

Genetic Determinants of Serum Prostate-specific Antigen levels in Healthy Men from a Multiethnic Cohort¹

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Abstract

We recently reported an association between prostate cancer risk and polymorphisms in the prostate-specific antigen (PSA) and androgen receptor (AR) genes. The purpose of this study is to test whether these two polymorphisms, AR CAG and PSA ARE1, influence serum PSA levels in healthy men. Serum PSA and the two genotypes were assayed for 420 healthy men from a multiethnic cohort, and regression models were fit to estimate the effects of AR CAG genotype and PSA ARE1 genotype on serum PSA levels. Predicted serum PSA decreased 3.5% with each additional AR CAG repeat decile ($P = 0.01$). Serum PSA was also associated with PSA ARE1 genotype, with PSA levels higher among men with the PSA AA genotype compared with men with the AG or GG genotypes ($P = 0.02$). The relationship between serum PSA level and AR CAG length differed according to PSA genotype ($P = 0.049$): for genotype GG, the slope was not significantly different from zero ($P = 0.74$); for genotype AG, serum PSA increased 4.5% with each decrease of one CAG repeat decile ($P = 0.03$); for genotype AA, serum PSA increased 7% with each decrease of one CAG repeat decile ($P = 0.02$). These results indicate that in healthy men, genetic variants in the PSA and AR genes contribute to variation in serum PSA levels. Men with the PSA AA genotype and short AR CAG alleles have, on average, higher serum PSA levels.

Introduction

Serum PSA³ is widely used as a tumor marker for early detection of prostate cancer. PSA, however, is not cancer specific. Benign prostatic epithelial cells also produce PSA. Any condition that increases prostate size, such as benign prostatic

hyperplasia, or that disrupts the prostatic architecture, such as prostatitis, prostatic ischemia, or infarction, can elevate serum PSA. Serum PSA gradually increases with age, because of a progressive increase in prostate size (1). Racial differences in serum PSA levels have been noted, with African-American men having markedly higher serum PSA levels than their Caucasian counterparts (2, 3), perhaps attributable in part to larger average prostate volume. Other factors that might influence PSA levels include those factors that directly or indirectly regulate PSA gene expression.

The major regulator of PSA gene expression is androgen. The AR, after binding to ligand (androgen), recognizes and binds to specific nucleotide sequences, called AREs, in the promoter regions of androgen-regulated genes. At least three AREs have been identified in the PSA gene promoter (4). The one nearest the transcription start site is referred to as ARE1. We recently reported that a single-nucleotide polymorphism in the ARE1 sequence was associated with prostate cancer risk and, furthermore, that this association may be modified by allelic variation in the AR gene (5). In this study, we set out to test whether polymorphisms in these two genes, PSA and AR, influence serum PSA levels in healthy men.

Materials and Methods

Subjects. Subjects were 456 men participating in the Hawaii-Los Angeles Multiethnic Cohort Study of diet and cancer. The male cohort consists of ~13,000 African Americans, 23,000 Hispanics, 27,000 Japanese Americans, and 23,000 non-Hispanic whites who were between the ages of 45 and 75 at entry into the cohort. All of the cohort members have completed a detailed health and dietary questionnaire and are periodically traced, primarily through population-based cancer registries, for occurrence of all incident cancers. Blood and urine specimens are collected from all incident cancer cases and from a 3% random sample of the cohort. AR CAG genotypes had been performed on approximately the first 1,000 samples (cases and controls) collected. Men eligible for the current study were those who have not been diagnosed with prostate cancer and for whom AR CAG genotypes were already available. Because our aim was to study men having normal prostate function, we excluded 36 men who had serum PSA levels above 4 ng/ml, leaving 420 men (100 African Americans, 113 non-Hispanic whites, 108 Hispanics, and 99 Japanese Americans) in the study. Forty men (9.5%) reported a history of prostate enlargement. Excluding these men did not alter our results. Written informed consent was obtained from each subject. The study was approved by the University of Southern California School of Medicine Institutional Review Board.

Genotyping. Two genes, AR and PSA, were examined in this study. In the AR gene, two microsatellite polymorphisms (CAG and GGC) in exon 1 were genotyped using methods described in our previous report (6). These microsatellites are length polymorphisms, with individual alleles defined by the number

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³ The abbreviations used are: PSA, prostate-specific antigen; AR, androgen receptor; ARE, androgen response element; IGF, insulin-like growth factor.

Table 1 Age and serum PSA levels in study population by ethnicity

	African Americans	Non-Hispanic whites	Hispanics	Japanese Americans
<i>n</i>	100	113	108	99
Age				
Mean (SD)	62.2 (8.2)	62.2 (8.7)	64.1 (8.0)	62.5 (9.7)
Median (25th, 75th percentile)	62 (57, 68)	62 (55, 69)	65 (58, 72)	62 (54, 71)
PSA				
Mean (SD)	1.3 (0.9)	1.2 (0.9)	1.3 (1.0)	1.2 (0.8)
Median (25th, 75th percentile)	1.0 (0.6, 1.7)	1.0 (0.5, 1.6)	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)

Table 2 Distribution of AR and PSA genotypes by ethnicity

Genotype	African Americans (<i>n</i> = 100) <i>n</i> (%)	Non-Hispanic whites (<i>n</i> = 113) <i>n</i> (%)	Hispanics (<i>n</i> = 108) <i>n</i> (%)	Japanese Americans (<i>n</i> = 99) <i>n</i> (%)	All of the groups (<i>n</i> = 420) <i>n</i> (%)
<i>AR CAG</i>					
7–16	23 (23)	4 (4)	5 (5)	2 (2)	34 (8)
17–18	23 (23)	10 (9)	9 (8)	5 (5)	47 (11)
19	8 (8)	18 (16)	6 (6)	6 (6)	38 (9)
20	13 (13)	17 (15)	19 (18)	9 (9)	58 (14)
21	13 (13)	12 (11)	15 (14)	19 (19)	59 (14)
22	5 (5)	15 (13)	14 (13)	26 (26)	60 (14)
23	1 (1)	14 (12)	13 (12)	15 (15)	43 (10)
24	5 (5)	13 (12)	12 (11)	8 (8)	38 (9)
25–26	5 (5)	8 (7)	7 (6)	5 (5)	25 (6)
27–37	4 (4)	2 (2)	8 (7)	4 (4)	18 (4)
<i>AR GGC^a</i>					
3–15	42 (45)	14 (12)	12 (11)	19 (19)	87 (21)
16	21 (23)	66 (59)	65 (61)	56 (57)	208 (51)
17–20	30 (32)	32 (29)	30 (28)	23 (24)	115 (28)
<i>PSA ARE1</i>					
AA	28 (28)	28 (25)	12 (11)	5 (5)	73 (17)
AG	48 (48)	52 (46)	56 (52)	31 (31)	187 (45)
GG	24 (24)	33 (29)	40 (37)	63 (64)	160 (38)
<i>PSA -252/-203^b</i>					
GG/ΔAΔA	84 (87)	52 (49)	49 (47)	38 (40)	223 (56)
GA/ΔA	12 (13)	46 (43)	46 (44)	50 (52)	154 (38)
AA/AA	0 (0)	8 (8)	9 (9)	8 (8)	25 (6)

^a AR GGC genotype missing for 10 samples.

^b PSA -252/-203 genotypes missing for 18 samples.

of repeated units (*CAG* or *GGC* repeats) that they contain. Genotypes were assayed by separating radioactively labeled PCR products on polyacrylamide gels. *GGC* genotype was missing for 10 subjects because of PCR failure.

In the *PSA* gene promoter, a *G/A* substitution polymorphism in the *ARE1* sequence was genotyped using methods described in our previous report (5). PCR products were digested with the *NheI* enzyme (New England Biolabs, Beverly MA) and genotypes were distinguished by running digested products on agarose gels: *AA* (300 bp), *AG* (150 and 300 bp), and *GG* (150 bp). Additionally, a 560-bp region surrounding this polymorphism was sequenced for all subjects using primers GTTGGGAGTGCAAGGAAAAG (forward) and GGACAGGGTGAGGAAGCAA (reverse). For 18 subjects, the complete sequence was not readable because of poor template quality.

Serum PSA Levels. Serum PSA levels were performed by the University of Southern California Norris Cancer Hospital Clinical Laboratory using a two-site immunoenzymometric assay with a Hybritech anti-PSA mouse monoclonal antibody (TOSOH Medics, Inc., Foster City, CA). The minimal detectable PSA concentration was 0.05 ng/ml, with intra-assay and

interassay coefficient of variations of 2.9 and 2.1%, respectively.

Statistical Methods. Serum PSA levels were log transformed, and linear regression models were fitted to estimate the effects of *AR* and/or *PSA* genotypes on serum PSA levels, adjusting for age and ethnicity. Because a few observations with extremely long or extremely short *AR CAG* length were highly influential in determining regression coefficients, *CAG* length was grouped into approximate deciles to improve robustness of the models. Decile 1 corresponds to 7–16 *CAG* repeats, decile 2 to 17–18 *CAG* repeats, each of deciles 3 through 8 corresponds to a single *CAG* repeat category (19–24 repeats, respectively), decile 9 corresponds to 25–26 *CAG* repeats, and decile 10 to 27–37 *CAG* repeats. The medians of the decile groups: 15, 17, 19, 20, 21, 22, 23, 24, 25, and 28 *CAG* repeats, were used as scores for coding *CAG* length in the regression equations. The resulting regression coefficient can be interpreted as representing the additive increase in $\ln(\text{PSA})$, and the exponentiated coefficient as the multiplicative increase in PSA for each decrease of one *CAG* unit. Heterogeneity tests were performed by calculating the likelihood ratio statistic, comparing the model

Table 3 PSA promoter haplotype frequencies (%) by ethnicity

	African Americans (n = 96)	Non-Hispanic whites (n = 106)	Hispanics (n = 104)	Japanese Americans (n = 96)
PSA*1	53	46	37	20
PSA*2	41	25	32	45
PSA*3	6	29	31	35

Fig. 1. Correspondence between PSA genotypes and haplotypes. A, classification of 402 subjects according to PSA genotypes at positions -252, -232, and -158. B, classification of 804 chromosomes according to PSA haplotypes (PSA*1, PSA*2, and PSA*3).

		-158 (ARE1)						
		AA	AG	GG	-252 A/G	-232 [A]	-158 A/G	+1
A	GG	69 (17%) PSA*1/*1	104 (26%) PSA*1/*2	50 (12%) PSA*2/*2	PSA*1	G	ΔA	A
	GA	0 (0%)	74 (18%) PSA*1/*3	80 (20%) PSA*2/*3	PSA*2	G	ΔA	G
	AA	0 (0%)	0 (0%)	25 (6%) PSA*3/*3	PSA*3	A	A	G

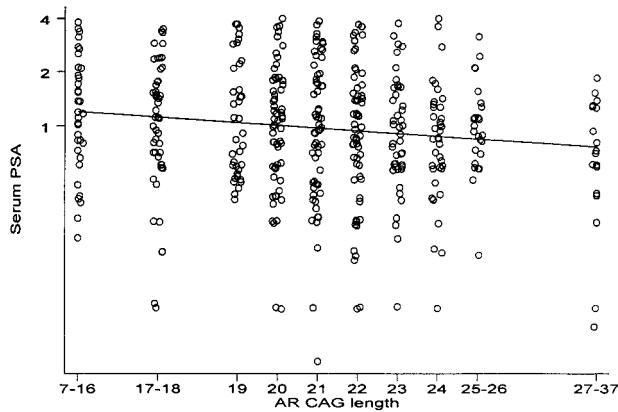


Fig. 2. Serum PSA as a function of AR CAG length. O, a single subject. Line, regression of ln(PSA) on AR CAG length, adjusted for age and ethnicity.

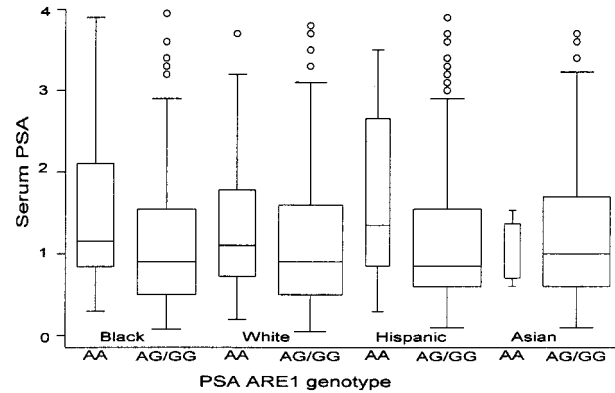


Fig. 3. Distribution of serum PSA levels by PSA ARE1 genotype and ethnicity. The width of each box is proportional to the square root of the number of observations in the group.

with a single regression line to a model with separate regression lines for each genotypic group. All *P*s were two-sided.

Because all of the AR GGC genotypes other than genotype 16 were relatively uncommon, GGC alleles were categorized as <16, 16, and >16, roughly corresponding to the bottom quartile, middle 50%, and upper quartile, respectively. GGC genotype group was modeled by including two indicator variables in the regression model.

Results

The age of the subjects at the time of blood collection ranged from 47 to 80 years, with a mean of 62.8 years. Mean and median ages were slightly higher for Hispanics than for other ethnic groups, but these differences were not statistically significant (Table 1). There were no significant ethnic differences in serum PSA (Table 1), either before or after adjusting for age. Age was weakly correlated with serum PSA (*R* = 0.16; *P* < 0.01).

The distributions of AR and PSA allele frequencies are shown in Table 2. Ethnic-specific allele frequencies were similar to those previously reported (5, 6). In the AR gene, short CAG length (<19 CAG repeats) and short GGC length (<16 GGC repeats) were more common, and GGC length of 16 was less common among African Americans than among men of

other ethnic groups. At the PSA ARE1 locus, the G allele was most frequent among Japanese Americans, intermediate among Hispanics, and least frequent among African Americans and non-Hispanic whites. Genotype frequencies were in agreement with Hardy-Weinberg equilibrium in all of the ethnic groups (data not shown).

In the PSA gene promoter, two new polymorphisms were identified. An A/G polymorphism at -252, 79 bp upstream from ARE1, and a single-base deletion polymorphism (A/ΔA) at -232. The two polymorphisms were in perfect linkage disequilibrium, with the -252A allele always corresponding to the -232A allele and the -252G to the -232ΔA allele (see Fig. 1). The -252A/-232A allele was much less common among African Americans than among men of other ethnic groups; in fact no -252A/-232A homozygotes were observed among African Americans (Table 2). The two polymorphisms were also in linkage disequilibrium with the ARE1 polymorphism, with the -252A/-232A allele occurring only in combination with the ARE1G allele (Fig. 1). Thus, there exist three PSA promoter haplotypes, -252G/-232ΔA/ARE1A, -252G/-232ΔA/ARE1G, and -252A/-232A/ARE1G, which we have designated as PSA*1, PSA*2, and PSA*3, respectively (Fig. 1), according to a recently recommended nomenclature system (7). Ethnic-specific haplotype frequencies are given in Table 3.

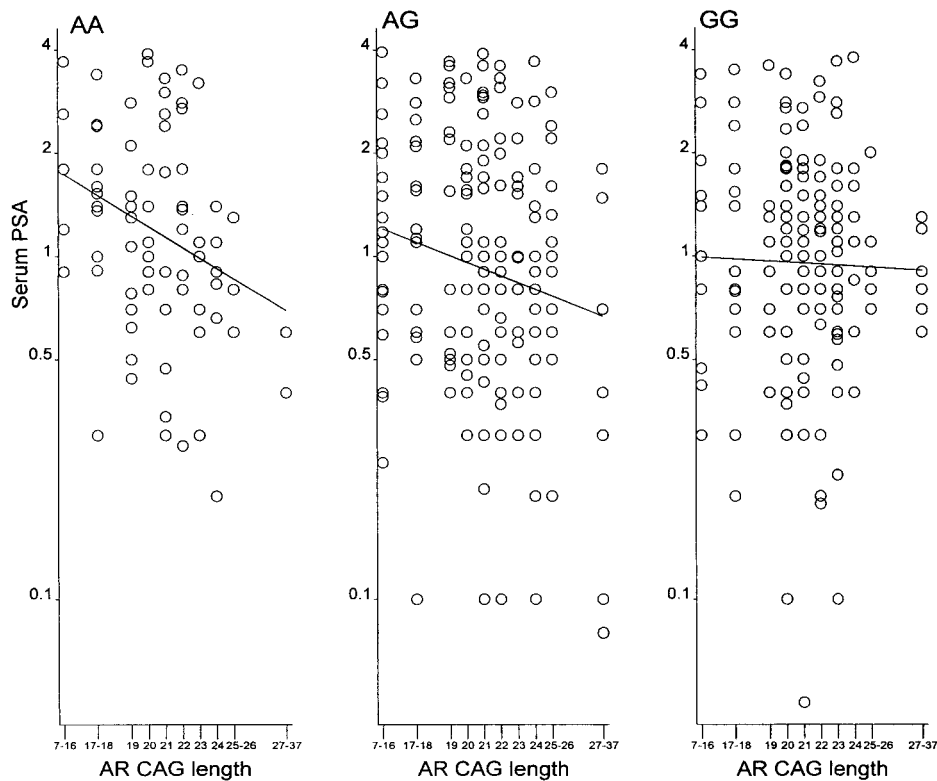


Fig. 4. Serum PSA as a function of AR CAG length, stratified by PSA genotype. \circ , a single subject. Line, regression of $\ln(\text{PSA})$ on AR CAG length, adjusted for age and ethnicity. A, PSA genotype AA; B, PSA genotype AG; C, PSA genotype GG.

Of the two AR polymorphisms, only CAG length was associated with serum PSA levels. Serum PSA is shown as a function of AR CAG length in Fig. 2. There was a subtle but significant ($P = 0.01$) decrease in serum PSA with increasing CAG length. Serum PSA was predicted to decrease by 3.5% for each additional CAG. In the lowest decile (CAG < 17), geometric mean PSA was 83% higher (1.19 ng/ml) than in the highest decile (CAG > 26; geometric mean PSA, 0.65 ng/ml). There was no evidence of heterogeneity in slope by ethnicity ($P = 0.33$). There was no association between serum PSA level and GGC length, either before ($P = 0.25$) or after ($P = 0.29$) adjusting for CAG length.

Fig. 3 shows the distribution of serum PSA by ethnicity and by PSA ARE1 genotype. Combining all ethnic groups, geometric mean PSA levels were higher among men with the AA genotype compared with men with the AG or GG genotypes ($P = 0.02$). PSA levels did not differ between genotypes AG and GG ($P = 0.80$). This same pattern was seen among African Americans ($P = 0.06$), non-Hispanic whites ($P = 0.28$), and Hispanics ($P = 0.11$) but was not statistically significant within each group, because of the smaller sample. The association of the AA genotype with higher PSA levels could not be evaluated among Japanese Americans ($P = 0.85$) because only five Japanese Americans had the AA genotype. Serum PSA levels were not associated with the newly identified $-252A/G$ and $-232A/A$ polymorphisms either alone ($P = 0.62$) or after adjusting for ARE1 genotype ($P = 0.33$). Haplotypes ($-252/-232/ARE1$) did not predict serum PSA better than ARE1 genotype alone ($P = 0.67$).

Because the AR regulates PSA transcription by binding the ARE1 sequence, we further examined the data for evidence of interaction between AR and PSA genotypes. Stratification on PSA ARE1 genotype (Fig. 4) provided a significantly better fit

to the data than did the unstratified model (Fig. 2; $P = 0.049$). For genotype GG, the slope was not significantly different from zero ($P = 0.74$). For genotype AG, serum PSA increased 4.5% with each decrease of one CAG repeat decile ($P = 0.03$), whereas for genotype AA, serum PSA increased 7% with each decrease of one CAG repeat decile ($P = 0.02$).

Discussion

This is the first report to identify genetic determinants of serum PSA levels. We found that variation in serum PSA levels among healthy men is associated with polymorphic variation in both the AR and the PSA genes. Log-transformed PSA levels were linearly and inversely associated with AR CAG length. Moreover, AR CAG length influenced serum PSA most strongly among men having PSA genotype AA, only modestly among men having genotype AG, and not at all among men with genotype GG. In other words, PSA and AR genotypes interact to influence serum PSA levels.

Physical interaction of the AR transcription complex with AREs in the PSA gene promoter activates PSA gene transcription. *In vitro* studies have established that ARs encoded by short CAG alleles are more efficient transactivators than those encoded by long CAG alleles (8, 9). The reduction in AR transactivation activity observed *in vitro* with increasing CAG length is modest (10) and is consistent with the subtle decrease in serum PSA levels observed in the present study.

The PSA ARE1 sequence lies 170 bp upstream of the transcription start site and has two allelic variants: AGAA-CAnnnAGTACT and AGAACAnnnAGTGCT. Experimental studies addressing the functional differences between these two alleles have not been reported. The allelic differences observed in this study were subtle and may be difficult to detect in an *in*

vitro system. Nevertheless, our data suggest that the *A* and *G* alleles interact differently with the AR, leading to quantitative differences in *PSA* expression. Alternatively, the *ARE1* polymorphism may be in linkage disequilibrium with undefined coding polymorphisms that influence *PSA* activity or with upstream or downstream regulatory elements that affect transcription efficiency. To address the possibility that the *ARE1* polymorphism may simply mark a nearby functional promoter polymorphism, we sequenced a 560-bp region surrounding the *ARE1*. Although we found two additional polymorphic sites, these sites do not appear to influence serum *PSA* levels.

Although *PSA* has been used as a tumor marker for many years, the role of *PSA* in prostate physiology is still unclear. Both protective and pathogenic functions have been attributed to *PSA*. *PSA* cleaves the major IGF-binding protein, IGFBP-3, and increases bioavailable IGF-I and IGF-II, potentially having a stimulatory effect on prostatic epithelial cell proliferation (11). On the other hand, *PSA* has been reported to be antiangiogenic (12). This function could help prevent progression of localized prostate cancers to a more advanced stage. In our previous study (5), we found that the *PSA GG* genotype, which is associated with lower serum *PSA* levels in the present study, was associated with increased risk of advanced prostate cancer. Although the number of subjects in that study was small, the result supports a protective role for *PSA* against prostate cancer progression.

The role of the *AR CAG* repeat polymorphism is less clear. The genotype associated with higher serum *PSA* levels, namely *CAG* short, was associated with increased risk of prostate cancer in our previous study (5) and in several other studies (13–15). This apparent inconsistency might be explained by multiple downstream effects of androgen signaling. The AR, by transactivating other genes in addition to *PSA*, might influence prostate cancer risk through several pathways, some that confer risk and others, such as *PSA*, that are protective. Both the *AR CAG* and the *PSA ARE1* polymorphisms need to be examined in large numbers of advanced and localized prostate cancer cases and controls to shed light on this situation.

One strength of this study is that subjects were chosen from a well-characterized cohort of healthy men. Men with elevated *PSA* levels (>4 ng/ml) were excluded. The remaining men are unlikely to have significant disruption of prostatic barriers; thus, differences in serum *PSA* levels are likely to be attributable to *PSA* production. Higher *PSA* production among certain genotypic groups might be attributable to either increased production by individual cells or to prostatic hyperplasia. We cannot rule out the possibility that the higher *PSA* levels among men with short *CAG* alleles might be attributable to an increase in benign prostatic hyperplasia among this group. However, our results were not changed by eliminating 40 men who reported a history of prostate enlargement. Additional studies will be necessary to determine whether intraprostatic *PSA* expression is associated with genotype.

In summary, we have shown that in healthy men, genetic

variants in the *PSA* and *AR* genes contribute to variation in serum *PSA* levels. Men with the *PSA AA* genotype and short *AR* alleles have, on average, higher serum *PSA* levels.

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