levels were higher in men with shorter repeats (CAG ≤ 21 or GGC ≤ 16) compared with men with longer repeats (CAG ≥ 22 or GGC ≥ 17), respectively (Table 2). However, the differences were not significant after adjustment for age ($P = 0.46$ and $P = 0.60$, for CAG and GGC repeats, respectively). The results were similar when the number of CAG repeats was analyzed as a quantitative variable. The \log_{10} PSA levels de-

Table 2 Serum PSA levels in white men with various genotypes at AR polymorphisms

Genotypes	$\log_{10}(\text{PSA})$			PSA Mean	P
	n	Mean	SD		
Nonprostate cancer, all PSA levels					
CAG repeats					
< = 21	192	0.06	0.4	1.15	
> = 22	203	0.02	0.41	1.05	0.46
GGC repeats					
< = 16	251	0.05	0.39	1.12	
> = 17	147	0.02	0.44	1.05	0.6
Nonprostate cancer, PSA < 4 ng/ml					
CAG repeats					
< = 21	179	0	0.35	1	
> = 22	182	-0.07	0.32	0.85	0.052
GGC repeats					
< = 16	229	-0.03	0.31	0.93	
> = 17	135	-0.05	0.37	0.89	0.5

^a P s were adjusted for age.

creased 0.004 units for every additional CAG repeat ($P = 0.61$). When the analyses were limited to the subset of men with PSA < 4 ng/ml, the difference in PSA levels between the men with shorter and longer CAG repeats was larger, although it remained nonsignificant ($P = 0.052$).

No significant association was observed between PSA levels and the polymorphisms in the ARE1 of APS. Men with the AG or GG genotypes tended to have higher mean PSA levels, compared with the subjects who had the AA genotype (Table 3). However, the differences were not significant (Table 3). When the "G" allele was assumed dominant, subjects with AG or GG genotypes had slightly higher PSA levels than men with the AA genotypes ($P = 0.07$ after adjusted for age). When the analyses were limited to the subset of men with PSA < 4 ng/ml, the difference in the PSA levels between men with AG or GG genotypes and men with the AA genotype was smaller ($P = 0.13$ after adjusted for age). It is worth noting that an opposite trend was observed in the study of Xue *et al.* (14), where subjects with the AA genotype had higher PSA levels.

Table 3 Serum PSA levels in white men with various genotypes at ARE1 polymorphisms

Genotypes (Nhe)	log ₁₀ (PSA)			PSA Mean	Ps ^a	Ps ^b
	n	Mean	SD			
Nonprostate cancer, all PSA levels						
AA	105	-0.02	0.41	0.95		
AG	210	0.08	0.4	1.2		
GG	88	0.01	0.38	1.02	0.08	0.07
Nonprostate cancer, PSA < 4 ng/ml						
AA	98	-0.07	0.37	0.85		
AG	189	-0.005	0.32	0.99		
GG	83	-0.04	0.32	0.91	0.26	0.13

^a Based on ANOVA tests.

^b Assuming a dominant model (AG/GG vs. AA), adjusted for age.

Table 4 Serum PSA levels in white men for the combined genotypes at AR and ARE1

Genotypes ARE1 (Nhe1)	AR (CAG or GGC)	log ₁₀ (PSA)			Mean	P ^a
		n	Mean	SD		
Nonprostate cancer, all PSA levels						
AA	CAG < = 21	56	0	0.43	1	
	CAG > = 22	46	-0.03	0.38	0.93	
AG	CAG < = 21	92	0.1	0.38	0.126	
	CAG > = 22	103	0.07	0.43	1.17	
GG	CAG < = 21	37	0.02	0.38	1.05	
	CAG > = 22	45	0.02	0.38	1.05	0.43
AA	CAG < = 16	63	-0.05	0.35	0.89	
	CAG > = 17	37	0.01	0.48	1.02	
AG	GGC < = 16	130	0.11	0.39	1.29	
	GGC > = 17	70	0.04	0.44	1.1	
GG	CAG < = 16	50	0.04	0.38	1.1	
	CAG > = 17	32	-0.01	0.39	0.98	0.15
Nonprostate cancer, and PSA < 4 ng/ml						
AA	CAG < = 21	54	-0.03	0.4	0.93	
	CAG > = 22	41	-0.12	0.31	0.76	
AG	CAG < = 21	84	0.03	0.32	1.07	
	CAG > = 22	91	-0.04	0.33	0.91	
GG	CAG < = 21	35	-0.02	0.33	0.95	
	CAG > = 22	42	-0.04	0.32	0.91	0.32
AA	CAG < = 16	60	-0.08	0.31	0.83	
	CAG > = 17	34	-0.06	0.44	0.87	
AG	GGC < = 16	115	0.02	0.3	1.05	
	GGC > = 17	64	-0.04	0.36	0.91	
GG	CAG < = 16	47	-0.01	0.32	0.98	
	CAG > = 17	30	-0.06	0.33	0.87	0.42

^a Ps were based on ANOVA tests.

Because AR binds to AREs of APS to regulate the expression of PSA levels, we tested the hypothesis that PSA levels are associated with the combined genotypes at AR and ARE1. Two types of tests were performed. The first test was a global test in which the mean PSA levels among the combinations of the genotypes at ARE1 (AA, AG, and GG) and AR [CAG repeats (<=21 or >=21) or GGC repeats (<=16 or >=17)] were compared using an ANOVA test. No significant differences in the mean PSA levels were found (Table 4). The second test examined the association between age-adjusted PSA levels and AR polymorphisms (CAG as a quantitative variable and GGC as a qualitative variable) in each ARE1 genotype, as performed by Xue *et al.* (14). No significant association was found in any of the ARE1 genotype strata. The regression coefficients between the log₁₀PSA levels and the number of CAG repeats were -0.02 ($P = 0.18$), -0.01 ($P = 0.22$), and 0.001 ($P = 0.95$), in the men

Table 5 Serum PSA levels in black men with various genotypes at AR and ARE1

Genotypes	log ₁₀ (PSA)			PSA Mean
	n	Mean	SD	
Nonprostate cancer, all PSA levels				
CAG repeats				
< = 21	28	-0.08	0.4	0.83
> = 22	16	0.09	0.27	0.123
GGC repeats				
< = 16	33	0.13	0.35	1.35
> = 17	11	0.17	0.44	1.48
ARE1				
AA	8	0.21	0.28	1.62
AG	20	0.08	0.39	1.2
GG	17	0.15	0.39	1.41
Nonprostate cancer, and PSA < 4 ng/ml				
CAG repeats				
< = 21	24	-0.03	0.32	0.93
> = 22	15	0.21	0.25	1.62
GGC repeats				
< = 16	30	0.07	0.31	1.17
> = 17	9	0.04	0.37	1.1
ARE1				
AA	8	0.21	0.28	1.62
AG	17	-0.02	0.33	0.95
GG	15	0.06	0.31	1.15

with AA, AG, and GG genotypes at ARE1, respectively. The regression coefficients between the log₁₀PSA levels and the number of GGC repeats were 0.02 ($P = 0.80$), -0.06 ($P = 0.24$), and -0.05 ($P = 0.44$), in the men with AA, AG, and GG genotypes at ARE1, respectively. Similar results were observed when these analyses were limited to the subset of men with PSA < 4 ng/ml.

The association between PSA levels and either the genotypes at AR or APS was also evaluated in the blacks (Table 5). Because of the small sample size, these analyses were descriptive rather than formal hypothesis tests. For the CAG repeats, higher mean log₁₀PSA levels were observed in men with >=22 repeats compared with men with <=21 repeats. For the GGC polymorphisms, mean log₁₀PSA levels were similar in men with <=16 or >=17 repeats. The highest mean log₁₀(PSA) levels were observed in the AA genotype of the ARE1 polymorphism.

Discussion

A better understanding of all of the factors associated with serum PSA levels could significantly increase the sensitivity and specificity of PSA testing. Currently, a PSA level >=4.0 ng/ml is generally used as a cutoff for recommending a biopsy. However, this threshold is controversial (18-20). On one hand, only 25% of men above the threshold who have a normal DRE will be diagnosed with prostate cancer after biopsy. The false positives result in unnecessary resource use, a chance of complications, and negative psychological consequences. On the other hand, ~20% of detectable cancers occur in men with PSA below the threshold. Many efforts have been made to obtain an ideal PSA cutoff that balances the early detection of cancer (reducing the mortality) with false positives. These efforts include race- and age-specific PSA cutoffs (21, 22), PSA velocity (change of PSA level over time; Ref. 23), PSA density (dividing PSA level by the volume of the prostate; Ref. 24), and free PSA (noncomplexed to other protein moieties; Ref. 25). Another potentially important effort is the use of a genotype-

specific cutoff, as some genes may have an important role in regulating PSA levels. To this end, Xue *et al.* (14) reported recently significantly different mean serum PSA levels among men with either different genotypes at ARE1 of APS or different CAG repeats of AR gene. This observation, if confirmed, may serve as a basis for setting different thresholds in men with different genotypes at these genes.

However, the results from our study did not confirm the finding of Xue *et al.* (14). We did not observe any significant association between serum PSA levels and either the polymorphisms at CAG and GGC repeats of AR or the ARE1 polymorphism of APS when these variants were analyzed alone or combined. For AR, we did observe slightly (but not statistically significant) higher mean serum PSA levels in men with shorter CAG repeats (≤ 21) or shorter GGC repeats (≤ 16). For the ARE1 of APS, we found slightly (but not statistically significant) lower PSA levels in men with the AA genotype. It is worth noting that this observation is opposite to the finding of Xue *et al.* (14), where significantly higher PSA levels were found in men with the AA genotype.

There are some similarities between the study of Xue *et al.* (14) and our study, as the subjects in both studies had similar mean ages, included men who were self-reported to be prostate cancer-free, and did not include DRE and prostate size. However, there are several differences. First, the sources of study subjects are different. Whereas their study subjects were from a general population participating in a study of diet and cancer, our study subjects were from workers potentially exposed to asbestos. This may be an important difference if the exposure to asbestos affects serum PSA levels. However, an extensive Pubmed search did not find any published data supporting this assumption. Second, the race composition is different for each study. Whereas their study subjects included African Americans, non-Hispanic whites, Hispanics, and Japanese Americans, the majority of our study subjects were non-Hispanic whites. However, this is unlikely to explain the different findings of the two studies, because the analyses in both studies were race-specific. Third, the sample sizes are different. Although there was a total of 420 men in their study, the sample size is small in each race group. For example, there were only 113 non-Hispanic whites in their study, leading to very few individuals with any given genotypes. In contrast, we have 469 non-Hispanic whites in our study.

The interpretation of the different results from these two studies is difficult. We hypothesize that the observed effects of ARE1 and AR genotypes on mean PSA levels may reflect the effect of other causal polymorphisms in these genes, which are in LD with the ARE1 or AR polymorphisms. The fact that two studies found opposite trends for mean PSA levels in the ARE1 polymorphism of APS is consistent with this hypothesis. In fact, there are several known polymorphisms in the promoter and enhancer regions of APS. Recently, Yang *et al.* (26) reported that novel polymorphisms in ARE2 of APS are associated with preoperative PSA levels in prostate cancer. A systematic approach is required to identify additional sequence variants in these genes and in other related genes, and to test for an association between each of these variants and PSA levels in large samples.

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BLOOD CANCER DISCOVERY

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