A genome-wide association study of prostate cancer in West African men

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Abstract

Background—Age-adjusted mortality rates for prostate cancer are higher for African American men compared with those of European ancestry. Recent data suggest that West African men also have elevated risk for prostate cancer relative to European men. Genetic susceptibility to prostate cancer could account for part of this difference.

Methods—We conducted a genome-wide association study (GWAS) of prostate cancer in West African men in the Ghana Prostate Study. Association testing was performed using multivariable logistic regression adjusted for age and genetic ancestry for 474 prostate cancer cases and 458 population-based controls on the Illumina HumanOmni-5 Quad BeadChip.

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Results—The most promising association was at 10p14 within an intron of a long non-coding RNA (lncRNA RP11-543F8.2) 360 kb centromeric of *GATA3* (p=1.29E−7). In sub-analyses, SNPs at 5q31.3 were associated with high Gleason score (7) cancers, the strongest of which was a missense SNP in *PCDHA1* (rs34575154, p=3.66E−8), and SNPs at Xq28 (rs985081, p=8.66E −9) and 6q21 (rs2185710, p=5.95E−8) were associated with low Gleason score (<7) cancers. We sought to validate our findings *in silico* in the African Ancestry Prostate Cancer GWAS Consortium, but only one SNP, at 10p14, replicated at p<0.05. Of the 90 prostate cancer loci reported from studies of men of European, Asian or African American ancestry, we were able to test 81 in the Ghana Prostate Study, and 10 of these replicated at p<0.05.

Conclusion—Further genetic studies of prostate cancer in West African men are needed to confirm our promising susceptibility loci.

Keywords

prostate cancer; Africa; GWAS; case-control

Introduction

In the United States, age-adjusted incidence rates of prostate cancer in African-Americans are two-fold higher than those observed in men of European ancestry (Li et al. 2012). Although age-adjusted estimates of prostate cancer from African cancer registries suggest lower rates for African men (Center et al. 2012; Chu et al. 2011), international comparisons are complicated by population screening, overdiagnosis (Welch and Black 2010), and incomplete cancer registration (Parkin et al. 2010). Despite their challenges, mortality statistics (Ferlay et al. 2010) can provide a stable and robust cancer statistic (Welch and Black 2010), particularly for international comparisons. Age-adjusted mortality rates of prostate cancer show a pattern distinct from that of incidence (Center et al. 2012; Rebbeck et al. 2013), with equal or higher rates in Africa—and specifically, the West African region— compared with North America or Western Europe. Since West Africa is the principal ancestral origin of a substantial proportion of African-American men (Bryc et al. 2010; Torres et al. 2012), one may hypothesize that genetic susceptibility loci that vary in allele frequency by ancestral population could account for part of the observed differences in prostate cancer rates within the United States (US).

Recent genome-wide association studies (GWAS) have shown that genetic variants associated with prostate cancer—such as those at 8q24 (Amundadottir et al. 2006; Freedman et al. 2006; Haiman et al. 2007) and 17q21 (Haiman et al. 2011b)—are more common among African Americans compared with men of European ancestry. Whether the differences in susceptibility allele frequencies can partially explain differences in incidence across regions can best be answered by discovery of a larger fraction of the set of common variants associated with risk. To date, approximately 90 independent prostate cancer loci have been identified through GWAS, primarily in men of European background. Based on empiric analyses of existing data sets, it is estimated that these loci represent perhaps less than the total number of common variants, which could be even higher in men of African ancestry (Park et al. 2010). To investigate genetic susceptibility to prostate cancer in West

Africa, we conducted a GWAS in the Ghana Prostate Study, a collaboration involving the US National Cancer Institute (NCI) and the University of Ghana.

Methods

Study Participants

Participants for analysis were recruited through the Ghana Prostate Study—a population-based component, and a clinical component. The population-based component was a probability sample designed using the 2000 Ghana Population and Housing Census data in an attempt to recruit approximately 1,000 men aged 50–74 years in the Greater Accra region (~3 million people) (Chokkalingam et al. 2012), which successfully recruited 1,037 healthy men between 2004 and 2006 with a response percentage of 98.8% (Chokkalingam et al. 2012). Consented individuals underwent an in-person interview, and within seven days had a digital rectal examination (DRE) and provided an over-night fasting blood sample for prostate specific antigen (PSA) testing, biomarker assays, and genetic analysis. Subjects who had a positive screen by PSA (>2.5 ng/ml) or DRE underwent a transrectal ultrasound-guided biopsy. A total of 73 histologically-confirmed prostate cancer cases were identified through the population-based screening component of the Ghana Prostate Study and are included in the case population analyzed herein. From the remaining 964 screen-negative individuals, 836 had at least 20 ug DNA extracted and available for analysis, and 500 of these were matched to cases for analysis by age (in 5 year categories).

In the Ghana Prostate Study, we recruited 676 prostate cancer cases at Korle Bu Teaching Hospital in Accra, Ghana between 2008 and 2012. All consented cases were interviewed and provided an overnight fasting blood sample. At the time of selection for this analysis we had recruited 582 prostate cancer cases, from which we selected 427 for analysis. Combined with the 73 cases diagnosed through the population-based component of the study, this yielded 500 available prostate cancer cases for analysis. Five technical replicates for each of three individuals served as quality control (QC) samples.

This Ghana Prostate Study was approved by institutional review boards in Ghana and at the National Cancer Institute.

Genotyping and Quality Control

DNA samples for this project were extracted from buffy coat samples using the Qiagen method according to the manufacturer's instructions. Pre-genotyping quality control metrics excluded six case samples and two controls. 494 prostate cancer cases, 498 screen-negative controls, plus 15 distinct quality control samples were genotyped on the Illumina HumanOmni5-Quad BeadChip (Clarke et al. 2012).

The initial overall completion rate of genotype calls was 97.38%. After excluding 57,489 loci with no genotype call, the overall completion rate increased to 98.70%. A total of 70,872 loci were excluded due to low completion rates (<90%) and 1,393,418 single nucleotide polymorphisms (SNP) monomorphic in men from Ghana were further excluded. We advanced 2,837,019 SNPs for association analysis. For the quality control samples, which included three distinct samples each with five technical replicates, the concordance

rate exceeded 99.99%. Twenty-seven (7 cases, 20 controls) samples were excluded due to low completion rate (lower than 94%) or extreme mean heterozygosity (lower than 13.5% or greater than 16.5%). A further five cases were excluded for having less than 80% African ancestry using the HapMap build 26 data (CEU, JPT+CHB, YRI) as the continental reference populations in a STRUCTURE analysis (Engelhardt and Stephens 2010). Principal components analysis (PCA) identified 16 individuals (five cases, 11 controls) with significant deviation of eigenvectors and thus, they were excluded (Reich et al. 2008). Finally, unexpected relatedness (1st–2nd degree), assessed using the GLU qc.ibds module (http://code.google.com/p/glu-genetics/) with an IBD0 threshold of 0.70, was detected for 11 pairs of full-sibling and one monozygotic twin; one individual randomly chosen from each related group was retained while two cases and nine controls were excluded. Note that one nuclear family involved three individuals and accounted for three related pairs, so, a total of 11 individuals were removed. In addition, one case sample was excluded due to incomplete phenotype with missing age. The final analytic data set included 474 prostate cancer cases and 458 screen-negative controls.

Statistical Analysis

Association tests for prostate cancer susceptibility were performed using multivariable unconditional logistic regression analyses (1 degree-of-freedom) adjusted for age and two eigenvectors (p<0.01 based on the null model) identified in PCA analysis. In addition, we stratified the analysis by Gleason score (6, 7). Follow-up analyses were conducted in the African Ancestry Prostate Cancer GWAS Consortium using a total 5,096 cases and 4,972 controls (Haiman et al. 2011a; Haiman et al. 2011b). Additional resources used for the analyses were dbSNP (Sherry et al. 2001), 1000 Genomes Project (Clarke et al. 2012), GENCODE (Harrow et al. 2012), HaploReg (Ward and Kellis 2012), RegulomeDB (Boyle et al. 2012), and Haploview 4.2 (Barrett et al. 2005).

Results

The results of the scan are shown in Table 1, which displays the 30 most promising SNPs associated with prostate cancer in the Ghana Prostate Study. Notable is a new locus marked by rs7918885 at 10p14 for prostate cancer risk (p value of 1.29E−7). Figure 1 depicts the eight correlated markers typed as part of our study, which are approximately 360 kb 5' of *GATA3*; notably they localize to an intronic region of lncRNA gene *RP11-543F8.2*. Assessment of the correlated variants in 1000 Genomes Project data, restricted to the West African populations, did not reveal notable variants in the coding or splicing regions of the lncRNA *RP11-543F8.2* (Supplementary Figure 1). Bioinformatic analyses of the eight correlated SNPs using the ENCODE resources point towards motif changes, DNase I hypersensitivity sites, and NHEK enhancer histone marks, but there was no overall significant enrichment for such elements (2012). Visual inspection of a quantile-quantile plot of the observed versus expected p values (Supplementary Figure 2), as well as the inflation factor of 1.01, indicated an absence of any systemic bias (e.g., residual population stratification). The results of the initial scan also suggested promising signals at 5q31.3, 3p26.1, and 8p23.2. Twenty-nine of our top 30 SNPs were analyzed in the African Ancestry Prostate Cancer GWAS Consortium; 12 SNPs were directly typed and 17 SNPs imputed

using 1000 Genomes Project data (Clarke et al. 2012) (Supplementary Table 1). Only one of the 29 tested SNPs were statistically significant (p < 0.05) in the African American dataset, and that was rs2993385 located at 10p14.

Results from a sub-analysis, stratified by Gleason score (<7, 136 cases; 7, 317 cases), are shown in Table 2. In the Gleason score 7 stratum, the 5q31.3 locus reached genome-wide statistical significance (5E−8) with the lowest p value being 3.66E−8 for rs34575154, a missense SNP in *PCDHA1*. In addition, SNPs at 22q13.31, 7q31.31 and 2q14.2 had p values less than E−7. In the Gleason score <7 stratum, seven loci were observed to have p values less than E−7, and two SNPs were below genome-wide statistical significance: rs985081 at Xq28 (p=8.66E−9) and rs2185710 at 6q21 (p=5.95E−8). We analyzed these SNPs stratified by Gleason score in the African Ancestry Prostate Cancer GWAS Consortium yet none of them replicated at p<0.05, although there was evidence for between-study heterogeneity of effect for several of these SNPs within the African American data (Haiman et al. 2011a; Haiman et al. 2011b).

Lastly, in our prostate cancer GWAS of African men we were able to assess 81 of the previously reported 90 prostate cancer susceptibility loci (Table 3), and observed that 10 of these SNPs were statistically significant (p<0.05), including SNPs within "Region 1" (rs7017300, rs10090154) and "Region 2" (rs13254738, rs16901979) of the 8q24 region (Haiman et al. 2007), as well as rs7210100 from the 17q21 region which was initially reported by the African Ancestry Prostate Cancer GWAS Consortium (Haiman et al. 2011b). Other SNPs previously associated with prostate cancer, mostly in populations of European ancestry, did not replicate in our African population.

Discussion

In this GWAS of prostate cancer in West African men, there is evidence for an association between a possible new locus at 10p14 and prostate cancer. In an additional sub-analysis, we observed SNPs at 5q31.3 associated with high Gleason score (7) prostate cancers, and of SNPs at Xq28 and 6q21 in relation to low Gleason score (<7) prostate cancers; however, these observations require further confirmation because of the small sample size reported herein. Because of the noted racial disparities in prostate cancer incidence between men of European and African descent, this unique analysis may provide insight into prostate cancer pathogenesis, particularly for African populations. Lastly, of the 90 prostate cancer loci reported from studies of men of European, Asian or African American ancestry, we were able to test 81 in the Ghana Prostate Study, and 10 of these replicated at p<0.05, differences that may be partly ascribed to distinct genomic architecture (including different patterns of underlying linkage disequilibrium), heterogeneous prostate cancer populations, and uncharacterized gene-environment interactions.

The strongest associated SNP, rs7918885, localizes to 10p14 and is approximately 360 kb 5' of *GATA3* within an intron of the lncRNA gene *RP11-543F8.2*. An assessment of highly correlated SNPs using the 1000 Genomes Project data did not reveal splice or exonic variants of RP11-543F8.2. In the NHGRI catalog of GWAS SNPs, the closest SNP associated with any cancer resides 227kb away (Chung and Chanock 2011; Hindorff et al.

2009). The locus is marked by rs10795668 in a colorectal GWAS but its underlying biology is still unknown (Tomlinson et al. 2008). We also note that there is minimal linkage disequilibrium between that rs10795668 and rs7918885 (r^2=0.001 in scan control set); moreover, there are several recombination-hot spots between the two markers.

Although we detected a promising association between the 10p14 SNPs and prostate cancer in this study of West African men, the highest p value did not quite reach the genome-wide threshold of 5×10^{-8}. It is possible that the signal we have detected at 10p14 is due to chance, but more likely insufficient power to detect a low effect SNP (Donnelly 2008; Kraft and Hunter 2009). We had 64% power to detect rs7918885 under 5E-8 and based on the observed allele frequencies and odds ratio.

We did attempt to replicate the findings presented herein using a large meta-analytic dataset comprised of African Americans—the African Ancestry Prostate Cancer GWAS Consortium—, but only one SNP (rs2993385 at 10p14) replicated at p<0.05. There are three primary, non-mutually exclusive reasons why genetic signals may not be observed in the ancestrally-related, but distinct, African American population. The first reason is that the genomic architecture of African American men is distinct from that of African men. A recent analysis estimated that the African American population has continuously received gene flow from European populations over 14 generations (Jin et al. 2012) that has resulted in the African American population having mean ancestral percentages of 75% West African, 20% European, and 5% Native American (Bryc et al. 2010; Tishkoff et al. 2009; Zakharia et al. 2009). Individuals who self-identify as African American are highly variable in degree of West African admixture (Bryc et al. 2010; Henn et al. 2010; Jin et al. 2012; Tishkoff et al. 2009). There are also large differences in allele frequencies (Adeyemo and Rotimi 2010; Ntzani et al. 2012), private SNPs (Campbell and Tishkoff 2008; Conrad et al. 2006), patterns of homozygosity (Pemberton et al. 2012), and LD structure (Campbell and Tishkoff 2008; Conrad et al. 2006) between African and African American populations. In addition, African ancestry of African Americans is most similar to the non-Bantu Niger-Kordofanian population of West Africa (Bryc et al. 2010; Tishkoff et al. 2009), tribes of which overlap with the geographical location of the Ghana Prostate Study.

The second reason is screening. In the United States the use of DRE and PSA screening has been widespread and has resulted in over-diagnosis (Welch and Black 2010) and a concurrent change in Gleason score distribution. SEER data indicates that, of the black men diagnosed with prostate cancer during 2003–2008, 1% were reported with Gleason 2-4, 48% with Gleason 5-6, and 51% with Gleason 7-10. Respective percentages for the 474 Ghanaian cases in the study were 1%, 29% and 70%. The greater proportion of advanced grades may be expected given that only 70 cases in the final analysis were detected through the population screening component of our study; a majority of the remaining 404 were symptomatic cases who presented at the clinic; the prevalence of PSA screening in Ghana, during the study period, was low (4% vs. >50% in US). Thus the majority of our case population is comprised of symptomatic disease rather than screen-detected cancers, which is especially important for this malignancy given it is expected to develop in 80% of men by age 80 years (Franks 1954; Haas et al. 2008; Sakr et al. 1993).

The third reason could be related to uncharacterized gene-environment interactions (Hemminki et al. 2006; Perez-Losada et al. 2011). In support of a strong environmental component is the fact prostate cancer mortality rates in the US are geographically variable both between and within racial groups [1], yet neither migration patterns (Tolnay 2003) nor genetic diversity (Zakharia et al. 2009) of the African American population can account for such patterns and trends.

Differences in population genetics, environments, and disease spectra can account for differences in observed associations with complex diseases across ancestrally diverse groups (Ioannidis 2007; Ntzani et al. 2012). For example, the African Ancestry Prostate Cancer GWAS Consortium replicated approximately half of the 49 SNPs previously associated and validated in populations of European ancestry (Haiman et al. 2011a). Other studies of European sub-populations (Gaj et al. 2012; Vijai et al. 2011), Asian populations (Liu et al. 2012; Takata et al. 2010) and populations of African descent (Chang et al. 2005; Xu et al. 2011) have reported similar results. Conversely, prostate cancer risk loci discrete to specific non-Caucasian populations have also been described (Akamatsu et al. 2012; Batra et al. 2011; Haiman et al. 2011b; Takata et al. 2010; Wang et al. 2012). In addition, functional studies support the idea that some of these differences by ancestry may have a biological grounding (Grisanzio et al. 2012). In summary, we present evidence for a promising novel prostate cancer locus at 10p14 in a West African population in our initial GWAS. Further studies of prostate cancer in West African men are required for validation of this locus as well as those associated with low or high Gleason score prostate cancers. Further efforts are required to recruit greater numbers of cases in high quality epidemiologic studies to investigate the underlying genetics—and in turn gene-environment interactions—of a complex disease such as prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments


[1]http://www.cdc.gov/features/canceratlas/

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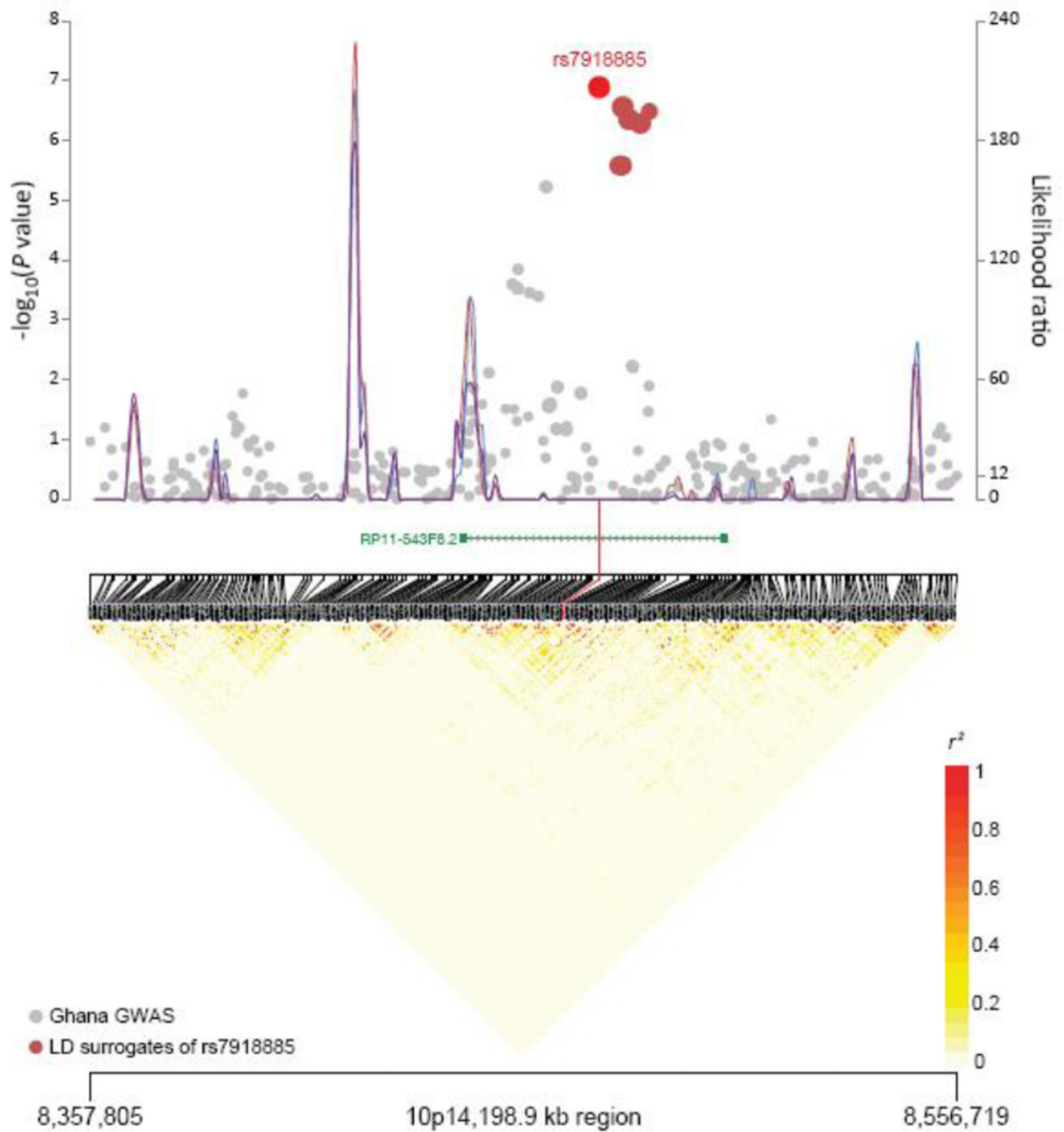
Figure 1. Association results, recombination plot and linkage disequilibrium structure for the 198.9kb region of 10p14

Association results from a trend test in –log10Pvalues (y axis, left) of the SNPs are shown according to their chromosomal positions (x axis). The r2 values were computed from rs7918885 to all of the other plotted SNPs to differentially size data points according to their level of linkage disequilibrium. SNPs that are highly correlated with rs7918885 (n=6) were colored red. Linkage disequilibrium structure based on controls (n=458) was visualized by snp.plotter software. The line graph shows likelihood ratio statistics (y axis, right) for

recombination hotspot by SequenceLDhot software and 3 different colors represent 3 tests of 100 controls without resampling. Physical locations are based on NCBI Build 37 of the human genome. Gene annotation was based on ENCODE/GENCODE version 12 from the UCSC Genome Browser.

Table 1

The 30 most significant SNP associations with prostate cancer in the Ghana Prostate Study GWAS

rs Number	Cytoband	Location[1]	Alleles (referent | effect)	Effect Allele Frequency (control | case)	Per Effect Allele OR (95%CI)	P value	In gene(s) or nearest gene(s) if distance specified[2]
rs7918885	10p14	8474595	T | G	0.145 | 0.076	0.40 (0.28, 0.57)	1.29E-07	358kb 5' of GATA3, RP11-543F8.2 (intron)
rs10905371	10p14	8480044	A | G	0.142 | 0.074	0.41 (0.29, 0.58)	2.77E-07	363kb 5' of GATA3, RP11-543F8.2 (intron)
rs7896254	10p14	8486161	G | A	0.100 | 0.044	0.33 (0.21, 0.51)	3.27E-07	369kb 5' of GATA3, RP11-543F8.2 (intron)
rs10905374	10p14	8481486	G | A	0.145 | 0.077	0.42 (0.29, 0.59)	4.43E-07	364kb 5' of GATA3, RP11-543F8.2 (intron)
rs7096374	10p14	8484113	C | T	0.143 | 0.076	0.42 (0.30, 0.59)	5.16E-07	368kb 5' of GATA3, RP11-543F8.2 (intron)
rs61749035	5q31.3	140718750	G | T	0.037 | 0.077	3.22 (2.00, 5.19)	7.50E-07	PCDHGA1 (intron), PCDHGA2 (missense)
rs114246623	3p26.1	6935066	G | A	0.015 | 0.078	4.93 (2.53, 9.59)	7.70E-07	GRM7-AS2 (AC066606.1) (intron)
rs147739031	8p23.2	3247408	A | G	0.005 | 0.039	11.48 (3.78, 34.90)	9.96E-07	CSMD1 (intron)
rs115850745	6p21.32	32655508	A | G	0.371 | 0.265	0.56 (0.44, 0.71)	1.05E-06	19kb 3' of AL662789.1, 21kb 3' of HLA-DQB1
rs10961884	9p22.3	15111573	T | C	0.023 | 0.086	3.96 (2.23, 7.02)	1.11E-06	32kb 5' of U6.1033, 59kb 3' of TTC39B
rs115899206	6p21.2	40084864	A | G	0.015 | 0.052	4.91 (2.49, 9.68)	1.59E-06	154kb 3' of RP11-552E20.1, 183kb 3' of MOCS1
rs12477565	2q14.2	121081260	G | T	0.420 | 0.514	1.68 (1.35, 2.08)	2.25E-06	AC012363.13 (intron), 22kb 5' of INHBB
rs12251624	10p14	8479257	T | C	0.159 | 0.091	0.46 (0.33, 0.64)	2.62E-06	362kb 5' of GATA3, RP11-543F8.2 (intron)
rs7090925	10p14	8479868	A | G	0.159 | 0.091	0.46 (0.33, 0.64)	2.62E-06	363kb 5' of GATA3, RP11-543F8.2 (intron)
rs17097185	5q31.3	140711097	C | G	0.039 | 0.077	3.02 (1.88, 4.84)	2.70E-06	PCDHGA1 (missense)
rs114799364	1p36.13	18900554	C | T	0.073 | 0.038	0.33 (0.20, 0.53)	2.72E-06	57kb 5' of PAX7
rs4151685	5q31.3	140213805	A | C	0.044 | 0.089	2.80 (1.79, 4.38)	3.52E-06	PCDHA1, PCDHA2, PCDHA3, PCDHA4, PCDHA5, PCDHA6 (intron for all)
rs34575154	5q31.3	140166953	A | G	0.044 | 0.089	2.80 (1.79, 4.38)	3.56E-06	PCDHA1 (missense)
rs370971	20q13.12	42371095	G | A	0.428 | 0.518	1.65 (1.33, 2.04)	4.92E-06	15kb 3' of GTSF1L
rs6878145	5q31.3	140718552	A | G	0.039 | 0.076	2.94 (1.83, 4.73)	4.94E-06	PCDHGA1 (intron), PCDHGA2 (missense)
rs2993385	10p14	8462439	T | C	0.178 | 0.110	0.50 (0.37, 0.68)	5.94E-06	345kb 5' of GATA3, RP11-543F8.2 (intron)
rs1329536	6p12.3	47663326	C | T	0.051 | 0.096	2.54 (1.68, 3.84)	6.20E-06	GPR111 (UTR-3)
rs116776862	5q31.3	140177075	G | A	0.045 | 0.089	2.67 (1.72, 4.14)	6.86E-06	PCDHA1 (intron)
rs13432692	2p25.2	6085200	C | T	0.541 | 0.443	0.63 (0.51, 0.77)	7.02E-06	LOC150622 (AC073479.1) (intron)
rs75404762	13q12.3	30562130	T | C	0.015 | 0.043	4.49 (2.27, 8.90)	7.04E-06	38kb 5' of LOC440131 (RP11-90M5.1)

rs Number	Cytoband	Location[1]	Alleles (referent | effect)	Effect Allele Frequency (control | case)	Per Effect Allele OR (95%CI)	P value	In gene(s) or nearest gene(s) if distance specified[2]
rs73146440	7q11.22	67865802	A | G	0.038 | 0.012	0.19 (0.09, 0.41)	7.53E-06	113kb 5' of RP5-945F2.3, 1.1Mb 5' of STAG3L4
rs285198	20q13.12	42364734	G | A	0.431 | 0.519	1.64 (1.32, 2.03)	7.87E-06	9.1kb 3' of GTSF1L, 19.4kb 3' of MYBL2
rs12057381	1p32.2	57769516	G | A	0.132 | 0.068	0.45 (0.31, 0.64)	8.44E-06	DAB1 (intron)
rs116679801	5q31.3	140711954	C | G	0.037 | 0.071	3.00 (1.83, 4.91)	8.49E-06	PCDHGA1 (missense)
rs2056150	2p24.3	14603290	G | A	0.321 | 0.405	1.70 (1.34, 2.15)	1.03E-05	62kb 5' of NCRNA00276, 170kb 5' of FAM84A

[1] Location is per GRCh37.p5.

[2] Gene information curated from Haploreg, dbSNP, Ensembl, and GENCODE.

Table 2

The most promising SNP associations with prostate cancer stratified by Gleason score in the Ghana Prostate Study GWAS, with estimates also from the African Ancestry Prostate Cancer GWAS Consortium

Gleason	rs Number	Cytoband	Location	Alleles (referent | effect)	Ghana Prostate Study			In gene(s) or nearest gene(s) if distance specified	African Ancestry Prostate Cancer GWAS Consortium			
					Effect Allele Frequency (control | case)	Per Effect Allele OR (95%CI)	P value		Effect Allele Frequency (control | case)	Per Effect Allele OR (95%CI)	P value	P Het
	rs34575154	5q31.3	140166953	A | G	0.044 | 0.098	3.79 (2.31, 6.20)	3.66E-08	PCDHA1 (missense)	0.048 | 0.050	1.05 (0.87, 1.27)	0.582	0.025
	rs4151685	5q31.3	140213805	A | C	0.044 | 0.098	3.77 (2.30, 6.16)	4.02E-08	PCDHA1 (intron); PCDHA@	0.045 | 0.047	1.06 (0.87, 1.28)	0.586	0.028
	rs116776862	5q31.3	140177075	G | A	0.045 | 0.098	3.53 (2.18, 5.73)	9.07E-08	PCDHA1 (intron); PCDHA@	0.048 | 0.050	1.04 (0.86, 1.26)*	0.675	0.028
	rs7706544	5q31.3	140070148	C | T	0.051 | 0.104	3.34 (2.09, 5.34)	1.94E-07	HARS (intron)	0.052 | 0.054	1.04 (0.87, 1.25)	0.665	0.053
	rs115338764	5q31.3	140041187	G | A	0.051 | 0.104	3.34 (2.09, 5.34)	1.98E-07	IK (intron)	0.051 | 0.054	1.04 (0.87, 1.25)*	0.660	0.053
	rs61749035	5q31.3	140718750	G | T	0.037 | 0.084	3.82 (2.26, 6.47)	2.07E-07	PCDHGA2 (missense); PCDHA@	0.045 | 0.047	1.10 (0.91, 1.34)*	0.339	0.022
	rs6889768	5q31.3	139929877	T | G	0.039 | 0.085	3.70 (2.20, 6.24)	3.81E-07	SRA1 (3'UTR)	0.035 | 0.041	1.18 (0.95, 1.46)	0.134	0.196
	rs6008813	22q13.31	46812585	G | A	0.389 | 0.490	1.90 (1.47, 2.44)	4.34E-07	CELSR1 (intron)	0.371 | 0.387	1.06 (0.97, 1.16)*	0.183	0.889
Greater than or even to 7	kgp22385671	5q31.3	140208753	A | G	0.044 | 0.092	3.59 (2.16, 5.97)	4.47E-07	PCDHA1 (intron); PCDHA@	0.048 | 0.049	1.04 (0.86, 1.26)*	0.654	0.029
	rs113425597	5q31.3	140187201	G | C	0.044 | 0.091	3.55 (2.13, 5.91)	6.36E-07	PCDHA1 (synonymous); PCDHA@	0.048 | 0.050	1.04 (0.86, 1.26)*	0.675	0.028
	rs12537079	7q31.31	117704706	T | G	0.146 | 0.071	0.35 (0.23, 0.53)	6.95E-07	61kb 5' of AC003084.2; 119kb 5' of NAA38	0.204 | 0.195	0.97 (0.87, 1.07)	0.540	0.818
	rs6880234	5q31.3	140215956	C | G	0.044 | 0.092	3.53 (2.12, 5.88)	7.49E-07	PCDHA7 (missense); PCDHA@	0.046 | 0.047	1.05 (0.87, 1.28)*	0.603	0.027
	rs12477565	2q14.2	121081260	G | T	0.420 | 0.528	1.85 (1.44, 2.38)	8.18E-07	AC012363.13; 22kb 5' of INHBB	0.514 | 0.526	1.06 (0.97, 1.16)*	0.222	0.571
	rs17097185	5q31.3	140711097	C | G	0.039 | 0.084	3.55 (2.10, 5.98)	8.41E-07	PCDHGA1 (missense)	0.045 | 0.047	1.10 (0.90, 1.33)*	0.342	0.022
	rs17119623	5q31.3	139961837	T | C	0.050 | 0.101	3.17 (1.97, 5.10)	1.19E-06	APBB3; 13kb 5' of SLC35A4	0.047 | 0.049	1.04 (0.86, 1.26)	0.661	0.292
	rs6878145	5q31.3	140718552	A | G	0.039 | 0.082	3.43 (2.03, 5.80)	1.93E-06	PCDHGA2 (missense); PCDHA@	0.045 | 0.047	1.10 (0.91, 1.34)*	0.339	0.022
	rs7715021	5q31.3	139941943	C | G	0.051 | 0.098	3.10 (1.92, 5.01)	2.09E-06	APBB3 (missense)	0.050 | 0.053	1.07 (0.89, 1.28)*	0.487	0.313
Less than 7	rs985081	Xq28	148538099	T | C	0.025 | 0.141	3.08 (2.01, 4.73)	8.66E-09	22kb 3' of IDS	0.070 | 0.082	1.08 (0.98, 1.20)	0.112	0.192
	rs2185710	6q21	113377048	A | G	0.166 | 0.295	2.77 (1.89, 4.05)	5.95E-08	84kb 3' of U6	0.334 | 0.348	1.05 (0.97, 1.14)*	0.229	0.573
	rs66504230	6q14.3	86871444	T | C	0.090 | 0.186	3.15 (2.01, 4.95)	1.77E-07	169kb 5' of U4	0.113 | 0.106	0.94 (0.84, 1.06)*	0.344	0.030
	rs1149918764	4q26	117370706	C | T	0.002 | 0.045	34.07 (6.45, 179.92)	3.65E-07	40kb 3' of RP11-55L3.1; 150kb 5' of MIR1973	0.002 | 0.002	0.93 (0.23, 3.70)*	0.915	0.280
	rs73043340	3p22.3	33126972	C | T	0.007 | 0.042	12.04 (3.98, 36.46)	3.76E-07	GLB1 (intron)	0.085 | 0.085	0.98 (0.86, 1.13)*	0.819	0.455
	rs62477096	7q31.33	124936442	A | G	0.178 | 0.283	2.45 (1.70, 3.53)	6.63E-07	RP11-3B12.2; 366kb 3' of POT1	0.196 | 0.194	0.99 (0.90, 1.09)*	0.814	0.619
	rs6965492	7q31.33	124944082	G | T	0.179 | 0.286	2.49 (1.72, 3.61)	6.92E-07	RP11-3B12.2; 375kb 3' of POT1	0.191 | 0.190	1.00 (0.91, 1.09)	0.947	0.484

*Imputed using 1000 Genomes Project data

Table 3

The association of previously reported prostate cancer susceptibility SNPs from European and Asian populations in relation to prostate cancer in African men.

SNP	Cytoband	Location[1]	Nearest Gene[2]	Study PMID(s)	Study Population Ancestry	Ghana SNP	Location	Reference | Effect Alleles	Case | Control Effect Allele Frequencies	P value	Per Allele OR (95%CI)
rs1218582	1q21.3	154834183	KCNN3 (intron)	23535732	European	rs1218582	154834183	G | A	0.31 | 0.33	0.12	0.84 (0.67, 1.05)
rs4245739	1q32.1	204518842	MDM4 (3'-URT)	23535732	European	rs4245739	204518842	C | A	0.78 | 0.77	0.82	0.97 (0.76, 1.25)
rs10187424	2p11.2	85794297	VAMP8 (intronic); 5.6kb 3' of GGCX	21743467	European, Asian	rs10187424	85794297	T | C	0.66 | 0.72	0.17	0.86 (0.68, 1.07)
rs721048	2p15	63131731	EHBP1 (intron)	18264098	European	rs721048[3]	63131731	G | A	0.00 | 0.00	0.90	0.79 (0.02, 38.16)
rs1465618	2p21	43553949	THADA (intron)	19767753	European, Asian	rs1465618	43553949	T | C	0.95 | 0.94	0.13	1.43 (0.90, 2.28)
rs11902236	2p25.1	10117868	GRHL1 (intron)	23535732	European	rs11902236	10117868	C | T	0.65 | 0.69	0.31	0.89 (0.72, 1.11)
rs12621278	2q31.1	173311553	ITGA6 (intron)	19767753	European, African American, Asian	-	-	-	-	-	-
rs2292884	2q37.3	238443226	MLPH (missense)	21743057	European	-	-	-	-	-	-
rs3771570	2q37.3	242382864	FARP2 (intron)	23535732	European	rs3771570	242382864	C | T	0.01 | 0.00	**0.030**	5.39 (1.17, 24.77)
rs7629490	3p11.2	87241497	34kb 3' of MIR4795	21743057	European	rs7629490	87241497	C | T	0.17 | 0.21	0.12	0.81 (0.62, 1.06)
rs2055109	3p11.2	87467332	142kb 3' of POU1F1	22366784	Asian	-	-	-	-	-	-
rs2660753	3p12.1	87110674	70kb 3' of VGLL3	18264097	European	-	-	-	-	-	-
rs9284813	3p12.1	87152169	112kb 5' of VGLL3	20676098	Asian	rs9284813	87152169	A | G	0.46 | 0.43	0.39	1.09 (0.89, 1.35)
rs17181170	3p12.1	87173324	102kb 3' of MIR4795	19767753	European, Asian	rs17181170	87173324	G | A	0.12 | 0.16	**0.031**	0.72 (0.54, 0.97)
rs7611694	3q13.2	113275624	SIDT1 (intron)	23535732	European	rs7611694	113275624	A | C	0.34 | 0.37	0.29	0.89 (0.71, 1.11)
rs10934853	3q21.3	128038373	EEFSEC (intron)	19767754	European	rs10934853	128038373	C | A	0.82 | 0.80	0.53	1.09 (0.83, 1.42)
rs6763931	3q23	141102833	ZBTB38 (intron)	21743467	European	rs6763931	141102833	G | A	0.91 | 0.90	**0.019**	1.53 (1.07, 2.18)
rs10936632	3q26.2	170130102	RP11-46914.3; 6.5kb 5' of CLDN11	21743467	European	rs10936632[3]	170130102	C | A	0.15 | 0.18	0.051	0.75 (0.57, 1.00)
rs1894292	4q13.3	74349158	AFM (intron)	23535732	European	rs1894292	74349158	G | A	0.26 | 0.27	0.76	0.96 (0.76, 1.22)
rs12500426	4q22.3	95514609	PDLIM5 (intron)	19767753	European	rs12500426	95514609	A | C	0.61 | 0.62	0.90	0.99 (0.80, 1.22)
rs17021918	4q22.3	95562877	PDLIM5 (intron)	19767753	European	rs17021918	95562877	C | T	0.21 | 0.21	0.71	1.05 (0.81, 1.36)
rs7679673	4q24	106061534	AC004069.2; 5.5kb 5' of TET2	19767753	European	rs7679673	106061534	C | A	0.60 | 0.63	**0.010**	0.75 (0.60, 0.93)
rs2121875	5p12	44365545	FGF10 intronic	21743467	European	rs2121875	44365545	C | A	0.20 | 0.20	0.79	0.97 (0.74, 1.25)
rs2242652	5p15.33	1280028	TERT (intron)	21743467	European	rs2242652[3]	1280028	G | A	0.12 | 0.13	0.34	0.85 (0.61, 1.19)
rs12653946	5p15.33	1895829	CTD-2194D22.4; 13kb 3' of IRX4	20676098	Asian	rs12653946	1895829	C | T	0.40 | 0.42	0.25	0.88 (0.72, 1.09)
rs6869841	5q35.1	172939426	28kb 3' of CTB-164N12.1	23535732	European	rs6869841	172939426	C | T	0.37 | 0.36	0.36	1.11 (0.89, 1.38)
rs3096702	6p21.32	32192331	486bp 5' of NOTCH4	23535732	European	rs3096702	32192331	A | G	0.87 | 0.87	0.72	1.06 (0.77, 1.45)
rs130067	6p21.33	31118511	CCHCR1 (missense)	21743467	European	-	-	-	-	-	-

SNP	Cytoband	Location[1]	Nearest Gene[2]	Study PMID(s)	Study Population Ancestry	Ghana SNP	Location	Reference | Effect Alleles	Case | Control Effect Allele Frequencies	P value	Per Allele OR (95%CI)
rs2273669	6q21	109285189	ARMC2 (intron)	23535732	European	rs2273669	109285189	A | G	0.37 | 0.35	0.22	1.15 (0.92, 1.42)
rs339331	6q22.1	117210052	RFX6 (intron)	20676098	Asian	rs339331	117210052	T | C	0.17 | 0.23	**0.002**	0.67 (0.52, 0.87)
rs1933488	6q25.2	153441079	RGS17 (intron)	23535732	European	rs1933488	153441079	A | G	0.43 | 0.44	0.78	0.97 (0.78, 1.20)
rs651164	6q25.3	160581374	1.6kb 3' of SLC22A1	19767753; 21743057	European, Asian; European	rs651164	160581374	A | G	0.76 | 0.74	0.42	1.12 (0.85, 1.49)
rs9364554	6q25.3	160833664	SLC22A3 (intron)	18264097	European	rs9364554	160833664	C | T	0.01 | 0.01	0.45	1.49 (0.53, 4.18)
rs10486567	7p15.2	27976563	JAZF1 (intron)	18264096	European	rs10486567	27976563	G | A	0.25 | 0.26	0.27	0.88 (0.69, 1.11)
rs12155172	7p15.3	20994491	AC006481.1	23535732	European	rs12155172	20994491	A | G	0.88 | 0.88	0.85	0.97 (0.70, 1.34)
rs6465657	7q21.3	97816327	LMTK2 (intron)	18264097	European	rs6465657	97816327	C | T	0.01 | 0.02	0.18	0.54 (0.22, 1.33)
rs1512268	8p21.2	23526463	9.7kb 3' of NKX3-1	19767753	European, African American, Asian	-	-	-	-	-	-
rs11135910	8p21.2	25892142	EBF2 (intron)	23535732	European	rs11135910	25892142	C | T	0.09 | 0.09	0.91	1.02 (0.70, 1.49)
rs13252298	8q24.21	128095156	689bp 5' of RP11-255B23.2	19767752	European	rs13252298	128095156	A | G	0.01 | 0.01	0.70	1.27 (0.39, 4.14)
rs7841060	8q24.21	128096477	2kb 5' of RP11-255B23.2	19767755	European	rs7841060	128096477	T | G	0.34 | 0.37	0.85	0.98 (0.79, 1.21)
rs16901979[3]	8q24.21	128124916	30kb 5' of RP11-255B23.2; 303kb 5' of POU5F1B	17401366	European	rs16901979[3]	128124916	C | A	0.56 | 0.50	**0.022**	1.27 (1.04, 1.57)
rs188140481	8q24.21	128191672	6.2kb 3' of RP11-255B23.4	23104005	European	-	-	-	-	-	-
rs16902094	8q24.21	128320346	RP11-382A18.1	19767754	European	rs16902094	128320346	A | G	0.10 | 0.11	0.65	0.92 (0.66, 1.30)
rs620861	8q24.21	128335673	RP11-382A18.1; 92kb 5' of POU5F1B	19767752; 19767755	European; European	rs620861	128335673	G | A	0.33 | 0.33	0.91	0.99 (0.79, 1.23)
rs6983267	8q24.21	128413305	RP11-382A18.1; 15kb 5' of POU5F1B	17401363; 18264097; 18264096; 19767752	European and African American; European; European; European	rs6983267	128413305	G | T	0.02 | 0.02	0.51	1.28 (0.62, 2.63)
rs6999921	8q24.21	128440928	RP11-382A18.1	21743057	European	rs6999921	128440928	A | G	0.13 | 0.09	0.060	1.38 (0.99, 1.93)
rs1447293	8q24.21	128472320	RP11-382A18.1 (intron)	21743057	European	rs1447293	128472320	C | T	0.08 | 0.06	0.053	1.51 (1.00, 2.29)
rs10090154	8q24.21	128532137	38kb 5' of RP11-382A18.1; 38kb 3' of LOC727677	19767752	European	rs10090154[3]	128532137	T | C	0.80 | 0.85	**0.005**	0.67 (0.51, 0.89)
rs7837688	8q24.21	128539360	45kb 5' of RP11-382A18.1	20676098	Asian	rs7837688	128539360	T | G	0.94 | 0.96	0.063	0.64 (0.40, 1.02)
rs817826	9q31.2	110156300	26kb 3' of RP11-363D24.1; 62kb 5' of RAD23B	23023329	Asian	rs817826	110156300	C | T	0.68 | 0.65	0.47	1.09 (0.87, 1.36)
rs10993994	10q11.23	51549496	TIMM23B; 55bp 5' of MSMB	18264097; 18264096	European; European	rs10993994	51549496	T | C	0.33 | 0.34	0.94	1.01 (0.81, 1.26)
rs3850699	10q24.32	104414221	TRIM8 (intron)	23535732	European	rs3850699	104414221	A | G	0.41 | 0.44	0.45	0.92 (0.74, 1.14)
rs2252004	10q26.12	122844709	94kb 5' of RP11-159H3.2; 176kb 5' of WDR11	22366784	Asian	rs2252004	122844709	C | A	0.65 | 0.63	0.52	1.07 (0.87, 1.33)
rs10749408	10q26.12	122967526	22kb 3' of RP11-159H3.2; 270kb 3' of FGFR2	22130093	European	rs10749408[3]	122967526	C | T	0.81 | 0.83	0.39	0.89 (0.68, 1.16)
rs11199874	10q26.12	123032519	87kb 3' of RP11-159H3.2; 205kb 3' of FGFR2	22130093	European	rs11199874[3]	123032519	G | A	0.11 | 0.12	0.30	0.84 (0.61, 1.17)
rs4962416	10q26.13	126696872	CTBP2 (intron)	18264096	European	rs4962416	126696872	T | C	0.16 | 0.13	0.055	1.33 (0.99, 1.79)
rs7127900	11p15.5	2233574	32kb 3' of AC132217.2; 39kb 5' of MIR-4686	19767753	European	rs7127900	2233574	A | G	0.55 | 0.57	0.50	0.93 (0.75, 1.15)
rs1938781	11q12.1	58915110	FAM111A (intron)	22366784	Asian	rs1938781	58915110	A | G	0.35 | 0.32	0.086	1.22 (0.97, 1.53)
rs10896438	11q13.3	68906570	8.1kb 5' of RP11-554A11.3; 48kb 5' of TPCN2	21531787	European	rs10896438	68906570	T | G	0.20 | 0.23	0.96	0.99 (0.77, 1.29)

SNP	Cytoband	Location[1]	Nearest Gene[2]	Study PMID(s)	Study Population Ancestry	Ghana SNP	Location	Reference | Effect Alleles	Case | Control Effect Allele Frequencies	P value	Per Allele OR (95%CI)
rs12793759	11q13.3	68974555	87kb 5' of MYEOV	21531787	European	rs12793759[3]	68974555	G | A	0.09 | 0.08	0.21	1.26 (0.87, 1.82)
rs10896449	11q13.3	68994667	67kb 5' of MYEOV	18264096; 21531787	European; European	rs10896449	68994667	A | G	0.79 | 0.74	**0.007**	1.40 (1.10, 1.79)
rs7940107	11q13.3	69027770	34kb 5' of MYEOV	21743057	European	rs7940107	69027770	G | A	0.34 | 0.36	0.69	0.96 (0.77, 1.19)
rs11568818	11q22.2	102401661	176bp 5' of MMP7	23535732	European	rs11568818	102401661	T | C	0.45 | 0.44	0.89	1.02 (0.83, 1.25)
rs10875943	12q13.12	49676010	8.9kb 5' of TUBA1C	21743467	European	rs10875943[3]	49676010	T | C	0.75 | 0.71	0.11	1.21 (0.96, 1.53)
rs902774	12q13.13	53273904	17kb 3' of KRT8	21743057	European	rs902774	53273904	G | A	0.09 | 0.08	0.087	1.39 (0.95, 2.02)
rs1270884	12q24.21	114685571	6kb 5' of RP11-139B1.1	23535732	European	rs1270884	114685571	A | G	0.87 | 0.87	0.80	0.96 (0.71, 1.30)
rs9600079	13q22.1	73728139	14kb 3' of U7.97; 76kb 5' of KLF5	20676098	Asian	rs9600079	73728139	G | T	0.54 | 0.62	**0.002**	0.71 (0.58, 0.88)
rs8008270	14q22.1	53372330	FERMT2 (intron)	23535732	European	rs8008270	53372330	T | C	0.70 | 0.67	0.093	1.21 (0.97, 1.51)
rs7141529	14q24.1	69126744	RAD51B	23535732	European	rs7141529	69126744	T | C	0.58 | 0.55	0.59	1.06 (0.85, 1.32)
rs1994198	15q21.1	46653167	9.2kb 5' of SNORD111; 670kb 5' of SQRDL	22130093	European	rs1994198	46653167	C | T	0.31 | 0.31	0.88	1.02 (0.81, 1.27)
rs684232	17p13.3	618965	VPS53	23535732	European	rs684232	618965	T | C	0.74 | 0.76	0.76	0.96 (0.76, 1.22)
rs11649743	17q12	36074979	HNF1B (intron)	18758462	European	rs11649743	36074979	G | A	0.04 | 0.04	0.71	1.12 (0.63, 1.98)
rs4430796	17q12	36098040	HNF1B (intron)	17603485	European	rs4430796	36098040	G | A	0.30 | 0.28	0.15	1.18 (0.94, 1.48)
rs7501939	17q12	36101156	HNF1B (intron)	19767753; 18264097; 17603485; 19318570	European, Asian; European; European; European	rs7501939	36101156	T | C	0.40 | 0.38	0.64	1.05 (0.85, 1.29)
rs138213197	17q21.3	46805705	HOXB13 (missense)	23104005	European	-	-	-	-	-	-
rs11650494	17q21.32	47345186	9.2kb 3' of RP1-6209.3	23535732	European	rs11650494	47345186	G | A	0.29 | 0.27	0.37	1.11 (0.88, 1.41)
rs7210100	17q21.33	47436749	ZNF652 (intron)	21602798	African American	rs7210100	47436749	G | A	0.08 | 0.05	**0.008**	1.78 (1.16, 2.72)
rs1859962	17q24.3	69108753	186kb 3' of U7.34; 933kb 5' of KCNJ2	17603485	European	rs1859962	69108753	G | T	0.76 | 0.78	0.40	0.90 (0.71, 1.15)
rs7241993	18q23	76773973	11kb 3' of SALL3	23535732	European	rs7241993	76773973	C | T	0.58 | 0.58	0.85	1.02 (0.83, 1.26)
rs8102476	19q13.2	38735613	6.3kb 3' of PPP1R14A	19767754	European	rs8102476	38735613	C | T	0.16 | 0.16	0.51	0.91 (0.69, 1.20)
rs11672691	19q13.2	41985587	35kb 3' of C19orf69	23065704	European	rs11672691	41985587	A | G	0.06 | 0.06	0.92	0.98 (0.64, 1.49)
rs2735839	19q13.33	51364623	602bp 5' of KLK3	18264097	European	rs2735839	51364623	A | G	0.67 | 0.67	0.64	1.05 (0.85, 1.30)
rs103294	19q13.42	54797848	2kb 3' of LILRA3	23023329	Asian	rs103294	54797848	C | T	0.08 | 0.06	0.20	1.31 (0.87, 1.96)
rs2427345	20q13.33	61015611	9kb 3' of RP5-908M14.5	23535732	European	rs2427345	61015611	C | T	0.56 | 0.55	0.81	1.03 (0.83, 1.27)
rs6062509	20q13.33	62362563	ZGPAT (intron)	23535732	European	rs6062509	62362563	G | T	0.94 | 0.95	0.79	0.94 (0.60, 1.48)
rs5759167	22q13.2	43500212	6.5kb 5' of BIK	21390317	European	rs5759167	43500212	G | T	0.17 | 0.19	0.53	0.92 (0.70, 1.20)
rs742134	22q13.2	43518275	BIK (intron)	21743057	European	rs742134	43518275	A | G	0.85 | 0.81	0.055	1.32 (0.99, 1.76)
rs5945572	Xp11.22	51229683	3.2kb 3' of NUDT11	18264098	European	rs5945572[3]	51229683	A | G	0.88 | 0.90	0.31	0.88 (0.68, 1.13)
rs2405942	Xp22.2	9814135	SHROOM2 (intron)	23535732	European	-	-	-	-	-	-
rs5919432	Xq12	67021550	77kb 5' of AR	21743467	European	rs5919432[3]	67021550	C | T	0.14 | 0.14	0.56	1.08 (0.84, 1.39)

[1] Location is per GRCh37.p5.

[2] Gene information curated from Haploreg, dbSNP, Ensembl, and GENCODE.

[3] Imputed using 1000 Genomes Project data. Table includes SNPs with published p values <5x10-8 for overall, advanced or aggressive prostate cancer. Loci detected in European populations only were pruned using 1000 Genomes Project data with pairwise r2 > 0.3 and the SNP with lower p value preferably chosen to be listed in the table.