Title: A systematic review of replication studies of prostate cancer susceptibility genetic variants in high-risk men originally identified from genome-wide association studies

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Running Title (60 char): Replication of prostate cancer GWAS markers in high-risk men

KEYWORDS: Prostate cancer, genetic variants, high-risk populations, African-American, familial prostate cancer

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ABSTRACT:
Background: Several prostate cancer (PCa) genome-wide association studies (GWAS) have identified risk-associated genetic variants primarily in populations of European descent. Less is known about the association of these variants in high risk populations, including men of African descent and men with a family history of PCa. This paper provides a detailed review of published studies of PCa-associated genetic variants originally identified in GWAS and replicated in high-risk populations.
Methods: Articles replicating GWAS findings (NHGRI GWAS database) were identified by searching PubMed and relevant data was extracted.
Results: Eleven replication studies were eligible for inclusion in this review. Of over 30 single nucleotide polymorphisms (SNPs) identified in PCa GWAS, 19 SNPs (63%) were replicated in men of African descent and 10 SNPs (33%) were replicated in men with familial and/or hereditary PCa. The majority of SNPs were located at the 8q24 region with modest effect sizes (OR 1.11-2.63 in African American men and OR 1.3-2.51 in men with familial PCa). All replicated SNPs at 8q24 among men of African descent were within or near Regions 2 and 3.
Conclusions: This systematic review revealed several GWAS markers with replicated associations to PCa in men of African descent and men with familial/hereditary PCa. The 8q24 region continues to be the most implicated in PCa risk. These replication data support ongoing study of clinical utility and potential function of these PCa-associated variants in high-risk men.
Impact: The replicated SNPs presented in this review hold promise for personalizing risk assessment for PCa for high-risk men upon further study.

INTRODUCTION:

Prostate cancer (PCa) is the most commonly diagnosed non-cutaneous cancer among men in the United States. (1) For 2011, the American Cancer Society projects approximately 240,890 new cases of PCa will be diagnosed and that about 33,720 men will die from PCa. (1) African-American men and men with a family history of PCa are at significantly increased risk for developing PCa, with some developing aggressive disease or having younger age of onset. (2) African American men are at twice the risk for developing PCa and are at more than twice the risk for dying from PCa.(3) Men with familial PCa (FPC), defined as having at least 1 first-degree relative with PCa, or hereditary PCa (HPC), defined as a family with 3 generations affected, 3 first-degree relatives affected or 2 relatives affected before age 55 years, are at 2-7 times increased risk for PCa.(4-5)

Many genetic linkage and association studies have attempted to identify high-penetrance genetic variants which confer increased risk of PCa and particularly of PCa in high-risk populations, which includes African American men and men with FPC/HPC. However, causal genetic variants underlying susceptibility remain unknown due to the genetic complexity of PCa. The increase in high-throughput technology and decreases in cost have made genome-wide association studies (GWAS) easier to perform and have lead to the ability to identify associations between disease and more common variants in the genome. To date, many PCa GWAS have been conducted, however these studies have primarily been in populations of European descent and have been powered by mostly sporadic PCa cases.(6) Further, most identified variants have shown very low penetrance and few have demonstrated biologic plausibility.

Replication studies have become increasingly important in order to validate associations in diverse race/ethnic populations, disease subtypes, and to place variants identified in the context of their potential clinical utility in predicting individual disease risk. Although, the genetic variants detected in GWAS have been of modest effect sizes (for example, odds ratios of 1.01 to 1.5), understanding the risk particularly in men of African descent men and men with FPC/HPC may have clinical prediction utility in high-risk men.(7) One area in need of accurate PCa risk prediction is PCa screening, particularly for high-risk men. PCa screening guidelines remain an issue of debate among the general population, and optimized approaches to screening high-risk men remain understudied. Therefore, identifying genetic variants associated with or predicting PCa risk in high-risk men is increasingly important in order to develop individualized screening and prevention strategies based on genetic risk.

Here we present a systematic review of published replication studies of single nucleotide polymorphisms (SNPs) associated with PCa initially identified in GWAS and replicated in men of African descent men and men with FPC/HPC. The goal of this review is to determine the rates of positive associations to PCa of GWAS SNPs in high-risk men and provide a consolidated source of SNPs to date associated with PCa in high-risk men for further validation and study of clinical utility.

METHODS:

The national GWAS database maintained by the National Human Genome Research Institute of the National Institutes of Health was searched for the term ‘‘prostate cancer’’ in order to identify PCa risk associated SNPs from published GWAS studies as of February 2011. (6) In addition, PubMed was searched using the search terms

"prostate cancer" and "GWAS" or "genome-wide association study" or genome-wide". There were no limitations placed on population studied, publication year or country. Relevant articles cited in the bibliography of retrieved articles were also included. Selection of articles was done by two independent researchers (M.I. and V.G.) to avoid bias. SNP-trait associations listed here include those with p-values < 1.0×10^{-5} in the original GWAS with at least one replication study in high-risk men. We opted to include three SNPs originally identified in GWAS where the level of significance in the original GWAS was >1.0×10^{-5} but had at least two replication studies reported in high-risk men. Over 30 unique genetic variants were found to be associated with PCa through GWAS. We present data on the earliest published GWAS detecting an association with a SNP if more than one GWAS detected an association. In addition, we included a SNP identified in a GWAS conducted in an African American population (8).

A second search was conducted to identify replication studies evaluating those genetic variants initially identified in GWAS and further studied in men of African descent men and in men with FPC/HPC. There were no limitations placed on publication year or language. PubMed was searched using the search terms: "prostate cancer" or "prostatic neoplasms " in combination with "African-American" and "African descent" in combination with "genetic" and "gene" and "SNP" or "single nucleotide polymorphism" or in combination with "replication". For replication studies in FPC/HPC, PubMed was searched using the search terms: "prostate cancer" or "prostatic neoplasms " in combination with "familial prostate cancer" or "FPC" and "hereditary prostate cancer" or "HPC" in combination with "genetic" and "gene" and "SNP" or "single nucleotide polymorphism" or in combination with "replication" . We excluded data on SNPs which were not previously identified in GWAS and only considered SNPs which reached a p-value of 0.05 in the specific high-risk populations due to a greater potential clinical impact of these genetic markers in risk assessment for high-risk men.

Extracted data from both GWAS and replication studies include study name, authors, population(s) studied, publication date (month, year), chromosomal region, potentially implicated gene(s), SNP reaching a statistical significance of alpha=0.05 or lower, risk allele, sample size (number of case patients and number of control subjects in the first and subsequent stages), frequency of the risk allele, respective effect size and 95% confidence interval, and *P* value. When available, we present the risk allele-specific odds ratio (OR). Otherwise, we presented the OR for particular genotypes.

The forest plots in this paper were performed using SAS 9.1.3 software and provide the OR and 95% CI for each replication study. LD visualizations were constructed in Haploview 4.2. (9)

RESULTS:

Ten GWAS were found to be eligible for inclusion in our study. (6) Eleven replication studies conducted in men of African descent and four replication studies in men with FPC/HPC were eligible for inclusion in our review. Table 1 shows the replication studies in men of African descent. Out of approximately 30 PCA susceptibility variants identified from GWAS, nineteen SNPs (63%) were found to be statistically significantly associated with PCa in men of African descent, nine of these SNPs (14% of PCa-associated SNPs from GWAS) mapping to the 8q24 chromosomal region. The replication studies that have demonstrated statistically significant associations between several SNPs on 8q24 and PCa risk in men of African descent include rs16901979, rs10086908, rs13254738, rs6983561, rs7000448, rs6983267, rs1447295, rs10090154, and rs7017300. In addition, replication studies in men of African descent have found associations with rs2660753 on 3p12, rs10486567 on 7p15.2, rs10993994 on 10q11.2 near the *MSMB* gene, rs7931342 and rs10896449 on 11q13, rs4430796 on 17q12, rs1859962 on 17q24.3, rs2735839 on 19q13.33 between the *KLK2* and *KLK3* genes and rs5945572 and

rs5945619 on Xp11.22. All 8q24 SNPs were replicated at statistical significance in more than one study, with the exceptions of rs10090154 and rs7017300.

Figure 1 presents regions 1 to 3 of the 8q24 locus and the linkage disequilibrium (LD) patterns. The map was based on D-prime using genotype data from the HapMap ASW population of African-Americans in the southwest United States. The positions of the replicated SNPs in the 8q24 region are noted in Figure 1. As can be seen, all nine of the replicated SNPs in men of African descent fall within or near Region 2 and Region 3 on 8q24.

Four replication studies conducted in FPC/HPC cases were eligible for inclusion in our review [Table 2]. A total of ten SNPs (33% of PCa-associated SNPs from GWAS) were associated with PCa in men with FPC/HPC. Replicated SNPS on 8q24 include rs1447295, rs4242382, rs6983561, rs6983267, rs7017300, rs7837688, rs10090154 and rs16901979. Further, rs5945572 and rs5945619 on Xp.11 have also been replicated in FPC/HPC. Figure 2 presents a forest plot comparison of the effect sizes as measured by odds ratios of SNPs at 8q24 replicated among FPC/HPC cases. For SNPs replicated in both men of African descent and FPC/HPC cases the effect sizes are larger among FPC/HPC studies, particularly for rs6983561, rs7017300, and rs10090154 .

DISCUSSION:

To date, GWAS have identified over 30 potential PCa susceptibility variants primarily in the 8q24 chromosomal region as well as on chromosomes 3, 7, 17, 22, and X.(6, 35) This review presents SNPs which were originally identified in GWAS conducted primarily in populations of European descent and in sporadic PCa cases and subsequently replicated in populations at higher risk for developing PCa, including men of African descent and cases of FPC/HPC. We

chose to focus on replicated SNPs in high-risk men as these men stand to gain a greater benefit by further validation of these replicated SNPs to assess the magnitude of risk for PCa and elucidating the function and clinical utility of replicated SNPs to inform future decision-making for PCa early detection and prevention. This review finds a promising rate of replication of GWAS SNPs particularly in men of African descent, and modest replication in men with FPC/HPC. Indeed, 63% of GWAS SNPs had replicated associations to PCa in men of African descent and 33% of the GWAS SNPs had associations to PCa in men with FPC/HPC. A recent meta-analysis of replicated SNPs from GWAS also identified 31 SNPs to have significant associations to PCa. (36) A subgroup analysis from this study revealed four SNPs to have significant associations to PCa among men of African descent (rs10486567, rs5945572, rs5945619, and rs7931342). Of note, our review also found these SNPs to have significant associations to PCa among men of African descent in 1-3 replication studies. Our review identifies several other SNPs with replicated associations to PCa in men of African descent that deserve further study for causal gene/variant identification and potential clinical utility in PCa risk assessment. Furthermore, our review is the first with an additional focus on replicated SNPs in men with FPC/HPC, which also deserve study among men of African descent as a positive family history of PCa significantly increases the risk for this disease. (37)

The rapid increase in GWAS has led to the identification of many loci which are potentially associated with disease. Replication studies are crucial to confirm associations with disease and drive next steps in elucidating disease mechanisms. Replication of associations to disease are needed to exclude potential false positive results from initial GWAS, assess application in diverse ethnic populations, and assess associations with heterogeneity in disease phenotypes, particularly for complex diseases such as PCa. (38) Ultimately, the functional consequence of these replicated variants needs to be identified in order to accurately incorporate genetic markers into clinical decision-making.

The majority of SNPs with replicated associations to PCa in men of African descent and men with FPC/HPC are in the 8q24 region. These results are further supported by whole genome admixture mapping performed in African-American men with PCa which found a 3.8Mb interval on chromosome 8q24 to be significantly associated with PCa risk with a LOD score of 7.1.(39) The 8q24 variants presented here are primarily located within this interval. The 8q24 chromosomal region is the most common region implicated in PCa susceptibility and is relatively gene-poor. (22) Although no well-annotated genes lie within the regions of 8q24, the independent associated variants may be regulating the expression patterns of a single gene or multiple genes involved in cancer tumorigenesis and/or progression in various tissue types. The proto-oncogene *MYC* lies downstream of this gene desert, raising the possibility that the associated regions of risk may be involved in long-range regulation of *MYC* expression.(40) One study evaluated the association between germline risk variants at 8q24 and transcript levels of multiple genes, focusing on the proto-oncogene, *MYC*. No evidence was found for changes in *MYC* expression levels in prostate tumor based on carrying 8q24 germline risk variants.(41) Somatic genetic studies have found the 8q24 region to be amplified in prostate tumors, which fosters continued interest in elucidating the biologic mechanisms of the 8q24 region in PCa risk.(42)

In populations with weaker LD structures, the likelihood of finding an association between disease trait and a causal variant is increased. LD occurs in smaller blocks in individuals of African descent as compared to individuals of European descent.(43) Examination of a 92-kb LD block in chromosome 8q24 in the Nigerian (YRI) Hapmap sample revealed both greater genetic diversity and weaker LD in the YRI sample than in populations of European ancestry.(24) Greater genetic diversity in African populations could make it potentially easier to uncover the yet unknown functional PCa risk variants located on chromosome 8q24 or

associated with the 8q24 region. For example, among a population of individuals of African descent in the Southwest United States (HapMap ASW), rs16901979 was found to be in high LD with rs1551512, a SNP which was found to be associated with PCa aggressiveness in a predominantly European population.(44) Interestingly, the magnitude of association to PCa was greater for a few 8q24 SNPs in men of FPC/HPC than for African American men in this review. This observation deserves further formal study and may have impact on clinical risk management based upon future study findings.

The functional significance of several other replicated variants outside of the 8q24 region is not fully understood, though research is ongoing to gain insights to causality to PCa. Rs10486567 was found to be associated with biochemical recurrence and with castrate resistant metastases in men of Ashkenazi Jewish descent. (45) Rs10486567 is located in *JAZF1.* The *JAZF1* gene appears to act as a transcriptional repressor of *NR2C2*, a nuclear orphan receptor which is expressed in PCa tissue.(12) However, there is yet no biological explanation for the functional implications for *JAZF1* or rs10486567 in prostate carcinogenesis. Rs5945619 and rs5945572 in chromosome Xp11.22 are downstream and upstream, respectively, of the *NUDT11* gene. However, the *NUDT11* gene has not been described as having functional significance in PCa. Rs4430796 located in the *HFN1B* gene which is involved in organ development and in the regulation of the expression of multiple genes.(46,47) Marker rs1859962 lies within a strong LD block within 17q24.3, the functional significance of which is unclear.(27) rs2735839 is located between the prostate protease genes, *KLK2* and *KLK3* and also been associated with PCa specific survival.(45) Both rs7931342 and rs10896449 at 11q13 are located in a gene poor region. Rs10896449 has been found to be significantly associated with PCa risk in a GWAS, confirmed in a study of four primarily Caucasian populations. (12, 48) rs10993994 is located near *MSMB* (beta-microseminoprotein) which encodes a product (PSP94) which at lower levels is associated with more aggressive PCa.(49) Recently, rs10993994 has also been reported to

be associated with PCa recurrence and metastasis.(50) Dedicated approaches with newer technologies, including fine-mapping and next generation sequencing, hold promise for honing in on causal genetic variants in loci identified by GWAS/replicated SNPs or identify genetic/epigenetic mechanisms contributing to the development of PCa.

This review focused on SNPs originally found to be associated with PCa from GWAS and then replicated in men at increased risk for PCa. Additional markers have been reported to be associated with PCa at 8q24 particularly in men of African descent that were not originally identified in GWAS based in European populations. These include rs7008482 (11,14,16), rs4871005 (11,14), rs6981122 (11,14), and bd11934905 (21,26,51). These markers also hold promise for further study of clinical utility in PCa risk assessment. In addition, a recent GWAS conducted in an African American population revealed SNP rs7210100 on chromosome 17q21 to be significantly associated with PCa (OR=1.51, $p=3.4x10^{-13}$). (8) This marker is located in intron 1 of *ZNF652* which encodes a zinc-finger protein transcription factor that interacts with co-repressor proteins and HDACs. (52) However, the function of this variant or link to a causal variant for PCa susceptibility remains to be determined.

In summary, we find a promising rate of replication of PCa-associated SNPs from GWAS in men of African descent and men with familial or hereditary PCa. Although the biologic mechanisms and potentially causal variants have yet to be fully defined, the consistent associations of the SNPs in this review provide greater support for validation studies of these replicated variants in high-risk men, give potential for identifying novel PCa-related genes, and support efforts to elucidate the functional consequence of these variants. Ultimately, the study of the clinical utility of these markers for PCa screening and prevention among high-risk men is warranted.

Abbreviations/Acronyms:
PCa – Prostate Cancer
GWAS – Genome-wide association study
FPC – Familial Prostate Cancer
HPC – Hereditary Prostate Cancer
SNP – Single Nucleotide Polymorphism
IA – Individual Ancestry
AIM – Ancestry Informative Markers
NCBI – National Center for Biotechnology Information

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Summary of prostate cancer associated SNPs discovered in genome-wide association studies and replicated in high-risk populations: Men of African descent and Hereditary/Familial prostate cancer

Table 1: SNPs replicated in studies of prostate cancer in men of African descent

Gene	rs number	Position*	Implicated in GWAS	Study Design	Disease Phenotype	Risk Allele	Association Test OR (95%CI)	P value	Reference	Correction for ancestry
3p12	rs2660753	87,193,364	Eeles et al., 2008(10)	Case-control (868 cases and 878 controls)	Sporadic PCa	T	OR(T allele) =1.17 (1.02-1.35)	0.029	Xu, J.et al., 2009(11)	Model adjusted for age, ancestry proportion, study population
7p15.2 (JAZF1)	rs10486567	27,943,088	Thomas et al., 2008(12)	Nested case-control (860 cases and 575 controls)	Sporadic PCa	G	OR(G allele) =1.18 (1.00-1.40)	------	Waters, K.M. et al, 2009(13)	Models adjusted for age and proportion of European ancestry
				Multicenter sample (2899 cases and 2538 controls)	Sporadic PCa	C	OR(C allele) =1.18 (1.08-1.29)	0.0002	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
8q24	rs16901979	128,194,098	Gudmundsson et al., 2007(15)	Case-Control (868 cases and 878 controls)	Sporadic PCa	A	OR(A allele) =1.38 (1.19-1.60)	1.7E-05	Xu, J. et al., 2009(11)	Model adjusted for age, ancestry proportion, study population

				Multicenter sample (2642 cases and 2584 controls)	Sporadic PCa	A	OR(A allele)= 1.39 (1.28-1.52)	1.9 E-14	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
				Hospital based case-control (490 cases and 567 controls)	Sporadic PCa	A	OR (A allele)=1.5 (1.1-2.2)	0.008	Robbins et al., 2007(16)	Model adjusted for age, global and local 8q24 ancestry
				Community based case-control (127 cases and 345 controls)	Sporadic PCa	A	OR (A allele) =1.60 (1.17-2.19)	0.003	Wang, Y et al., 2010(17)	None†
				Case-control (338 cases. 426 controls)	Sporadic PCa	A	OR (A allele) = 1.41 (1.02-1.95)	0.03	Okobia, M.N. et al, 2011 (18)	None
				Case-Control (156 cases, 231 controls)	Early-Onset PCa (diagnosed ≤65 y.o.)	A	OR (A allele) = 2.30 (1.40-3.77)	0.001	Okobia, M.N. et al., 2011 (18)	None
	rs10086908	128,081,119	Al Olama et al., 2009 (19)	Case-Control (868 cases and 878 controls)	Sporadic PCa	T	OR (T allele) =1.31 (1.11-1.55)	1.1E-03	Xu, J. et al., 2009(11)	Model adjusted for age, ancestry proportion, study population
				Multicenter sample (861 cases and	Sporadic PCa	T	OR (T allele) =1.31 (1.11-1.54)	0.001	Chang, B.L. et al, 2011(14)	Model adjusted for age and

				876 controls)						study center
	rs13254738	128,173,525	Ghoussaini et al., 2008(20)	Case-Control (868 cases and 878 controls)	Sporadic PCa	C	OR (C allele) =1.36 (1.17-1.58)	4.9E-05	Xu, J. et al., 2009(11)	Model adjusted for age, ancestry proportion, study population
				Multicenter sample (2557 cases and 2277 controls)	Sporadic PCa	C	OR (C allele) =1.29 (1.18-1.41)	1.03 x 10-8	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
				Nested case control (1,614 cases, 837 controls	Sporadic PCa	C	OR (C allele) =1.24 (1.09-1.42)	------	Haiman,C. A. et al., 2007(21)	Model adjusted for genome-wide European ancestry and study
	rs6983561	128,176,062	Al Olama et al., 2009(19)	Case-Control (868 cases and 878 controls)	Sporadic PCa	C	OR (C allele) =1.31 (1.13-1.52)	2.8E-04	Xu, J. et al., 2009(11)	Model adjusted for age, ancestry proportion, study population
				Multicenter sample (2764 cases and 3255	Sporadic PCa	C	OR (C allele) =1.37 (1.27-1.49)	3.5 E-15	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center

				controls)						
				Community based case-control (127 cases and 345 controls)	Sporadic PCa	C	OR (C allele) =1.55 (1.15-2.09)	0.0039	Wang, Y et al., 2010(17)	None†
				Nested Case Control (1,614 cases and 837 controls	Sporadic PCa	C	OR (C allele) =1.34 (1.18-1.53)	---------	Haiman, C.A. et al., 2007(21)	Model adjusted for genome-wide European ancestry and study
	rs7000448	128,510,352	Ghoussaini et al., 2008(20)	Case-Control (868 cases and 878 controls)	Sporadic PCa	T	OR (T allele) =1.20 (1.03-1.40)	0.016	Xu, J. et al., 2009(11)	Model adjusted for age, ancestry proportion, study population
				Multicenter sample (1698 cases and 2329 controls)	Sporadic PCa	T	OR (T allele) =1.27(1.15-1.41)	3.0 E-6	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
				Community based case-control (127 cases and 345 controls)	Sporadic PCA	T	OR (T allele) = 1.41 (1.03-1.94)	0.03	Wang, Y. et al., 2010(17)	None†
				Nested case control (1,614 cases	Sporadic PCa	C	OR (C allele) =1.33 (1.12-1.58)	------	Haiman, C.A. et al., 2007(21)	Model adjusted for genome-

				and 837 controls						wide European ancestry and study
	rs6983267	128,482,487	Yeager et al., 2007(22); Thomas et al., 2008(12)	Multicenter sample (3666 cases and 2992 controls)	Sporadic PCa	G	OR (G allele) =1.32 (1.18-1.49)	3.3 E-6	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
				Population based case study (417 cases and 925 Illumina controls)	Sporadic PCa	T	OR (T allele) =0.6 (0.4-0.7)	1.3 E-4	Xu, Z. et al., 2010 (23)	Model adjusted for proportion of W. African ancestry
				Nested case control (1,614 cases and 837 controls	Sporadic PCa	G	1.43 (1.17-1.75)	---------	Haiman, C.A. et al., 2007(21)	Model adjusted for genome-wide European ancestry and study
	rs1447295	128,554,220	Amundadottir et al., 2006 (24)	Multicenter sample (3167 cases and 3325 controls)	Sporadic PCa	A	OR (A allele) =1.11(1.02-1.21)	0.014	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
				Case-control (171 cases and 256 cases)	Sporadic PCa; men diagnosed ≤65 y.o.	A	OR AA genotype = 2.63 (1.14-6.05)	--------	Schumacher, F.R. et al., 2007(25)	None

	rs10090154	128,601,319	Al Olama et al., 2009(19)	Multicenter Sample (1683 cases and 1403 controls)	Sporadic PCa	T	1.20 (1.04-1.37)	0.011	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
	rs7017300	128,594,450	Eeles et al., 2008(10)	Population based case study (417 cases and 925 Illumina controls)	Sporadic PCa	C	OR (C allele) =1.2 (1.0-1.5)	0.03	Xu, Z. et al, 2010(23)	Model adjusted for proportion of W. African ancestry
10q11.2 MSMB	rs10993994	51,219,502	Eeles et al., 2008(10)	Multicenter sample (3374 cases and 2982 controls)	Sporadic PCa	T	OR (T allele) = 1.12 (1.03-1.21)	0.005	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
11q13	rs7931342	68,751,073	Eeles et al., 2008(10)	Multicenter sample (2445 cases and 2018 controls)	Sporadic PCa	G	OR (G allele) = 1.15 (1.03-1.29)	0.014	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
	rs10896449	68,751,243	Thomas et al., 2008(12)	Multicenter sample (2056 cases and 1898 controls)	Sporadic PCa	G	OR (G allele) = 1.12 (1.01-1.24)	0.031	Chang, B.L. et al, 2011(14)	Model adjusted for age and study center
				Hospital based case-control (454 cases and 301 controls)	Sporadic PCa	A	OR (A allele) =0.7 (0.54-0.93)	0.009	Hooker S. et al, 2010(26)	Model adjusted for individual ancestry (IA) estimates from 100

										AIMs; same SNP not asoc with aggressive disease
17q12 (HNF1B)	rs4430796	33,172,153	Gudmundsson et al., 2007 (27)	Hospital based case-control study (364 cases and 353 controls)	Sporadic PCa	T	OR (T allele) = 1.26 (1.01-1.56)	0.04	Sun, J. et al., 2008(28)	None‡
				Multicenter sample (3112 cases and 2911 controls)	Sporadic PCa	T	OR (T allele) = 1.08 (1.00-1.18)	0.053	Chang B.L. et al., 2011 (14)	Model adjusted for age and study center
				Hospital based case-control (454 cases and 301 controls)	Sporadic PCa	A	OR (A allele)=1.48 (1.11-1.96)	0.008	Hooker S. et al., 2010(26)	IA estimates from 100 AIMs; same SNP not asoc with aggressive disease
				Case-Control (868 cases and 878 controls)	Sporadic PCa	T	OR (T allele) =1.16 (1.00-1.34)	0.056	Xu, J. et al., 2009(11)	Model adjusted for age, ancestry proportion, study population
17q21 (ZNF652)	rs7210100	44,791,748	Haiman et al. 2011 (8)	Original GWAS in AA men			OR (per allele) = 1.51	3.4×10^{-13}	--	Adjusted for age and

										ancestry
17q24.3	rs1859962	66,620,348	Eeles et al., 2008(10)	Population based case study (417 cases and 925 Illumina controls)	Sporadic PCa	G	OR (G Allele) =1.2 (1.0-1.5)	0.033	Xu, Z. et al, 2010(23)	Model adjusted for proportion of W. African ancestry
19q13.33 (KLK2 & KLK3)	rs2735839	56,056,435	Eeles et al., 2008(10)	Hospital based case-control (454 cases and 301 controls)	Sporadic PCa	A	OR (A allele) = 0.78 (0.60-1.00)	0.04	Hooker S. et al., 2010(26)	Model adjusted for IA estimates from 100 AIMs; same SNP not asoc with aggressive disease
Xp11.22 (NUDT10/11)	rs5945572	51,246,423	Gudmundsson et al., 2008(29)	Nested case-control (860 cases and 575 controls)	Sporadic PCa	A	OR (A allele) =1.34 (1.05-1.71)	------	Waters, K.M. et al., 2009(13)	Models adjusted for age and proportion of European ancestry
				Hospital based case-control (454 cases and 301 controls)	Sporadic PCa	A	1.48 (1.01-2.16)	0.05	Hooker et al, 2010(26)	Model adjusted for IA estimates from 100 AIMs; same SNP not asoc with aggressive disease
				Multicenter sample	Sporadic PCa	A	OR (A allele) = 1.11 (1.02-	0.02	Chang et al.,	Model adjusted for

				(1764 cases and 1235 controls)			1.20)		2011(14)	age and study center
	rs5945619	51,258,412	Eeles et al., 2008(10)	Multicenter sample (1390 cases and 1845 controls)	Sporadic PCa	G	OR (G allele) = 1.09 (1.00-1.18)	0.039	Chang et al., 2011(14)	Model adjusted for age and study center

*Position based on NCBI Build 36
† Study reports similar results found when adjusted for age, proportion of African ancestry
‡ Study reports similar results found when models adjusted for proportion of African ancestry

Table 2: SNPs replicated in familial /hereditary prostate cancer (FPC/HPC)

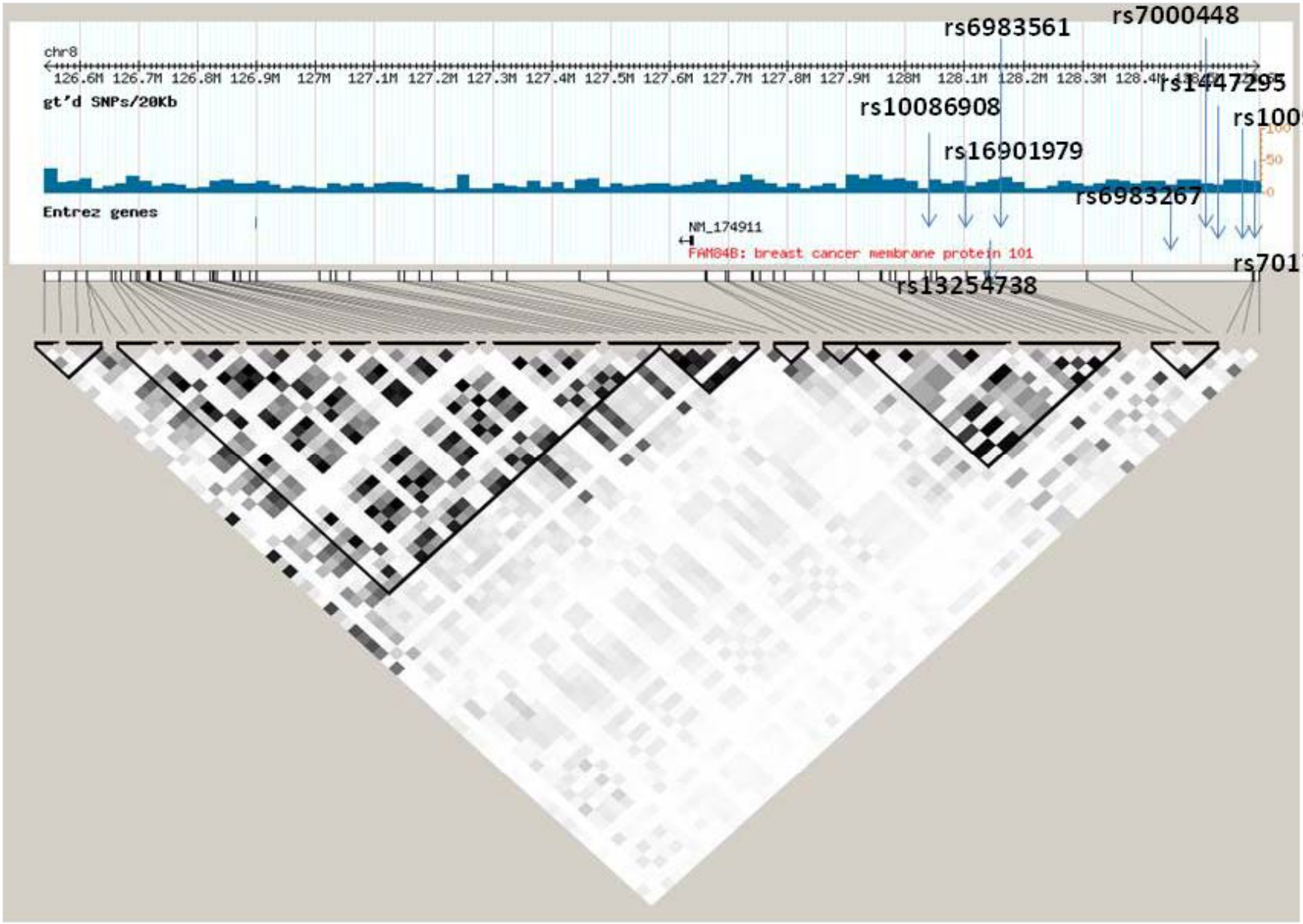
Gene	rs number	Position*	Implicated in GWAS	Study Design	Disease Phenotype	Risk Allele	Association Test OR (95% CI)	P value	Ref	Model Description
Xp11	rs5945572	51,246,423	Gudmundsson et al., 2008(29) Eeles et al., 2008(10)	168 HPC Families	HPC (≥2 1stdegree affected family members)	A	------	0.009	Lu et al., 2009(30)	P value reported for overtransmission from parents to affected offspring
	rs5945619	51,258,412	Eeles et al., 2008(10)	168 HPC Families	HPC (≥2 1stdegree affected family members)	C	-------	0.03	Lu et al., 2009(30)	P value reported for overtransmission from parents to affected offspring
8q24	rs1447295	128,554,220	Amundadottir et al., 2006(24)	Case-Control (435 FPC cases, 545 population based controls)	FPC (Families have ≥3 affected family members)	A	OR (A allele) =1.93 (1.37-2.72)	0.0004	Wang, L. et al., 2007(31)	None, similar results when adjusted for age
				Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	A	$OR_{hom/het}$ = 2.25 (1.52-3.32)	$4.8x10^{-5}$	Sun J. et al., 2008(32)	Model adjusted for age

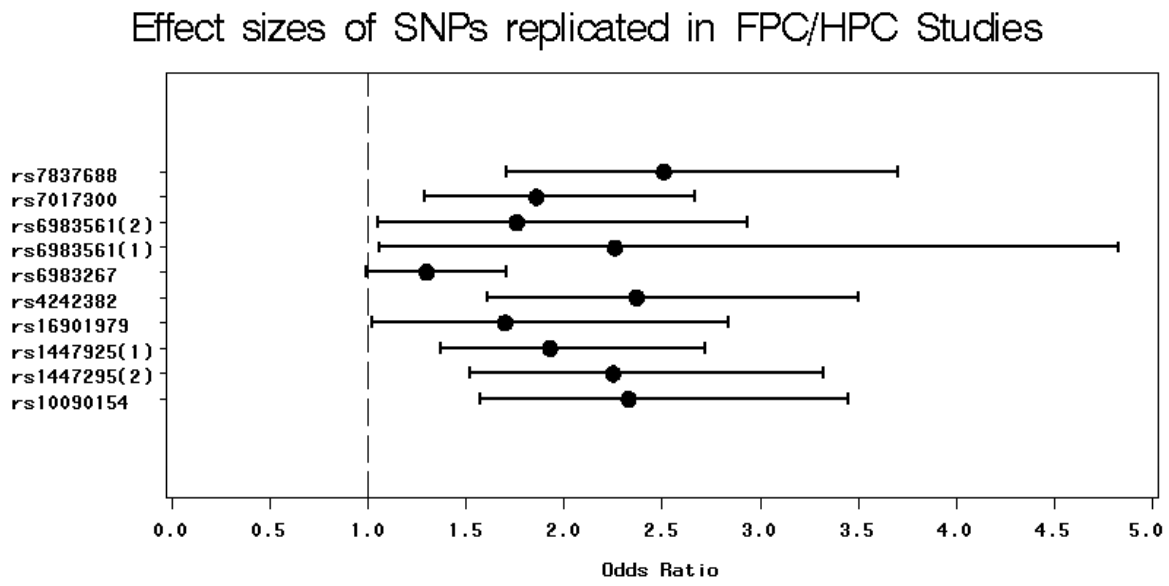
	rs4242382	128,586,755	Thomas et al., 2008(12)	Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	A	$OR_{hom/het}$ = 2.37 (1.61-3.50)	$1.39x10^{-5}$	Sun, J. et al., 2008(32)	Model adjusted for age
	rs6983561	128,176,062	Al Olama et al., 2009(19)	Case control (542 affected men and 473 of their unaffected brothers)	FPC (Men diagnosed with PCa with ≥1 1st or 2nd degree living affected family member	C	OR (C allele) =2.26 (1.06-4.83)	0.03	Beebe-Dimmer, J.L. et al., 2008(33)	None
				Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	C	$OR_{hom/het}$ = 1.76 (1.05-2.94)	0.03	Sun, J. et al., 2008(32)	Model adjusted for age
	rs6983267	128,482,487	Yeager et al., 2007(22); Thomas et al., 2008(12)	Case control (542 affected men and 473 of their unaffected brothers)	FPC (Men diagnosed with PCa with ≥1 1st or 2nd degree living affected family member	G	OR (G allele)=1.30 (0.99-1.71)	0.04	Beebe-Dimmer, J.L. et al., 2008(33)	None

	rs7017300	128,594,450	Eeles et al., 2008(10)	Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	C	$OR_{hom/het}$ = 1.86 (1.29-2.67)	$8.0x10^{-4}$	Sun, J. et al., 2008(32)	Model adjusted for age
	rs7837688	128,608,542	Takata et al., 2010(34)	Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	T	$OR_{hom/het}$ = 2.51 (1.71-3.70)	$3.2x10^{-6}$	Sun, J. et al., 2008(32)	Model adjusted for age
	rs10090154	128,601,319	Al Olama et al., 2009(19)	Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	T	$OR_{hom/het}$ = 2.33 (1.57-3.45)	$2.4x10^{-5}$	Sun, J. et al., 2008(32)	Model adjusted for age
	rs16901979	128,194,098	Gudmundsson et al., 2007(15)	Hospital-based case-control study (221 HPC Cases and 560 controls)	HPC (≥2 first degree affected family members)	A	$OR_{hom/het}$ = 1.70 (1.02-2.84)	0.04	Sun,J. et al., 2008(32)	Model adjusted for age

*Position based on NCBI Build 36

Figure 1: Map of linkage disequilibrium structure in the HapMap population of African-Americans in the Southwest United States (ASW) of chromosome 8q24 regions 1 Region 1 (126.54 - 128.62 Mb), Region 2: (128.14 - 128.28) and Region 3 (128.47 - 128.54)





Note: 8q24 SNPs replicated in FPC/HPC in more than one study
rs1447295(1) – Wang et al., 2007
rs1447295(2)- Sun et al., 2008
rs6983561(1)- Beebe-Dimmer et al., 2008
rs6983561(2)- Sun et al., 2008

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

A systematic review of replication studies of prostate cancer susceptibility genetic variants in high-risk men originally identified from genome-wide association studies

Miriam B Ishak and Veda N Giri

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