# Genetic Determinants of Serum Prostate-specific Antigen levels in Healthy Men from a Multiethnic Cohort[1]

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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 PSA[3] 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.

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

| | African Americans | Non-Hispanic whites | Hispanics | Japanese Americans |
|---|---|---|---|---|
| *n* | 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 ($n = 100$) *n* (%) | Non-Hispanic whites ($n = 113$) *n* (%) | Hispanics ($n = 108$) *n* (%) | Japanese Americans ($n = 99$) *n* (%) | All of the groups ($n = 420$) *n* (%) |
|---|---|---|---|---|---|
| *AR CAG* | | | | | |
| 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) |
| *AR GGC*[a] | | | | | |
| 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) |
| *PSA ARE1* | | | | | |
| *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) |
| *PSA* −252/−203[b] | | | | | |
| *GG*/*ΔAΔA* | 84 (87) | 52 (49) | 49 (47) | 38 (40) | 223 (56) |
| *GA*/*AΔA* | 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 *Nhe*I 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 GGACAGGGTGAGGAAGACAA (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(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

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*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*).

**A**

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

**B**

| | | -252 A/G | -232 [A] | -158 A/G |
|---|---|---|---|---|
| PSA*1 | 316 (39%) | G | ΔA | A |
| PSA*2 | 284 (35%) | G | ΔA | G |
| PSA*3 | 204 (26%) | A | A | G |

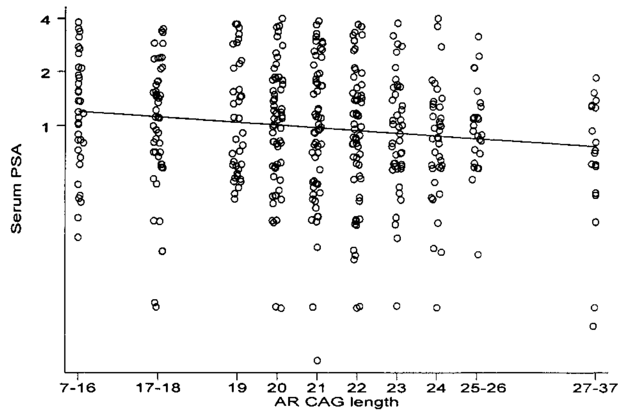


*Fig. 2.* Serum PSA as a function of *AR CAG* length. ○, a single subject. *Line*, regression of ln(PSA) on *AR CAG* length, adjusted for age and ethnicity.

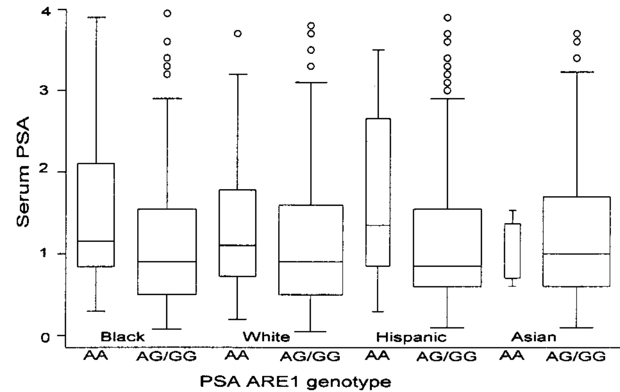


*Fig. 3.* Distribution of serum PSA levels by *PSA ARE1* genotype and ethnicity. The width of each box is proportional to the square root of the number of observations in the group.

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.

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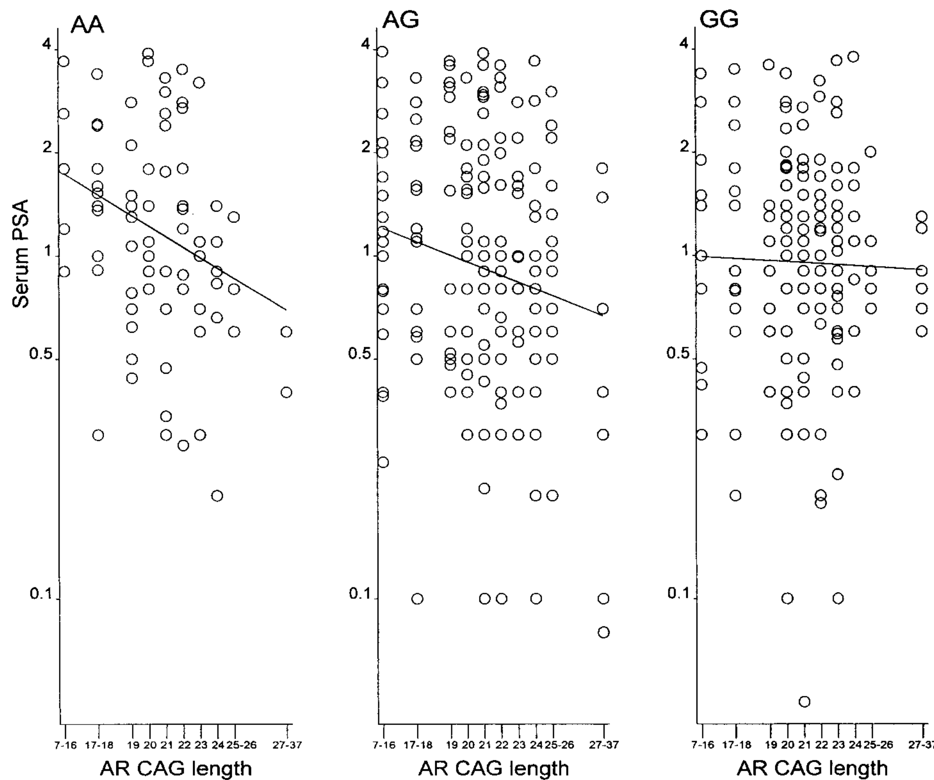


*Fig. 4.* Serum PSA as a function of *AR CAG* length, stratified by *PSA* genotype. ○, a single subject. *Line*, regression of ln(PSA) on *AR CAG* length, adjusted for age and ethnicity. *A*, *PSA* genotype *AA*; *B*, *PSA* genotype *AG*; *C*, *PSA* genotype *GG*.

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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 −252*A/G* and −232*A/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 transciption 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: AGAACAnnnAGT$\underline{\text{A}}$CT and AGAACAnnnAGT$\underline{\text{G}}$CT. 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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## References

1. Collins, G. N., Lee, R. J., McKelvie, G. B., Rogers, A. C. N., and Hehir, M. Relationship between prostate-specific antigen, prostate volume, and age in the benign prostate. Br. J. Urol., *71:* 445–450, 1993.

2. Morgan, T. O., Jacobsen, S. J., McCarthy, W. F., Jacobson, D. J., McLeod, D. G., and Moul, J. W. Age-specific reference ranges for serum prostate-specific antigen in black men. N. Engl. J. Med., *335:* 304–310, 1996.

3. Henderson, R. J., Eastham, J. A., Culkin, D. J., Kattan, M. W., Whatley, T., Mata, J., Venable, D., and Sartor, O. Prostate-specific antigen (PSA) and PSA density: racial differences in men without prostate cancer. J. Natl. Cancer Inst. (Bethesda), *89:* 134–138, 1997.

4. Schuur, E. R., Henderson, G. A., Kmetec, L. A., Miller, J. D., Lamparski, H. G., and Henderson, D. R. Prostate-specific antigen expression is regulated by an upstream enhancer. J. Biol. Chem., *271:* 7043–7051, 1996.

5. Xue, W., Irvine, R. A., Yu, M. C., Ross, R. K., Coetzee, G. A., and Ingles, S. A. Susceptibility to prostate cancer: interaction between genotypes at the androgen receptor and prostate-specific antigen loci. Cancer Res., *60:* 839–841, 2000.

6. Irvine, R. A., Yu, M. C., Ross, R. K., and Coetzee, G. A. The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. Cancer Res., *55:* 1937–1940, 1995.

7. Garte, S., and Crosti, F. A nomenclature system for metabolic gene polymorphisms. *In:* P. Vineis, N. Malats, M. Lang, A. d'Errico, N. Caporaso, J. Cuzick, and P. Boffetta, (eds.), Metabolic Polymorphisms and Susceptibility to Cancer, IARC Scientific Publ. No. 148, pp. 5–12. Lyon, France: IARC, 1999.

8. Chamberlain, N. C., Driver, E. D., and Miesfeld, R. L. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res., *22:* 3181–3186, 1994.

9. Kazemi-Esfarjani, P., Trifiro, M. A., and Pinsky, L. Evidence for a repressive function of the long polyglutamine tract in the human androgen receptor: possible pathogenic relevance for the $(CAG)_n$-expanded neuropathies. Hum. Mol. Genet., *4:* 523–527, 1995.

10. Irvine, R. A., Ma, H., Yu, M. C., Ross, R. K., Stallcup, M. R., and Coetzee, G. A. Inhibition of p160-mediated coactivation with increasing androgen receptor polyglutamine length. Hum. Mol. Genet., *9:* 267–274, 2000.

11. Cohen, P., Peehl, D. M., Graves, H. C. B., and Rosenfeld, R. G. Biological effects of prostate specific antigen as an insulin-like growth factor binding protein-3 protease. J. Endocrinol., *142:* 407–415, 1994.

12. Fortier, A. H., Nelson, B. J., Grella, D. K., and Holaday, J. W. Antiangiogenic activity of prostate-specific antigen. J. Natl. Cancer Inst. (Bethesda), *91:* 1635–1640, 1999.

13. Ingles, S. A., Ross, R. W., Yu, M. C., Irvine, R. A., La Pera, G., Haile, R. W., and Coetzee, G. A. Association of prostate cancer risk with vitamin D receptor and androgen receptor genetic polymorphisms. J. Natl. Cancer Inst. (Bethesda), *89:* 166–170, 1997.

14. Stanford, J. L., Just, J. J., Gibbs, M., Wichlund, K. G., Neal, C. L., Blumenstein, B. A., and Ostrander, E. A. Polymorphic repeats in the androgen receptor gene: molecular markers for prostate cancer risk. Cancer Res., *57:* 1194–1198, 1997.

15. Giovannucci, E., Stampfer, M. J., Krithivas, K., Brown, M., Brufsky, A., Talcott, J., Hennekens, C. H., and Kantoff, P. W. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proc. Natl. Acad. Sci. USA, *94:* 3320–3323, 1997.

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