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Validation of Association of Genetic Variants at 10q with PSA Levels in Men at High Risk for Prostate Cancer

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Abstract

- Men with a family history of prostate cancer and African American men are at increased risk for prostate cancer and stand to benefit from individualized interpretation of PSA to guide screening strategies.
- The purpose of this study was to validate six previously identified markers among high-risk men enrolled in the Prostate Cancer Risk Assessment Program - a prostate cancer screening study.
- Eligibility for PRAP includes men ages 35–69 years with a family history of prostate cancer, any African American male regardless of family history, and men with known *BRCA* gene mutations.
- GWAS markers assessed included rs2736098 (5p15.33), rs10993994 (10q11), rs10788160 (10q26), rs11067228 (12q24), rs4430796 (17q12), and rs17632542 (19q13.33).
- Genotyping methods included either Taqman® SNP Genotyping Assay (Applied Biosystems) or pyrosequencing.
- Linear regression models were used to evaluate the association between individual markers and log-transformed baseline PSA levels, while adjusting for potential confounders.
- 707 participants (37% Caucasian, 63% African American) with clinical and genotype data were included in the analysis.

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- Rs10788160 (10q26) strongly associated with PSA levels among high-risk Caucasian participants (p<0.01), with a 33.2% increase in PSA level with each A-allele carried.
- Furthermore, rs10993994 (10q11) demonstrated an association to PSA level (p=0.03) in high-risk Caucasian men, with a 15% increase in PSA with each T-allele carried.
- A PSA adjustment model based on allele carrier status at rs10788160 and rs10993994 is proposed specific to high-risk Caucasian men.
- Genetic variation at 10q may be particularly important in personalizing interpretation of PSA for high-risk Caucasian men.
- Such information may have clinical relevance in shared decision-making and individualized prostate cancer screening strategies for high-risk Caucasian men. Further study is warranted.

Keywords

genetics; prostate-specific antigen; screening; prostatic neoplasms; family history

Introduction

Prostate cancer is the second-leading cause of cancer-related deaths in men in the United States (1). Men with a family history of prostate cancer and African American men are considered to be at high-risk for prostate cancer (1–4), with subsets at increased risk for younger age at diagnosis and aggressive disease (5–10). Given these factors, high-risk men in particular stand to benefit from optimized prostate cancer screening approaches.

PSA-based methods for prostate cancer screening remain controversial for the general population due to lack of consistency in reducing mortality and the estimated number needed to screen to prevent a prostate cancer death (11–14). There is concern for early detection leading to significant overdiagnosis and overtreatment of indolent prostate cancer, and standard therapy commonly results in significant morbidity and well-documented negative impacts on urinary, bowel and sexual function (15). Furthermore, PSA may show “false-positive” elevations, thus leading to unnecessary testing and prostate biopsies, which have the potential for serious complications (16). Yet, prostate cancer detection has been reported even at lower PSA values <3.0 (6, 7, 17). Based on these studies, several national organizations have offered sharply different recommendations regarding PSA-based screening for prostate cancer. The US Preventative Services Task Force recently recommended against routine PSA testing for men at any age unless having symptoms of prostate cancer, stating that the harms resulting from screening outweigh potential benefits (18). The American Cancer Society advocates that patients and doctors engage in informed and shared decision-making regarding PSA testing for prostate cancer screening, and further recommends that high-risk men have this discussion at age 45 (19). The American Urologic Association supports the appropriate use of the PSA test for screening (20) and recommends men speak with their doctors about their risk for prostate cancer. In addition, the American Society of Clinical Oncology (ASCO) issued a provisional opinion that clinicians should discuss the benefits and potential harms of PSA-based screening for prostate cancer in men

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with a life expectancy > 10 years (21). ASCO also stressed the importance of shared decision-making between patients and providers. Thus there is a need to develop approaches to optimize risk assessment for prostate cancer particularly for high-risk men, and one approach is to individualize interpretation of PSA in order to make appropriately informed prostate cancer screening recommendations.

Genetic variation has been reported to associate with PSA levels, with potential implications for adjustment of PSA based on genotype. A prior genomewide association study for prostate cancer reported the association of multiple genetic variants, particularly on chromosomes 10 and 19, with PSA levels (22). A subsequent study from the Baltimore Longitudinal Study of Aging reported the association of genetic variants on chromosomes 10 and 19 with prostate cancer risk at specific PSA levels, suggesting that genotypes could improve upon PSA for prostate cancer risk stratification (23). In 2010, Gudmundsson et al reported findings from a PSA-focused genomewide association study and identified six genetic variants associated with PSA in primarily average-risk Caucasian men (24). An additional goal of this previous study was to develop individualized PSA-cutoffs based on genetic variation to guide recommendations for prostate biopsy. Other studies have evaluated the use of single nucleotide polymorphisms (SNPs) in prostate cancer screening with conflicting results. One study reported marginal benefit to adding 33 prostate cancer-associated SNPs to PSA (25), while another study reported that four genetic variants can be useful in correcting PSA, leading to a reduction in unnecessary prostate biopsies (26). These prior studies primarily included Caucasian men at average-risk for prostate cancer. Since men with a family history of prostate cancer and African American men are considered at high-risk for developing prostate cancer and are in need of personalized screening recommendations, candidate genetic variants deserve further study for PSA association and potential adjustment of PSA particularly in this high-risk population who may benefit.

Our study was performed to validate the findings of the association of six genetic variants previously found to be associated with PSA levels (24) in a high-risk, ethnically diverse cohort of men undergoing prostate cancer screening in the Prostate Cancer Risk Assessment Program (PRAP) (7). Since high-risk men are at increased risk for a diagnosis of prostate cancer (particularly at younger ages)(6, 7), PRAP is an ideal, diverse cohort in which to study candidate genetic variants for association to PSA levels and to develop adjustments to PSA based on genetic information particularly relevant to high-risk men.

Patients and Methods

Prostate Cancer Risk Assessment Program (PRAP)

The Prostate Cancer Risk Assessment Program (PRAP) at Fox Chase Cancer Center (FCCC) was established in 1996 to provide screening and perform research for men at high risk for prostate cancer (7). Briefly, eligibility for PRAP include any man ages 35–69 years without a previous diagnosis of prostate cancer with one first-degree relative with prostate cancer, two second-degree relatives with prostate cancer on the same side of the family, any African American man regardless of family history, and men with known *BRCA1* or *BRCA2* mutations. *BRCA* mutation carriers account for approximately 1% of the PRAP cohort. Accrual to PRAP is ongoing and participants are followed longitudinally for prostate cancer

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screening and cancer detection. The current study includes 707 participants out of the 740 participants (96%) that had been consecutively accrued from 1996–2008. The PRAP study is approved by the Institutional Review Board at FCCC and at all previous and currently active community hospital sites that enrolled participants to PRAP.

Screening Approach in PRAP

PRAP participants undergo annual prostate cancer screening, which includes the total PSA, percent free PSA (fPSA), digital rectal examination (DRE), and estimation of PSA velocity. Biopsy criteria, prostate cancer incidence, and prostate cancer features have been described previously (7). Current biopsy criteria include suspicious DRE, PSA >=2.0ng/mL, or total PSA <10ng/mL but with PSA velocity >=0.75 ng/mL/year. All biopsies are transrectal ultrasound-guided 5-region patterned prostate biopsies (27, 28).

Genotyping of six candidate PSA-associated polymorphisms

Six genetic variants previously reported to be associated with PSA levels (22–24) were chosen for this study: rs2736098 (5p15.33), rs10993994 (10q11), rs10788160 (10q26), rs11067228 (12q24), rs4430796 (17q12), and rs17632542 (19q13.33). Genotyping for all variants except rs10788160 was performed on genomic DNA using a fluorogenic 5′ nuclease allelic discrimination assay (TaqMan® SNP Genotyping Assay, Applied Biosystems). Reactions were prepared using TaqMan® Universal PCR Mastermix, No AmpErase UNG or TaqMan® Genotyping MasterMix (Applied Biosystems) according to manufacturer's instructions. Thermal cycling and analysis were performed using an ABI7900 Sequence Detection System (Applied Biosystems). Control DNA samples with known genotypes were included in each run. In addition, a no template (water) control was included to assess DNA contamination. Genotype assignment was achieved automatically with the SDS software (Applied Biosystems) using a proprietary algorithm. In addition, genotypes were confirmed on a random selection of 2% of the samples by standard sequencing with 100% concordance.

Marker rs10788160 was genotyped using pyrosequencing. Briefly, PCR amplification was carried out using the following primer pairs: forward primer 5′-TTC GAT GTG TAC TTA GCC AAA AGG and reverse primer 5′-GAA CTC CCA ACC TCA GGT GAT CT. The reverse primers were biotinylated to facilitate single-strand DNA template preparation for pyrosequencing using forward sequencing primer 5′-TTA ATA ATT GAA TCT CAT GG. Primers were synthesized and HPLC-purified by Integrated DNA Technologies (Coralville, IA). Reactions were prepared using Choice Taq Blue Mastermix (Denville Scientific Inc.) and 30ng of genomic DNA according to manufacturer's instructions. Thermal cycling was performed using the following conditions: 95°C for 5 minutes; 35 cycles of 95°C for 45 seconds, 60°C for 45 seconds and 72°C for 45 seconds; and finally 72°C for 10 minutes. Amplicon size and purity were verified on a 2% agarose gel containing 0.5 ug/ml ethidium bromide. Preparation of the single-stranded DNA template for pyrosequencing was performed utilizing the PSQ™ Vacuum Prep Tool (Biotage) according to manufacturer's instructions. Twenty µl of biotinylated PCR product was immobilized on Streptavidin-coated Sepharose™ High Performance beads (GE Healthcare, Piscataway, NJ) and processed to obtain a single-stranded DNA using the PSQ 96 Sample Preparation Kit

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(Biotage) according to manufacturer's instructions. The template was incubated with 0.4 μM sequencing primer at 80°C for 2 min in a PSQ™96 plate. The sequencing-by-synthesis reaction of the complementary strand was automatically performed using the PSQ™ 96MA instrument (Biotage) at room temperature using PyroGold reagents (Biotage). SNP assignment and quality assessment of the raw data was performed using PSQ 96 SNP Software (Biotage).

Statistical Methods

Distribution of candidate genetic variants was summarized by self-reported race and compared using the chi-squared test. In addition, Hardy-Weinberg equilibrium was tested for each allele using the Chi-Square Goodness-of-Fit Test (29). Linear regression models were used to assess the association between individual variants and log-transformed baseline PSA levels in Caucasian and African American PRAP participants separately, while adjusting for age. False-discovery rate p-values were calculated based on Benjamini-Hochberg step-up procedure as implemented in SAS 9.2. Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) to measure the association between individual genotypes and prostate cancer at biopsy, adjusted for age and number of biopsies. A personalized PSA cutoff value based on genotypes of two variants, rs10788160 and rs10993994, corresponding to the commonly used cutoff of 4 ng/ml was calculated for each genotype combination for these two variants as per Gudmundsson et al. (24). Briefly, this was performed by multiplying the value of 4 ng/ml with the estimated relative genetic effect for the variants, assuming a multiplicative model. All analyses were performed either using PLINK (http://pngu.mgh.harvard.edu/purcell/plink/) (30), or SAS 9.2.

Results

At the time of this analysis, 740 participants were accrued to PRAP, and the primary analysis of six candidate genetic variants and association with PSA levels included 707 PRAP participants with complete clinical, demographic, and genotype data available. Exclusions from the analysis included men of self-identified race other than Caucasian or African American (n=8), African American men with any undetermined genotypes (n=19), and Caucasian men with any undetermined genotypes (n=6). Table 1 describes the characteristics of these 707 participants by self-reported race. As can be seen from Table 1, the mean age at entry into PRAP was similar by race, with African American participants at 49.6 years and Caucasian participants at 50.1 years. Mean PSA at entry for African American men was 1.67 ng/mL and for Caucasian participants was 1.70 ng/mL. Mean PSA prior to diagnosis was identical for both race groups at 3.4 ng/mL. There was a significant difference noted in percentage of men with any follow-up, with a greater percentage of Caucasian men following-up (80%) compared to African American men (59%) ($p<0.01$). No other significant differences were observed between race groups. Table 2 describes the allele frequencies of the six candidate genetic variants evaluated in this analysis. As seen in Table 2, significant differences were observed in candidate allele frequencies by self-reported race. No differences were observed on Hardy-Weinberg equilibrium tests.

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Table 3 describes the results of association analyses between the candidate variants and PSA levels by self-reported race. As seen in Table 3, rs10788160 at 10q26 was strongly associated with PSA levels among Caucasian PRAP participants of whom 98% had a family history of prostate cancer (p<0.01), with a 33.2% increase in PSA level with each A-allele carried. The association of rs10788160 with PSA levels was not as strong among African American PRAP participants (p=0.02), with significance disappearing after correcting for false discovery rate (FDR). Among Caucasian participants, rs10993994 (10q11) demonstrated an association to PSA level (p=0.03) which dissipated somewhat after correction for false-discovery (FDR-corrected p=0.09), with a 15% increase in PSA level with each T-allele carried. No association was observed to PSA levels among African American PRAP participants for rs10993994. In addition, no significant associations to prostate cancer were observed for the six candidate variants in the PRAP cohort, though sample sizes for these comparisons were small (Table S1).

Since rs10788160 and rs10993994 had the strongest associations to PSA level among Caucasian PRAP participants, these two markers were incorporated into a genetically-based PSA-adjustment model with a similar approach as per Gudmundsson et al (24). Table 4 shows the suggested PSA cutoffs in high-risk Caucasian men at which, after further confirmation, one could consider further clinical evaluation (such as more frequent PSA checks or perhaps a biopsy). For example, using this model, a Caucasian male with a family history of prostate cancer with no PSA-associated alleles at rs10788160 and rs10993994 could be considered for further evaluation when the PSA is 2.97 ng/mL rather than a PSA of 4.0ng/mL. Conversely, if the same patient carries all four alleles, then further evaluation could be delayed until a PSA of 6.96 ng/mL. Thus, the PSA may be interpreted on an individual basis for recommending further evaluations and sparing unnecessary biopsies and testing.

Discussion

Risk assessment for prostate cancer is a field in evolution, with one main challenge being the controversy over PSA-based screening for the disease in the general population (11–14). Yet men with familial prostate cancer and African American men are both considered to be at high risk for prostate cancer (1–4), and subsets have been found to develop aggressive disease and ultimately die from prostate cancer (5–10). Most experts agree that the downstream impact of PSA-based screening is the key concern, with risk for overdiagnosis of indolent prostate cancer, overtreatment with exposure to risks and side effects, and unnecessary biopsies with risks of bleeding, infection, and potentially sepsis. Appropriate interpretation of PSA on an individual basis holds promise for informing patients and providers on making decisions for prostate cancer screening, especially in individuals having greater than average risk for the development of prostate cancer. Thus, efforts have commenced to identify factors that impact the significance and interpretation of PSA levels.

Previous studies have shown genomic variants to be associated with PSA levels, primarily in Caucasian men at average-risk for prostate cancer (23–25). In 2010, Gudmundsson et al. identified six genetic variants associated with PSA levels from a PSA-focused genomewide association study in primarily average-risk Caucasian men and proposed genetically-

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adjusted PSA cut-offs (25). Since men with a family history of prostate cancer and African American men are in need of strategies to individualize interpretation of PSA, our study sought to validate these previous SNP associations in an ethnically-diverse cohort of men all at high-risk for prostate cancer to gain insight into the potential role of six of these variants in prostate cancer risk assessment specifically for this high-risk population. We validated the association of two markers at 10q (rs10788160 at 10q26 and rs10993994 at 10q11) to PSA levels among Caucasian men with a family history of prostate cancer and further propose a genetically-based adjustment to PSA interpretation specific to high-risk Caucasian men. To our knowledge, this is the first report of genetic impact on interpretation of PSA specifically among high-risk Caucasian men.

Among Caucasian men in PRAP, rs10788160 at 10q26 had the strongest association to PSA levels with the greatest increase in PSA per risk allele, which confirms prior findings from a PSA-focused GWAS (24). This variant was not previously reported to associate with prostate cancer, and therefore this variant may prove to have more utility in adjusting PSA particularly among Caucasian men with a family history of prostate cancer and thereby avoid unnecessary prostate biopsies. Marker rs10993994 at 10q11 had a weaker association to PSA levels among high-risk Caucasian men in our cohort. This variant has previously been reported to associate with prostate cancer (31–33) and PSA levels (22–24, 34). Rs10993994 is close to the transcription start site of *MSMB*, and the T-allele of rs10993994 has been reported to associate with decreased transcript levels and expression of MSMB in normal and tumor prostate tissues (35). It is noted that discerning the effect of rs10993994 on PSA levels vs. prostate cancer is challenging. A prior study did not include this marker in their genetic correction model for PSA adjustment (24). We chose to include rs10993994 in our genetic correction model for high-risk Caucasian men since there was no association to prostate cancer found in our study. It is noted that other studies have reported the association of rs10993994 with prostate cancer but not with aggressive disease to our knowledge (36). Thus, if rs10993994 is associated with PSA level and/or with less aggressive prostate cancer, correction of PSA by including this marker may limit unnecessary biopsies, some of which may have indolent prostate cancer. Further study is needed to confirm our findings and characterize the influence of rs10788160 and rs10993994 in prostate cancer biology.

There are some limitations to be noted. Four of the six previously reported variants were not associated with PSA levels in our cohort, which may have been due to sample size. A larger study confirming our findings among high-risk men is warranted. We observed a modest association of rs10788160 to PSA levels among African American PRAP participants which disappeared after correction for false discovery. None of the other variants were observed to be associated with PSA levels in African American PRAP men, which may be due to sample size and/or race-specific genetic variation influencing PSA levels. Further study is needed in larger cohorts of men of African descent to study the genetic influence on PSA levels. In addition, since SNP prevalence differs by race, there may be inherent limitations in detecting SNP associations to PSA either among Caucasian or African American men in the PRAP cohort.

In summary, our study finds that allelic variation of two genetic polymorphisms at 10q - rs10788160 (10q26) and rs10993994 (10q11) - may be of particular importance in impacting

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interpretation of PSA for Caucasian men with a family history of prostate cancer. Given the current controversy over the benefits vs. risks of PSA-based screening for prostate cancer, individualized interpretation of PSA holds promise for informing discussions of prostate cancer risk assessment to ultimately identify clinically meaningful prostate cancer while minimizing harm. Men with familial risk for prostate cancer and African American men in particular stand to benefit from such research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics and Prostate Cancer Characteristics of 707 PRAP Participants by Self-reported Race

	African American (n=447)			Caucasian (n=260)		
	n	**Mean**	**Range**	**n**	**Mean**	**Range**
Age at entry (years)	447	49.6	35–69	260	50.1	35–69
Family history of prostate cancer		144 (32.2%)			255* (98.1%)	
Duration of follow-up (months)	262	51.9	0.3–164.0	209	57.7	0.4–169.5
PSA at baseline (ng/mL)	442	1.67	0.1–27.2	259	1.70	0.1–22.5
DRE at baseline, n (%)						
Normal/BPH		425 (95.9%)			244 (95.7%)	
Abnormal		18 (4.1%)			11 (4.3%)	
Number participants biopsied after enrollment into PRAP, n(%)		96 (21.5%)			78 (30%)	
Prostate cancer diagnosis, n(%)		44 (9.8%)			39 (15.0%)	
Age at diagnosis (years)	44	56.6	38–74	39	57.9	43–70
Last PSA prior to diagnosis (ng/mL)	44	3.4	0.6–15.3	39	3.4	2.1–22.5
Gleason Score	44	6.2	5–8	39	6.2	5–7

Note: 262 of 447 (59%) African American men had any follow-up and 209 of 260(80%) Caucasian men had any follow-up; Fisher's exact test $p<0.01$.

*Remainder of Caucasian men were *BRCA* mutation carriers (n=5).

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Table 2

Allele Frequencies by Race

			Caucasians		African Americans		Test for allele frequency differences by race	
Chromosome	**SNP***	**Risk Allele****	**RAF*****	**# of participants with genotypes**	**RAF**	**# of participants with genotypes**	**Chi-sq**	**Chi-sq p-value**
5	rs2736098	T	0.26	257	0.11	438	68.05	1.59×10^{-16}
10	rs10993994	T	0.43	258	0.63	428	51.95	5.69×10^{-13}
10	rs10788160	A	0.27	242	0.06	381	109.01	1.61×10^{-25}
12	rs11067228	A	0.54	256	0.81	441	115.86	5.10×10^{-27}
17	rs4430796	A	0.53	237	0.33	427	54.42	1.62×10^{-13}
19	rs17632542	T	0.93	255	0.98	442	28.04	1.19×10^{-7}

*SNP = Single Nucleotide Polymorphism

**Risk allele is the allele associated with change in PSA level in Gudmundsson et al (24).

***RAF = Risk Allele Frequency

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Table 3

Association of Candidate SNPs to PSA levels at Baseline in 707 PRAP participants by self-reported race, adjusted for age at entry

	Chromosomal locus	SNP	Risk Allele*	# Subjects with Genotype	%PSA change per allele	p-value	FDR- corrected p-value**
Caucasian (n=260)	5p15.33	rs2736098	T	256	−8.1	0.25	0.30
	10q11	rs10993994	T	257	15	**0.03**	**0.09**
	10q26	rs10788160	A	241	33.2	**<0.01**	**<0.01**
	12q24	rs11067228	A	255	−4.5	0.47	0.47
	17q12	rs4430796	A	236	13.4	0.09	0.13
	19q13.33	rs17632542	T	254	29.4	0.05	0.09
African Americans (n=447)	5p15.33	rs2736098	T	434	2.8	0.76	0.76
	10q11	rs10993994	T	423	9.9	0.12	0.35
	10q26	rs10788160	A	378	31.6	0.02	0.14
	12q24	rs11067228	A	437	−3.4	0.62	0.74
	17q12	rs4430796	A	422	−5.9	0.29	0.59
	19q13.33	rs17632542	T	438	−16.1	0.43	0.64

*Risk allele is the allele associated with higher PSA level in Gudmundsson et al. 2010 (24)

**p-value corrected for false discovery rate using Benjamini-Hochberg step-up procedure (SAS 9.2).

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Table 4

Proposed Genotype-Adjusted PSA Cut-Offs for Caucasian PRAP Participants

	Proposed Adjusted PSA cutoff for biopsy (ng/mL)
Genotype combination (# of PSA-increasing alleles)	
rs10788160 (0)/ rs10993994 (0)	2.97
rs10788160 (0)/ rs10993994 (1)	3.42
rs10788160 (0)/ rs10993994 (2)	3.93
rs10788160 (1)/ rs10993994 (0)	3.96
rs10788160 (1)/ rs10993994 (1)	4.55
rs10788160 (1)/ rs10993994 (2)	5.23
rs10788160 (2)/ rs10993994 (0)	5.26
rs10788160 (2)/ rs10993994 (1)	6.05
rs10788160 (2)/ rs10993994 (2)	6.96