A Germline Variant at 8q24 Contributes to Familial Clustering of Prostate Cancer in Men of African Ancestry

Supplementary Information

Supplementary Methods

Methods

Participants

Participants included men of African ancestry with genome-wide genotyping data, with N=9,463 from the African Ancestry Prostate Cancer (AAPC) GWAS Consortium and N=8,184 from the ELLIPSE/PRACTICAL OncoArray Consortium (Supplemental Table 3)[1, 2]. This study was conducted with the approval of the institutional review boards at each participating institution, and all subjects provided written informed consent to participate in the study.

An additional 144 participants were included from the following high-risk prostate cancer family studies.

Prostate Cancer Genetic Research Study (PROGRESS) (11 cases genotyped)
Hereditary prostate cancer families were ascertained from North America and several other countries by advertising a toll-free number via public media, health-related publications, and the internet, as well as communications with urologists, other health-care professionals, and prostate cancer support groups[3-5]. Eligible families met at least one of the following criteria: (1) having three or more first-degree relatives with prostate cancer; (2) having three generations with prostate cancer, either through

paternal or maternal lineage; or (3) having two first-degree relatives with prostate cancer diagnosed before age 65 or who were African-American. Participants completed a study questionnaire on medical and family cancer history and provided a blood sample. Affected men were also asked to sign a consent form for release of medical records related to the prostate cancer diagnosis and treatment. Study forms and protocols were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Louisiana State University Health Sciences Center (20 cases genotyped)

African American hereditary prostate cancer families were recruited primarily through collaborating hospitals and physicians in Louisiana[6, 7]. In addition to being African American, families enrolled met the following inclusion criteria: three or more family members with prostate cancer, histopathological evidence of prostate cancer with clinical staging, and two or more living affected family members. Affected participants provided a blood sample for genotyping and consent to obtain medical records to verify prostate cancer diagnosis. For deceased family members with a reported history of prostate cancer, disease status was verified with medical documentation when available from the treating hospitals, confirmation through Louisiana Tumor Registry records, or death certificates. All study-related materials were approved by Louisiana State University Health Sciences Center Institutional Review Board.

ICPG for Identifying Prostate Cancer Genes (63 cases genotyped)

Participants included men with prostate cancer who had at least one first- or second-degree relative who also had prostate cancer or those in whom prostate cancer had

been diagnosed at an age of 55 years or less, regardless of family history[8]. Families were ascertained from three sources. A majority were ascertained through referrals generated as a response to a letter to 8,000 urologists throughout the US. The second source was from family history records of the patient population seen at Johns Hopkins Hospital for treatment of prostate cancer. The third source was the respondents to articles published in a variety of lay publications describing the prostate cancer family studies. The diagnosis of prostate cancer was confirmed by reviewing medical records in each proband and whenever possible in other family members. African ancestry was self-reported. All subjects provided written informed consent to participate in the study. The protocol and consent documents were approved by the Institutional Review Board at the Johns Hopkins University, School of Medicine.

University of Michigan Prostate Cancer Genetics Project (UM-PCGP) (49 cases genotyped)

Samples from the University of Michigan Prostate Cancer Genetics Project (UM-PCGP) were used for this analysis. The UM-PCGP enrolled men with prostate cancer who had at least one living first- or second-degree relative who also had prostate cancer or men diagnosed with prostate cancer at or before age 55 years, regardless of family history. The diagnosis of prostate cancer was confirmed by reviewing medical records whenever possible. African ancestry was self-reported. All subjects provided written informed consent to participate in the study. The protocol and consent documents were approved by the institutional review board at the University of Michigan Medical School and Duke University Medical School.

Genotyping

AAPC samples were genotyped on the Illumina Human 1M array and ELLIPSE/PRACTICAL samples were genotyped on the Illumina OncoArray. Genotype calling and quality control for AAPC and the OncoArray are described in detail elsewhere[1, 9, 10]. Data were phased using SHAPEIT[11], and imputations were performed using Phase 3 of the 1000 Genomes as the reference panel[12]. The rs72725854 variant (A>T) was imputed using IMPUTEv2[13, 14] in AAPC samples and Minimac3 Version 1.0.12[15] in OncoArray samples. The info score for rs72725854 was 0.965 for AAPC samples and 0.972 in the OncoArray samples. We genotyped rs72725854 using TaqMan in a subset of 1,093 AAPC samples and found a high concordance between the imputed and genotyped variant (concordance rate=98.35%). Genotyping of rs72725854 in the 144 participants from hereditary prostate cancer family studies was performed using TaqMan (genotyping call rate=100%). These sample were additionally genotyped using the Illumina H3Africa array to calculate principal components (described below). Using genotyping data from this array, one familial case from UM-PCGP was genetically identified as female and excluded from analyses.

Statistical Analyses

To assess the association between germline variant rs72725854 and prostate cancer, logistic regression models were run in SAS version 9.4, adjusting for age at diagnosis for cases or at last study visit for controls, study, and the first two principal components (described below) to account for potential population stratification. Models were run separately for participants from the AAPC and OncoArray, and the resulting summary statistics were meta-analyzed using METAL[16]. Analyses were repeated comparing

controls to cases with and without a family history of prostate cancer (defined as one or more first-degree relatives with prostate cancer), cases stratified by age of diagnosis (<60 vs. ≥60 years), cases with lethal prostate cancer (metastatic disease or PSA>100 or died of prostate cancer), cases with low-risk disease (Gleason scores<7 and localized), familial cases, familial cases with two or more first-degree relatives with prostate cancer, and familial cases with an age of diagnosis <60 years. We also stratified cases and controls according to carrier status and family history, creating six subgroups (non-carrier FH-, non-carrier FH+, heterozygote carrier FH-, heterozygote carrier FH+, homozygote carrier FH-, and homozygote carrier FH+), and estimated risk in each group relative to non-carriers without a family history. Additive models were used to test the effect of each additional minor allele, and genotypic models were used to compare individuals who were major allele homozygotes (AA) to heterozygotes (TA) and to minor allele homozygotes (TT). *P*-values less than 0.05 were considered statistically significant.

Principal component analyses were performed to calculate principal components (PCs) used to account for potential population stratification. PCs were calculated using 2,546 ancestry-informative SNPs in AAPC (Illumina 1M), 18,176 uncorrelated SNPs on the OncoArray, and 20,588 uncorrelated SNPs in the high-risk prostate cancer family studies (H3Africa array). EIGENSTRAT[17] was used to calculate PCs separately for each of the three sets of participants (details for AAPC and OncoArray have been previously described[1]).

The calculation of global ancestry has been previously described[1]. Briefly, local ancestry was estimated using RFMix[18] (using the forward-backward option, without EM nor phase error correction) and Phase 1 1000 Genomes data[19] (AFR and EUR)

with 220,474 genotyped common (MAF≥0.01) autosomal variants overlapping between AAPC and ONCO. Global ancestry was then calculated by averaging the local AFR estimates across all autosomal variants, and these estimates were very comparable to STRUCTURE estimates[20]. Risk allele frequencies were then calculated among cases and controls by decile of global African ancestry.

Genetic Risk Score

We constructed a genetic risk score (GRS) using 180 prostate cancer-associated variants and corresponding weights from previous prostate cancer GWAS meta-analyses: 174 from a European study[21, 22], four from an African study[1], and two from an Asian study[23]. A weighted GRS was calculated for each participant as the sum of the number of risk alleles carried by an individual, weighted by previously estimated variant-specific effects. Association tests were performed to assess the association between the GRS and prostate cancer for each GRS decile, using the average 40%-60% category as the reference group. A separate GRS was calculated that included five 8q24 variants previously identified to be associated with prostate cancer within men of African ancestry[1]. Both GRS were recalculated excluding rs72725854 for comparison purposes.

Absolute Risk

Absolute risks of prostate cancer were estimated by rs72725854 genotype and family history (positive and negative) using the odds ratios for each genotype/family history category combined with mortality and incidence rates for African American men from the Multiethnic Cohort (MEC), while accounting for competing causes of death. This

included 6,607 deaths and 1,819 incident cases for African American men identified over a 20-year period (1993-2013)[24, 25]. The averages of the genotype absolute risks were constrained to be comparable with the population incidence[24-27]. The approach constrains the risk category-specific absolute risks for a given age to be equivalent to the age-specific incidences for the entire population. In other words, age-specific incidence rates are calculated to increase or decrease based on the category's estimated risk and the proportion of the population within the category. The calculation accounts for competing causes of death, as well.

Specifically, for a given ethnic group and a given risk category *k* (e.g. heterozygous carriers with positive family history), the absolute risk by age *t* is computed as: $AR_k(t) = \sum_0^t P_{ND}(t)\, S_k(t) I_k(t)$. This calculation consists of three components:

(1) $P_{ND}(t)$ is the probability of not dying from another cause of death by age *t* using age-specific mortality rates, $\mu_D(t)$: $P_{ND}(t) = \exp[-\sum_0^t \mu_D(t-1)]$. Age-specific mortality rates are provided from a reference cohort.

(2) $S_k(t)$ is the probability of surviving prostate cancer by age *t* in the risk category *k* and uses the prostate cancer incidence by age *t* for category *k*: $S_k(t) = \exp[-\sum_0^t I_k(t-1)]$.

(3) The prostate cancer incidence by age *t* for risk category *k* is $I_k(t)$ and is calculated by multiplying the population prostate cancer incidence for the reference category, $I_0(t)$ and the corresponding risk ratio for category *k,* as estimated from the odds ratio obtained from the population-specific individual-level analysis: $I_k(t) = I_0(t)\exp(\beta_k)$.

To complete the calculations, the prostate cancer incidence for age *t* for the reference category, $I_0(t)$, is obtained by constraining the weighted average of the population cancer incidences for all the risk categories to the population age-specific

prostate cancer incidence, $\mu(t)$.

$I_0(t) = \mu(t)\frac{\sum_K f_k S_k(t-1)}{\sum_K f_k S_k(t-1)\exp(\beta_k)}$. f_k is the frequency of the risk category *k* with $f_k = 0.1$ for all non-reference categories.

By leveraging the definition that $S_k(t=0) = 1$, for all *k*, the absolute risks were calculated iteratively by first getting $I_0(t=1)$, then $I_k(t=1)$, then $S_k(t=1)$ and finally $AR_k(t=1)$. Subsequent values were then calculated recursively for all *t*. Confidence intervals for absolute risk estimates were obtained via a parametric bootstrap repeating the above calculations for 1000 bootstraps with the β_k's sampled from their corresponding estimated distributions using the standard error of the estimate.

Contribution to Familial Relative Risk

The contribution of the SNP to the familial relative risk (i.e. sibling recurrence risk) was calculated as log(λ_m)/log(λ_0), where the SNP-specific familial relative risk is calculated as $\lambda_m = \frac{(p*r^2+q)}{(p*r+q)^2}$. Here, *r* is the estimated odds ratio for the additive genetic variant, *p* is the risk allele frequency, and *q* is 1-*p*[28, 29]. Effect estimates and allele frequencies were obtained from a large African ancestry prostate cancer GWAS[1]. λ_0 is the observed familial risk to first degree relatives of prostate cancer cases and is assumed to range between 2.0 and 2.5.[30-32]

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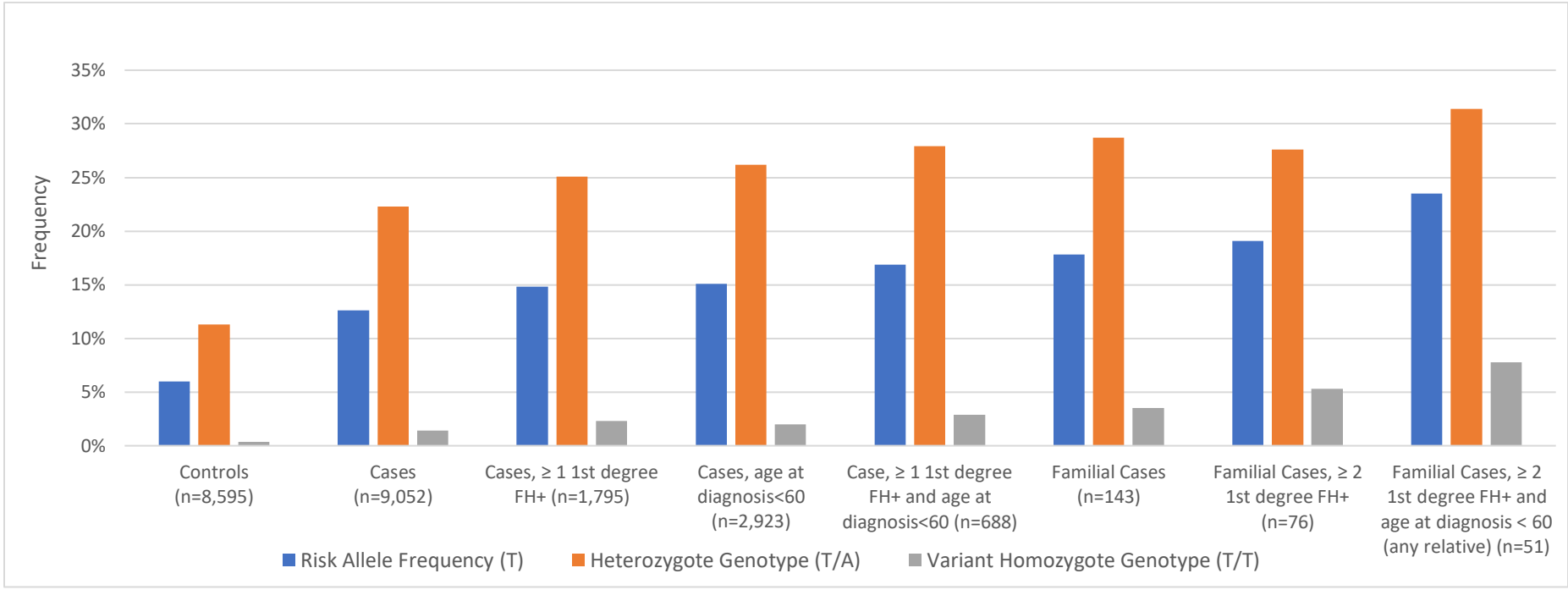
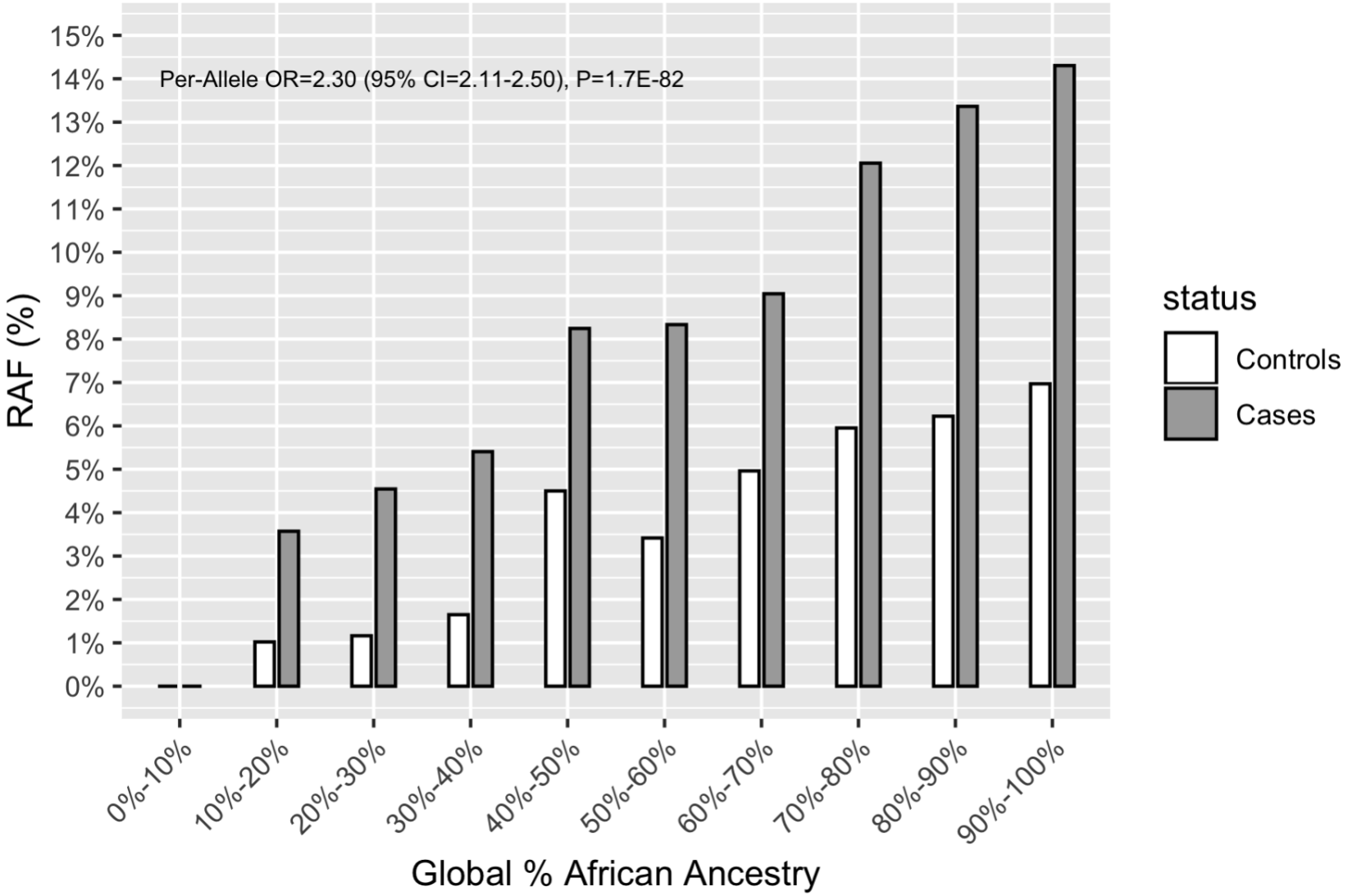
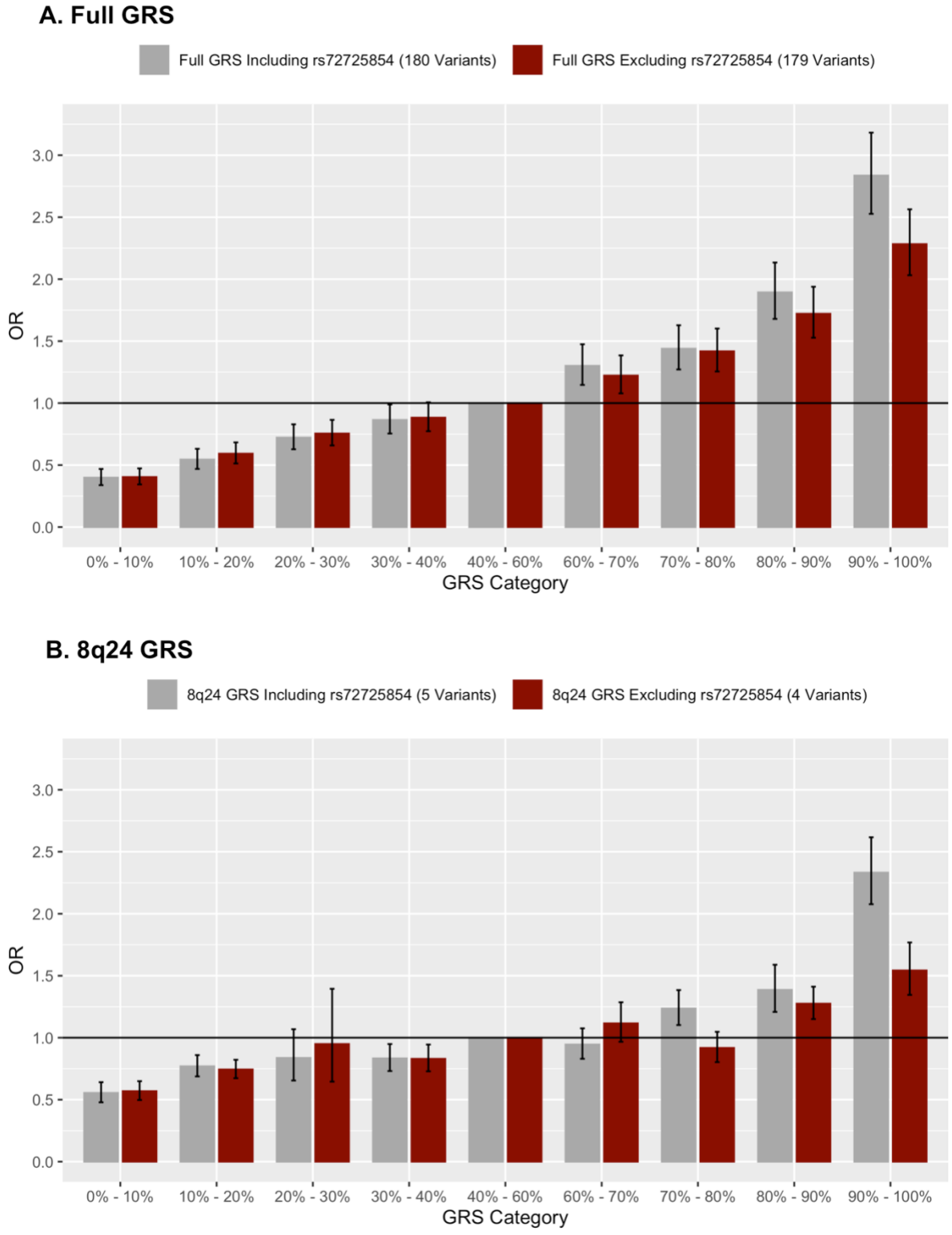
Supplemental Figure 1. Frequency of the T allele and risk genotypes of rs72725854 by family history of prostate cancer and age at diagnosis.



Supplemental Figure 2. Frequency of the T allele of rs72725854 by percentage of global African ancestry.



Supplemental Figure 3. Genetic risk score (GRS) including and excluding rs72725854.



Supplemental Table 1. Description and study design of the studies included. *

Study Name	Study Abbreviation	Group	No. of Cases	No. of Controls	No. of Cases in analysis	No. of Controls in analysis	Design, location	Source of cases	Source of controls	Study Reference
Multiethnic Cohort, African Americans	MEC	AAPC GWAS	1841	1758	1765	1648	Case-control in cohort, HI and CA, U.S.	MEC	MEC	PMID: 10695593
Southern Community Cohort Study	SCCS	AAPC GWAS	263	523	250	513	Case-control in cohort, Southeastern U.S.	SCCS	SCCS	PMID: 16080667
The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	PLCO	AAPC GWAS	286	269	231	240	Case-control in screening trial, U.S.	PLCO	PLCO	PMID: 11189683
The Cancer Prevention Study II Nutrition Cohort	CPS-II	AAPC GWAS	76	152	64	112	Case-control in cohort, U.S.	CPS-II	CPS-II	PMID: 12015775
Prostate Cancer Case-Control Studies at MD Anderson	MDA	AAPC GWAS	543	474	527	437	Case-control, Houston, TX, U.S.	Houston Medical Center	Random-digit-dialing or hospital visitors	PMID: 15264247
Identifying Prostate Cancer Genes	IPCG	AAPC GWAS	368	172	353	157	Case-control, Maryland, U.S.	Johns Hopkins Hospital and Sidney Kimmel Cancer Center	Men undergoing screening for prostate cancer at the same institutions	PMID: 17401366
The Los Angeles Study of Aggressive Prostate Cancer	LAAPC	AAPC GWAS	296	303	286	285	Case-control, Los Angeles County, CA, U.S.	Los Angeles County Cancer Surveillance Program	Los Angeles County, neighborhood walk algorithm and the MEC	PMID: 20364112
Prostate Cancer Genetics Study	CaP Genes	AAPC GWAS	75	85	71	85	Case-control, Cleveland, OH, U.S.	Medical institutions in Cleveland, Ohio	Screened men at same medical institutions	PMID: 16931544
Case-Control Study of Prostate Cancer among African Americans in Washington, DC	DCPC	AAPC GWAS	292	359	263	339	Case-control, Washington, DC, U.S.	Howard University Hospital (HUH)	Men undergoing screening for prostate cancer at HUH	PMID: 19902474
King County (Washington) Prostate Cancer Studies	KCPCS	AAPC GWAS	145	81	141	75	Case-control, King County, WA, U.S.	Seattle-Puget Sound SEER cancer registry	Random-digit-dialing	PMID: 10548316
The Gene-Environment Interaction in Prostate Cancer Study	GECAP	AAPC GWAS	234	92	224	89	Case-control, Detroit, MI, U.S.	The Henry Ford Health System (HFHS)	HFHS population base	PMID: 17067754

North Carolina Prostate Cancer Study	NCPCS	AAPC GWAS	216	249	203	231	Case-control, NC, U.S.	North Carolina Central Cancer Registry	Friend referral, same county	PMID: 19117981
Selenium and Vitamin E Cancer Prevention Trial	SELECT	AAPC GWAS	223	224	212	208	Case-control in clinical trial, U.S.	SELECT	SELECT	PMID: 19066370
Prostate Cancer in a Black Population	PCBP	AAPC GWAS	238	231	231	223	Case-control, Barbados	All newly diagnosed cases in Barbados	Selected from a national database	PMID: 22402288
Vanderbilt Bio VU	BioVU	ELLIPSE/ OncoArray	213	0	204	0	Opt-out clinical biobank linked to de-identified electronic health records, Nashville, TN, USA	Patients who had an outpatient visit at VUMC with a blood draw ordered for clinical care who did not opt-out of the VUMC biobank (BioVU) and who were 18 years of age or older at the time his or her electronic health record was accessed for prostate cancer case status (in early 2014).	N/A (no matching controls)	PMID: 18500243 PMID: 23424142
Center for Prostate Disease Research	CPDR	ELLIPSE/ OncoArray	145	44	134	41	Retrospective cohort study; Greater Washington DC Metro Area, USA	Patients enrolled at Walter Reed National Military Medical Center with biopsy-confirmed prostate cancer who underwent radical prostatectomy	Patients enrolled at Walter Reed National Military Medical Center who had a negative DRE and PSA <2.0 ng/mL	PMID: 20056617
EPIdemiology of Prostate CAncer	EPICAP	ELLIPSE/ OncoArray	64	63	20	9	Case-control, France	North African origins living in the France Metropolitan, Cancer registry	Population-based	PMID: 24552491
Karuprostate	Karuprostate	ELLIPSE/ OncoArray	384	411	363	386	Population-based case-control in Guadeloupe and hospital-based case-control in DR Congo	Incident cases from Guadeloupe (Afro-Caribbean) and the DR Congo (African)	Free health screening program open to the general population (Guadeloupe); Men attending for prostate cancer screening or benign prostatic hyperplasia (DR Congo)	PMID: 20566993
Multiethnic Cohort Study	MEC	ELLIPSE/ OncoArray	489	529	462	499	Case-control in cohort, HI and CA, U.S.	MEC	MEC	PMID: 10695593
Moffitt Prostate Cancer Study	MOFFITT	ELLIPSE/ OncoArray	106	93	100	91	Case-control at Moffitt Cancer Center	Moffitt Cancer Center	Non-cancer visitors	PMID: 21802122
Nashville Men's Health Study	NMHS	ELLIPSE/ OncoArray	188	201	175	188	Case-control, Nashville, TN	Men seeking a prostate biopsy in all urology clinics in Nashville, TN	Men without PC at biopsy from these urology clinics.	PMID: 23079532

Prostate Cancer Prevention Trial	PCPT	ELLIPSE/ OncoArray	44	129	43	113	Case-control drawn from a randomized clinical trial; US and Canada	PCPT	PCPT	PMID: 12824459
The North Carolina-Louisiana Prostate Cancer Project	PCaP	ELLIPSE/ OncoArray	1022	0	958	0	Population-based Case-only	North Carolina Central Cancer Registry for NC cases and LSUHSC Cancer (SEER) Registry for LA cases	NA	PMID: 16676364
The Prostate Cancer and Environment Study	PROtEuS	ELLIPSE/ OncoArray	72	58	70	57	Case-control, Montreal, Canada	New incident cases across Montreal hospitals	Electoral list, from same residential areas as cases	PMID: 26385727
CerePP French Prostate Cancer Case-Control Study	ProGene	ELLIPSE/ OncoArray	107	105	101	85	Case-control, France	North Africa, Africa or Caribbean origins, living in France Metropolitan	Controls were recruited as participating in a systematic health screening program	PMID: 18264096
Southern Community Cohort Study	SCCS	ELLIPSE/ OncoArray	301	1557	286	1468	Case-control in cohort, Southeastern U.S.	SCCS	SCCS	PMID: 16080667
South Carolina Prostate Cancer Study	SCPCS	ELLIPSE/ OncoArray	64	39	57	32	Case-control, South Carolina, U.S.	South Carolina Central Cancer Registry	Health Care Financing Administration Medicare Beneficiary File	PMID: 15280622
Selenium and Vitamin E Cancer Prevention Trial	SELECT	ELLIPSE/ OncoArray	30	173	27	166	Case-control in clinical trial, U.S.	SELECT	SELECT	PMID: 19066370
San Francisco Prostate Cancer Study	SFPCS	ELLIPSE/ OncoArray	86	37	79	36	Case-control in Bay Area, CA	Non-Hispanic African-American men ages 40-79 years diagnosed with advanced prostate cancer from 1997-2000. Cases were identified through the Greater Bay Area Cancer Registry.	Non-Hispanic African-American men ages 40-79 years without a history of prostate cancer	PMID: 1595859]
A Case Control Study in Uganda	UGANDA	ELLIPSE/ OncoArray	571	485	560	480	Case-control in Kampala, Uganda	Incident cases from Mulago Hospital	Patients in other clinics at Mulago	PMID: 29356057
UK Prostate Cancer Study	UKGPCS	ELLIPSE/ OncoArray	375	0	365	0	Cases from the UK	Cases identified through clinics at the Royal Marsden hospital and nationwide NCRN hospitals	NA	http://www.icr.ac.uk/research/team_leaders/Eeles_Rosalind/Eeles_Rosalind_RES/index.shtml
San Antonio Biomarkers of Risk	SABOR	ELLIPSE/ OncoArray	106	106	105	103	Case-control from SA, TX	Incident and Prevalent cases from SABOR	SABOR	PMID: 20086112

Wake Forest Prostate Cancer Study	WFPCS	ELLIPSE/ OncoArray	59	66	54	47	Case-control, Winston-Salem, NC	Incident cases from Wake Forest Baptist Health Urology Clinic	Men with normal PSA/DRE from the same clinic	PMID: 15342424
Washington University Prostate Cancer Study	WUGS	ELLIPSE/ OncoArray	75	153	70	150	Case Control from St. Louis MO	Incident and Prevalent cases from Barnes Jewish Hospital	St. Louis MO	PMID: 21602798
University of Michigan Prostate Cancer Genetics Project	UM-PCGP	HRPCF	--	--	49	0	Case-only, cases from high risk prostate cancer families in Michigan	Prostate cancer patients evaluated at the University of Michigan	NA	PMID: 14601029
The International Consortium for Prostate Cancer Genetics (Johns Hopkins site)	ICPCG	HRPCF	--	--	63	0	Case-only, cases from high risk prostate cancer families throughout U.S.	Johns Hopkins cases recruited via urologist referrals and family history records at Johns Hopkins Hospital	NA	PMID: 15988677
Louisiana State University Health Sciences Center	LSUHSC	HPC	--	--	20	0	Case-only, hereditary prostate cancer families from LA, U.S.	Hospitals and physicians in LA	NA	PMID: 18268528
Prostate Cancer Genetic Research Study	PROGRESS	HPC	--	--	11	0	Case-only, hereditary prostate cancer families from North America and several other countries	Public advertising, urologists, prostate cancer support groups	NA	PMID: 14601027

*AAPC GWAS = African Ancestry Prostate Cancer Genome-Wide Association Study; ELLIPSE = Elucidating Loci Involved in Prostate Cancer Susceptibility; HRPCF = High Risk Prostate Cancer Families; HPC = Hereditary Prostate Cancer; NA = not available; PMID = identifier number used in PubMed

Supplemental Table 2. Study participant characteristics. *

Study	Group	#Ca in analysis	#Co in analysis	Median Age (IQR) in Ca	Median Age (IQR) in Co	FH+/FH- in Ca, n (%)	FH+/FH- in Co, n (%)	Low Risk, n (%)	Intermediate Risk, n (%)	High Risk, n (%)	Lethal, n (%)	RAF in Ca	RAF in Co	Median %Global AFR in Ca (IQR)	Median %Global AFR in Co (IQR)
MEC	AAPC GWAS	1765	1648	67 (12)	69 (11)	328 (19) / 1296 (73)	179 (11) / 1280 (78)	341 (19)	730 (41)	391 (22)	195 (11)	11.4%	5.1%	81 (17)	80 (20)
SCCS	AAPC GWAS	250	513	62 (9)	59 (11)	20 (8) / 203 (81)	32 (6.2) / 422 (82)	75 (30)	90 (36)	46 (18)	23 (9.2)	15.0%	5.9%	88 (9.8)	88 (9.4)
PLCO	AAPC GWAS	231	240	68 (9)	63 (8.2)	19 (8.2) / 203 (88)	24 (10) / 210 (88)	115 (50)	56 (24)	37 (16)	15 (6.5)	10.4%	8.5%	82 (13)	83 (17)
CPS-II	AAPC GWAS	64	112	70 (8)	70 (9)	5 (7.8) / 59 (92)	3 (2.7) / 109 (97)	24 (38)	15 (23)	8 (12)	7 (11)	13.3%	5.8%	77 (21)	74 (21)
MDA	AAPC GWAS	527	437	60 (12)	58 (14)	132 (25) / 384 (73)	62 (14) / 372 (85)	113 (21)	183 (35)	170 (32)	16 (3)	13.5%	6.8%	84 (13)	85 (13)
IPCG	AAPC GWAS	353	157	57 (10)	52 (22)	80 (23) / 206 (58)	3 (1.9) / 3 (1.9)	133 (38)	77 (22)	122 (35)	0 (0)	15.0%	8.0%	82 (14)	85 (12)
LAAPC	AAPC GWAS	286	285	63 (12)	64 (11)	63 (22) / 223 (78)	24 (8.4) / 243 (85)	132 (46)	0 (0)	114 (40)	22 (7.7)	11.5%	5.3%	82 (14)	80 (20)
CaP Genes	AAPC GWAS	71	85	67 (10)	66 (10)	16 (23) / 55 (77)	8 (9.4) / 77 (91)	0 (0)	35 (49)	15 (21)	3 (4.2)	13.4%	7.6%	82 (12)	86 (14)
DCPC	AAPC GWAS	263	339	64 (14)	58 (14)	33 (13) / 122 (46)	27 (8) / 140 (41)	44 (17)	9 (3.4)	23 (8.7)	24 (9.1)	13.5%	7.1%	86 (18)	86 (19)
KCPCS	AAPC GWAS	141	75	59 (10)	53 (9.5)	27 (19) / 114 (81)	8 (11) / 67 (89)	47 (33)	40 (28)	32 (23)	6 (4.3)	16.0%	7.3%	82 (16)	80 (14)
GECAP	AAPC GWAS	224	89	62 (11)	62 (11)	50 (22) / 162 (72)	15 (17) / 69 (78)	78 (35)	69 (31)	52 (23)	6 (2.7)	12.5%	3.9%	83 (12)	84 (13)
NCPCS	AAPC GWAS	203	231	61 (9)	52 (14)	61 (30) / 142 (70)	5 (2.2) / 16 (6.9)	30 (15)	36 (18)	19 (9.4)	0 (0)	12.8%	5.6%	84 (13)	85 (13)
SELECT	AAPC GWAS	212	208	64 (11)	64 (10)	60 (28) / 133 (63)	31 (15) / 161 (77)	109 (51)	47 (22)	14 (6.6)	3 (1.4)	10.6%	5.5%	84 (14)	80 (18)
PCBP	AAPC GWAS	231	223	66 (14)	66 (13)	27 (12) / 135 (58)	15 (6.7) / 140 (63)	0 (0)	0 (0)	0 (0)	11 (4.8)	10.6%	5.4%	91 (7.4)	91 (9.9)
BioVU	ELLIPSE/ OncoArray	204	0	61 (11)	--	0 (0) / 0 (0)	--	1 (0.49)	54 (26)	94 (46)	2 (0.98)	12.0%	--	81 (17)	--
CPDR	ELLIPSE/ OncoArray	134	41	56 (11)	65 (2.9)	43 (32) / 69 (51)	4 (9.8) / 37 (90)	55 (41)	23 (17)	35 (26)	0 (0)	13.4%	6.1%	82 (14)	80 (18)
EPICAP	ELLIPSE/ OncoArray	20	9	65 (6.5)	62 (8)	6 (30) / 13 (65)	0 (0) / 8 (89)	0 (0)	0 (0)	1 (5)	3 (15)	7.5%	5.6%	21 (13)	18 (6.5)
Karuprostate	ELLIPSE/ OncoArray	363	386	67 (11)	60 (12)	140 (39) / 216 (60)	70 (18) / 309 (80)	110 (30)	127 (35)	109 (30)	0 (0)	16.7%	9.2%	94 (19)	93 (22)
MEC	ELLIPSE/ OncoArray	462	499	66 (12)	69 (10)	127 (27) / 295 (64)	38 (7.6) / 412 (83)	118 (26)	158 (34)	110 (24)	40 (8.7)	11.0%	4.9%	80 (19)	79 (21)

MOFFITT	ELLIPSE/ OncoArray	100	91	62 (11)	56 (10)	30 (30) / 70 (70)	6 (6.6) / 83 (91)	49 (49)	34 (34)	13 (13)	1 (1)	15.0%	8.2%	85 (15)	86 (10)
NMHS	ELLIPSE/ OncoArray	175	188	64 (12)	62 (10)	27 (15) / 148 (85)	32 (17) / 156 (83)	63 (36)	16 (9.1)	24 (14)	1 (0.57)	12.0%	6.6%	81 (14)	81 (14)
PCPT	ELLIPSE/ OncoArray	43	113	67 (7)	67 (7)	3 (7) / 40 (93)	17 (15) / 96 (85)	26 (60)	11 (26)	3 (7)	0 (0)	8.1%	2.2%	78 (20)	78 (18)
PCaP	ELLIPSE/ OncoArray	958	0	62 (12)	--	239 (25) / 719 (75)	--	446 (47)	242 (25)	94 (9.8)	72 (7.5)	12.3%	--	84 (14)	--
PROtEuS	ELLIPSE/ OncoArray	70	57	63 (9)	64 (10)	7 (10) / 63 (90)	7 (12) / 50 (88)	19 (27)	11 (16)	10 (14)	1 (1.4)	13.6%	7.0%	92 (12)	92 (17)
ProGene	ELLIPSE/ OncoArray	101	85	63 (11)	62 (13)	13 (13) / 81 (80)	8 (9.4) / 77 (91)	38 (38)	33 (33)	27 (27)	3 (3)	8.4%	1.2%	75 (80)	27 (78)
SCCS	ELLIPSE/ OncoArray	286	1468	58 (11)	61 (14)	61 (21) / 202 (71)	95 (6.5) / 1276 (87)	25 (8.7)	90 (31)	47 (16)	16 (5.6)	11.2%	6.8%	86 (12)	86 (11)
SCPCS	ELLIPSE/ OncoArray	57	32	71 (7)	68 (5.2)	14 (25) / 43 (75)	6 (19) / 26 (81)	27 (47)	12 (21)	14 (25)	0 (0)	11.4%	1.6%	89 (15)	89 (10)
SELECT	ELLIPSE/ OncoArray	27	166	64 (11)	60 (12)	6 (22) / 21 (78)	23 (14) / 139 (84)	9 (33)	9 (33)	2 (7.4)	0 (0)	24.1%	5.1%	84 (14)	82 (16)
SFPCS	ELLIPSE/ OncoArray	79	36	62 (11)	62 (7.5)	21 (27) / 58 (73)	6 (17) / 30 (83)	0 (0)	0 (0)	63 (80)	16 (20)	12.7%	6.9%	83 (13)	82 (12)
UGANDA	ELLIPSE/ OncoArray	560	480	70 (13)	65 (10)	54 (9.6) / 351 (63)	11 (2.3) / 437 (91)	43 (7.7)	50 (8.9)	229 (41)	167 (30)	14.1%	5.7%	99 (3)	99 (4)
UKGPCS	ELLIPSE/ OncoArray	365	0	63 (11)	--	58 (16) / 212 (58)	--	93 (25)	59 (16)	80 (22)	16 (4.4)	13.2%	--	94 (14)	--
SABOR	ELLIPSE/ OncoArray	105	103	63 (14)	64 (15)	0 (0) / 0 (0)	0 (0) / 0 (0)	32 (31)	18 (17)	14 (14)	0 (0)	12.1%	4.8%	83 (13)	83 (12)
WFPCS	ELLIPSE/ OncoArray	54	47	60 (11)	57 (13)	13 (24) / 40 (74)	2 (4.3) / 45 (96)	17 (31)	10 (19)	9 (17)	2 (3.7)	12.0%	5.3%	80 (15)	81 (13)
WUGS	ELLIPSE/ OncoArray	70	150	63 (14)	69 (5)	12 (17) / 57 (81)	15 (10) / 135 (90)	3 (4.3)	6 (8.6)	20 (29)	21 (30)	14.3%	3.0%	84 (9.7)	81 (15)
UM-PCGP	HRPCF	49	0	57 (9)	--	49 (100) / 0 (0)	--	--	--	--	--	17.3%	--	--	--
ICPCG	HRPCF	63	0	59 (12)	--	61 (97) / 1 (1.6)	--	--	--	--	--	15.9%	--	--	--
LSUHSC	HPC	20	0	64 (11)	--	20 (100) / 0 (0)	--	--	--	--	--	25.0%	--	--	--
PROGRESS	HPC	11	0	54 (6)	--	11 (100) / 0 (0)	--	--	--	--	--	18.2%	--	--	--

*AAPC GWAS = African Ancestry Prostate Cancer Genome-Wide Association Study; ELLIPSE = Elucidating Loci Involved in Prostate Cancer Susceptibility; HRPCF = High Risk Prostate Cancer Families; HPC = Hereditary Prostate Cancer; IQR=Interquartile range; FH+/FH-=Family history positive/negative; RAF=Risk allele frequency

Supplemental Table 3. Prostate cancer risk associated with germline variant rs72725854 by disease aggressiveness.

					Heterozygote Genotype			Homozygote Variant Genotype		
Group	n	Risk Allele Frequency	Carrier Frequency	Homozygote Genotype Frequency	Frequency	OR (95% CI)	P value	Frequency	OR (95% CI)	P value
Controls (reference group)	8595	6.0%	11.6%	88.3%	11.3%			0.35%		
Cases with low-risk disease	2415	11.4%	21.4%	78.6%	20.0%	1.97 (1.74-2.24)	6.6E-26	1.4%	4.84 (2.85-8.23)	5.6E-09
Cases with intermediate-risk disease	2350	13.0%	24.6%	75.4%	23.2%	2.41 (2.13-2.73)	1.5E-44	1.4%	5.22 (3.06-8.89)	1.2E-09
Cases with high-risk disease	2041	13.5%	25.4%	74.6%	23.8%	2.45 (2.16-2.79)	5.4E-42	1.6%	4.90 (2.88-8.34)	4.4E-09
Cases with lethal disease	692	13.8%	26.0%	74.0%	24.4%	2.65 (2.18-3.24)	4.8E-22	1.6%	7.95 (3.79-16.72)	4.4E-08

Low risk disease: Gleason<7, stage T1/T2, and PSA<10; Intermediate-risk disease: Gleason=7, stage T1/T2, and PSA=10–20 ng/ml;
High-risk disease: Gleason 8–10, stage T3/T4, PSA=20–100 ng/ml; Lethal disease: metastatic disease, PSA>100, or died of prostate cancer

Supplemental Table 4. Prostate cancer risk associated with germline variant rs72725854 and family history of prostate cancer.

Group	#Controls	#Cases	OR (95% CI)	P value
Non-carrier FH- (reference group)	5875	4747		
Non-carrier FH+	675	1304	2.15 (1.93–2.41)	6.8E-42
Heterozygote carrier FH-	728	1316	2.25 (2.02–2.51)	2.9E-48
Heterozygote carrier FH+	96	450	5.31 (4.19–6.73)	2.5E-43
Homozygote carrier FH-	22	72	3.85 (2.29–6.50)	4.1E-07
Homozygote carrier FH+	5	41	10.77 (4.15–27.95)	1.1E-06

FH+: Participants with at least 1 first or second-degree relative with prostate cancer; FH-: Participants with no family history of prostate cancer

Supplemental Table 5. Absolute risk (AR) of prostate cancer based on the log-additive effects of rs72725854 and family history. Effects shown in Supplemental Table 3 are used to calculate AR.

Group	#Controls	#Cases	AR at Age 60
Non-carrier FH- (reference group)	5875	4747	4.3% (4.1%-4.5%)
Non-carrier FH+	675	1304	9.0% (8.2%-9.8%)
Heterozygote carrier FH-	728	1316	9.0% (8.6%-10%
Heterozygote carrier FH+	96	450	21% (17%-25%)
Homozygote carrier FH-	22	72	16% (8.7%-23%)
Homozygote carrier FH+	5	41	38% (13%-65%)

FH+: Participants with at least 1 first or second-degree relative with prostate cancer; FH-: Participants with no family history of prostate cancer

Supplemental Table 6. Risk allele frequency of rs72725854 by African population. Study acronym is provided in parentheses or indicated in the footnote.

African Population	N	Risk Allele Frequency
Africa		
Botswana [1]	71	8.5%
Ghana [2]	634	7.7%
Uganda		
Kampala [3]	480	5.7%
Northwest [1]	197	4.1%
North-Central [1]		
Langi	233	3.7%
Acholi	81	2.5%
Democratic Republic of the Congo (FWI)	127	15.0%
Esan in Nigeria (ESN) [4]	99	6.1%
Gambian in Western Division (GWD) [4]	113	11.1%
Luhya in Webuye, Kenya (LWK) [4]	99	10.1%
Mende in Sierra Leone (MSL) [4]	85	7.6%
Yaruba in Ibadan, Nigeria (YRI) [4]	108	9.7%
North America		
Montreal, Canada (PROtEuS)	57	7.0%
United States	7,016	5.9%
Mid-Atlantic	198	7.6%
Southern/Southeastern	2,570	6.5%
South-Central	542	6.4%
African Ancestry in Southwest US (ASW) [4]	61	4.9%
Western	2,543	5.2%
Midwest	324	4.5%
Caribbean Islands		
Barbados (PCBP)	223	5.4%
African Caribbean in Barbados (ACB) [4]	96	6.2%
Guadeloupe (FWI)	259	6.4%

Risk allele frequencies are calculated in controls, with the exception of Botswana and 1000 Genomes, which did not have PCa status. Studies included in the United States: WUGS, WFPCS, SABOR, SFPCS, SELECT, SCPCS, SCCS, PCPT, NMHS, MOFFITT, MEC, CPDR, SELECT, NCPCS, GECAP, KCPCS, DCPC, CaP Genes, LAAPC, IPCG, MDA, CPS-II, PLCO. Studies included in the Mid-Atlantic US: CPDR, DCPC, IPCG. Studies included in Southern/Southeastern US: WFPCS, SCPCS, SCCS, NMHS, MOFFITT, NCPCS. Studies included in South-Central US: SABOR, MDA. Studies included in Western US: SFPCS, MEC, KCPCS, LAAPC. Studies included in Midwest US: WUGS, GECAP, CaP Genes.

[1]Botswana and North-Central Uganda frequencies are based on Gouveia et al., MBE 2020[33].

[2]Ghana frequencies are based on data from Conti et al., JNCI 2017[1].

[3]Ugandans from Kampala are from a PSA-screened population, with all controls having PSA<4 ng/mL, which may contribute to the lower frequency in this population.

[4]Risk allele frequencies are based on 1000 Genomes[12].

Supplemental Table 7. Prostate cancer risk associated with four other known African-ancestry 8q24 germline variants by family history[a] of prostate cancer and age at diagnosis.

SNP ID (position/risk allele/other allele)	Group	n	RAF	Carrier Freq.	Homozygote Genotype Freq.	Heterozygote Genotype			Homozygote Variant Genotype		
						Freq.	OR (95% CI)	P value	Freq.	OR (95% CI)	P value
rs7463326 (128027954/G/A)	Controls (reference group)	8595	84.0%	97.6%	2.4%	27.2%			70.4%		
	Cases	9052	87.0%	98.2%	1.8%	22.5%	1.09 (0.88–1.36)	0.4	75.7%	1.40 (1.13–1.74)	2.0E-03
	Cases FH+	1795	86.8%	98.3%	1.7%	23.1%	1.21 (0.81–1.82)	0.4	75.3%	1.55 (1.04–2.30)	0.03
	Cases FH-	6135	86.9%	98.2%	1.8%	22.6%	1.07 (0.83–1.37)	0.6	75.6%	1.35 (1.06–1.73)	0.01
	Cases Age Dx<60	2923	86.7%	97.9%	2.1%	22.3%	0.91 (0.65–1.27)	0.6	75.6%	1.18 (0.85–1.64)	0.3
	Cases Age Dx≥60	6129	87.1%	98.4%	1.6%	22.7%	1.16 (0.89–1.51)	0.3	75.7%	1.51 (1.16–1.96)	2.2E-03
	Cases FH+ & Age Dx<60	688	86.3%	97.7%	2.3%	22.7%	0.83 (0.46–1.48)	0.5	75.0%	1.10 (0.63–1.93)	0.7
rs72725879 (128103969/T/C)	Controls (reference group)	8595	34.0%	56.2%	43.8%	44.4%			11.8%		
	Cases	9052	42.1%	66.3%	33.7%	48.6%	1.42 (1.33–1.52)	2.9E-25	17.8%	1.97 (1.79–2.17)	8.2E-45
	Cases FH+	1795	42.9%	67.9%	32.1%	50.0%	1.55 (1.38–1.75)	1.5E-13	17.9%	2.09 (1.78–2.45)	1.4E-19
	Cases FH-	6135	41.9%	65.8%	34.2%	47.9%	1.38 (1.28–1.48)	1.7E-17	17.9%	2.01 (1.81–2.23)	2.2E-39
	Cases Age Dx<60	2923	44.1%	68.8%	31.2%	49.5%	1.50 (1.35–1.67)	2.3E-13	19.3%	2.09 (1.81–2.42)	2.8E-23
	Cases Age Dx≥60	6129	41.1%	65.1%	34.9%	48.1%	1.39 (1.28–1.50)	8.9E-17	17.0%	1.94 (1.74–2.17)	4.7E-32
	Cases FH+ & Age Dx<60	688	44.1%	68.6%	31.4%	49.0%	1.53 (1.26–1.85)	1.1E-05	19.6%	2.10 (1.64–2.70)	5.0E-09
rs7812894 (128520479/A/G)	Controls (reference group)	8595	16.0%	29.7%	70.3%	27.2%			2.4%		
	Cases	9052	18.1%	32.9%	67.1%	29.5%	1.14 (1.06–1.22)	1.8E-04	3.4%	1.50 (1.25–1.80)	1.7E-05
	Cases FH+	1795	17.9%	32.6%	67.4%	29.6%	1.14 (1.01–1.27)	0.03	3.1%	1.32 (0.97–1.81)	0.08
	Cases FH-	6135	18.3%	33.1%	66.9%	29.6%	1.14 (1.06–1.23)	4.1E-04	3.5%	1.55 (1.27–1.90)	1.8E-05
	Cases Age Dx<60	2923	19.0%	34.4%	65.6%	30.8%	1.17 (1.06–1.31)	3.1E-03	3.6%	1.56 (1.18–2.05)	1.5E-03
	Cases Age Dx≥60	6129	17.7%	32.2%	67.8%	28.9%	1.11 (1.03–1.21)	6.7E-03	3.2%	1.51 (1.22–1.87)	1.6E-04
	Cases FH+ & Age Dx<60	688	19.3%	35.5%	64.5%	32.4%	1.28 (1.06–1.53)	8.8E-03	3.1%	1.41 (0.86–2.31)	0.17
rs12549761 (128540776/C/G)	Controls (reference group)	8595	95.2%	99.7%	0.3%	9.0%			90.7%		
	Cases	9052	96.6%	99.8%	0.2%	6.3%	1.04 (0.55–1.94)	0.9	93.5%	1.58 (0.86–2.89)	0.14
	Cases FH+	1795	96.8%	99.9%	0.1%	6.2%	2.04 (0.46–9.13)	0.4	93.6%	3.24 (0.76–13.75)	0.11
	Cases FH-	6135	96.6%	99.7%	0.3%	6.4%	0.78 (0.40–1.51)	0.5	93.4%	1.23 (0.66–2.31)	0.5
	Cases Age Dx<60	2923	96.8%	99.9%	0.1%	6.1%	1.71 (0.45–6.45)	0.4	93.8%	2.50 (0.70–8.93)	0.16
	Cases Age Dx≥60	6129	96.5%	99.8%	0.2%	6.4%	0.87 (0.44–1.75)	0.7	93.3%	1.36 (0.69–2.66)	0.4
	Cases FH+ & Age Dx<60	688	96.7%	99.9%	0.1%	6.3%	0.38 (0.04–3.49)	0.4	93.6%	1.35 (0.16–11.54)	0.8

[a]Family history in non-familial cases and controls includes first- or second-degree relatives with prostate cancer.

Supplemental Table 8. Association between genetic risk scores and prostate cancer by family history[a] of prostate cancer and age at diagnosis.

Group	GRS Category	Full GRS (180 SNPs)				Full GRS Minus rs72725854 (179 SNPs)				8q24 GRS (5 AFR SNPs)				8q24 GRS Minus rs72725854 (4 AFR SNPs)			
		nCo	nCa	OR (95% CI)	P	nCo	nCa	OR (95% CI)	P	nCo	nCa	OR (95% CI)	P	nCo	nCa	OR (95% CI)	P
Cases vs. Controls	0% - 10%	861	302	0.4 (0.34–0.47)	2.1E-28	861	326	0.4 (0.34–0.47)	7.4E-29	879	469	0.55 (0.48–0.64)	2.1E-15	918	556	0.57 (0.5–0.65)	1.1E-16
	10% - 20%	859	422	0.54 (0.47–0.63)	1.1E-15	859	476	0.59 (0.51–0.68)	6.5E-13	1502	1166	0.77 (0.69–0.86)	3.9E-06	1697	1410	0.74 (0.67–0.82)	5.8E-09
	20% - 30%	859	569	0.72 (0.63–0.83)	4.2E-06	859	617	0.75 (0.66–0.86)	5.1E-05	198	164	0.84 (0.65–1.07)	0.15	64	66	0.95 (0.65–1.39)	0.8
	30% - 40%	859	645	0.86 (0.75–0.99)	0.03	859	692	0.88 (0.77–1.01)	0.06	902	705	0.83 (0.73–0.95)	6.0E-03	759	685	0.83 (0.73–0.94)	4.8E-03
	40% - 60%	1719	1532	REF		1719	1623	REF		1707	1720	REF		2195	2453	REF	
	60% - 70%	859	996	1.3 (1.15–1.47)	4.2E-05	859	1002	1.22 (1.08–1.38)	1.6E-03	857	798	0.94 (0.83–1.08)	0.4	581	692	1.12 (0.97–1.29)	0.13
	70% - 80%	859	1104	1.44 (1.27–1.63)	8.2E-09	859	1173	1.42 (1.26–1.6)	2.0E-08	1124	1359	1.24 (1.1–1.38)	2.8E-04	665	659	0.92 (0.8–1.05)	0.2
	80% - 90%	859	1401	1.89 (1.68–2.13)	1.6E-25	859	1380	1.72 (1.53–1.94)	4.5E-19	604	822	1.39 (1.21–1.59)	3.1E-06	1217	1702	1.27 (1.15–1.41)	3.4E-06
	90% - 100%	861	2078	2.84 (2.53–3.18)	2.9E-70	861	1760	2.28 (2.03–2.56)	5.2E-44	822	1846	2.33 (2.08–2.62)	9.4E-47	499	829	1.54 (1.35–1.77)	5.2E-10
FH+ Cases vs. Controls	0% - 10%	861	57	0.38 (0.28–0.53)	6.9E-09	861	59	0.35 (0.25–0.48)	5.3E-11	879	83	0.48 (0.36–0.64)	3.3E-07	918	104	0.49 (0.38–0.63)	3.3E-08
	10% - 20%	859	59	0.39 (0.28–0.54)	1.1E-08	859	73	0.42 (0.31–0.56)	8.6E-09	1502	207	0.68 (0.55–0.84)	3.6E-04	1697	256	0.65 (0.54–0.78)	4.7E-06
	20% - 30%	859	85	0.56 (0.42–0.75)	7.5E-05	859	94	0.56 (0.43–0.74)	3.9E-05	198	28	0.83 (0.52–1.33)	0.4	64	11	0.84 (0.4–1.76)	0.7
	30% - 40%	859	112	0.75 (0.58–0.98)	0.04	859	131	0.82 (0.64–1.04)	0.10	902	140	0.87 (0.68–1.1)	0.2	759	138	0.83 (0.66–1.04)	0.11
	40% - 60%	1719	306	REF		1719	332	REF		1707	333	REF		2195	502	REF	
	60% - 70%	859	198	1.37 (1.1–1.71)	5.3E-03	859	214	1.25 (1–1.55)	0.045	857	166	1.08 (0.86–1.35)	0.5	581	140	1.2 (0.94–1.53)	0.14
	70% - 80%	859	213	1.6 (1.29–1.98)	2.1E-05	859	222	1.37 (1.11–1.7)	3.3E-03	1124	268	1.26 (1.03–1.55)	0.02	665	155	1.11 (0.89–1.39)	0.3
	80% - 90%	859	306	2.2 (1.8–2.7)	2.9E-14	859	282	1.8 (1.47–2.2)	1.1E-08	604	162	1.44 (1.14–1.82)	2.4E-03	1217	339	1.23 (1.03–1.47)	0.02
	90% - 100%	861	458	3.34 (2.77–4.04)	9.5E-36	861	387	2.47 (2.04–2.98)	1.2E-20	822	407	2.71 (2.24–3.27)	5.3E-25	499	150	1.43 (1.14–1.8)	2.4E-03
FH- Cases vs. Controls	0% - 10%	861	207	0.39 (0.33–0.47)	8.2E-23	861	227	0.41 (0.34–0.49)	4.4E-22	879	334	0.58 (0.49–0.68)	3.6E-11	918	389	0.59 (0.5–0.68)	3.7E-12
	10% - 20%	859	306	0.55 (0.47–0.65)	3.1E-12	859	340	0.62 (0.53–0.72)	3.5E-09	1502	821	0.8 (0.71–0.9)	3.8E-04	1697	982	0.77 (0.69–0.86)	3.7E-06
	20% - 30%	859	423	0.77 (0.66–0.9)	9.6E-04	859	454	0.8 (0.69–0.93)	4.6E-03	198	104	0.82 (0.62–1.08)	0.15	64	49	1.02 (0.67–1.56)	0.9
	30% - 40%	859	457	0.89 (0.77–1.04)	0.13	859	477	0.91 (0.78–1.05)	0.2	902	480	0.81 (0.7–0.94)	5.6E-03	759	450	0.81 (0.7–0.93)	4.0E-03
	40% - 60%	1719	1048	REF		1719	1105	REF		1707	1165	REF		2195	1644	REF	
	60% - 70%	859	657	1.25 (1.08–1.43)	2.0E-03	859	650	1.19 (1.03–1.37)	0.02	857	540	0.92 (0.8–1.06)	0.3	581	464	1.15 (0.99–1.35)	0.08
	70% - 80%	859	755	1.42 (1.23–1.62)	7.1E-07	859	783	1.4 (1.22–1.61)	1.1E-06	1124	916	1.26 (1.11–1.43)	3.6E-04	665	429	0.84 (0.72–0.98)	0.02
	80% - 90%	859	908	1.81 (1.59–2.07)	1.8E-18	859	919	1.73 (1.52–1.98)	3.1E-16	604	550	1.35 (1.16–1.58)	9.3E-05	1217	1137	1.3 (1.16–1.46)	5.5E-06
	90% - 100%	861	1372	2.74 (2.41–3.11)	8.5E-55	861	1178	2.29 (2.02–2.61)	5.4E-37	822	1224	2.28 (2.01–2.58)	4.7E-37	499	591	1.63 (1.4–1.89)	1.5E-10
Age Dx <60 Cases vs. Controls	0% - 10%	861	75	0.35 (0.26–0.49)	1.2E-10	861	77	0.35 (0.25–0.47)	2.6E-11	879	142	0.59 (0.45–0.76)	4.7E-05	918	179	0.61 (0.49–0.77)	2.1E-05
	10% - 20%	859	90	0.47 (0.35–0.63)	3.8E-07	859	117	0.54 (0.41–0.7)	4.4E-06	1502	331	0.71 (0.58–0.86)	5.9E-04	1697	410	0.68 (0.57–0.8)	7.2E-06
	20% - 30%	859	155	0.78 (0.61–1)	0.047	859	182	0.86 (0.68–1.08)	0.2	198	43	0.73 (0.46–1.15)	0.17	64	22	0.84 (0.44–1.59)	0.6
	30% - 40%	859	183	0.85 (0.67–1.08)	0.19	859	197	0.88 (0.7–1.1)	0.3	902	213	0.83 (0.67–1.04)	0.11	759	203	0.71 (0.57–0.88)	2.3E-03
	40% - 60%	1719	445	REF		1719	481	REF		1707	515	REF		2195	796	REF	
	60% - 70%	859	319	1.39 (1.13–1.72)	1.9E-03	859	328	1.24 (1.01–1.52)	0.04	857	233	0.9 (0.72–1.13)	0.4	581	223	0.99 (0.78–1.26)	0.9
	70% - 80%	859	349	1.35 (1.09–1.66)	5.1E-03	859	382	1.47 (1.2–1.8)	1.8E-04	1124	436	1.23 (1.02–1.49)	0.03	665	202	0.92 (0.73–1.14)	0.4
	80% - 90%	859	474	2 (1.64–2.43)	3.0E-12	859	473	1.86 (1.53–2.25)	3.1E-10	604	281	1.41 (1.13–1.76)	2.3E-03	1217	595	1.29 (1.1–1.52)	1.9E-03
	90% - 100%	861	832	3.18 (2.66–3.8)	2.9E-37	861	684	2.37 (1.98–2.84)	5.5E-21	822	728	2.77 (2.31–3.31)	1.3E-28	499	293	1.56 (1.26–1.93)	3.4E-05
Age Dx ≥60 Cases vs. Controls	0% - 10%	861	227	0.4 (0.33–0.49)	1.7E-21	861	249	0.41 (0.34–0.49)	7.8E-22	879	327	0.54 (0.46–0.64)	1.3E-12	918	377	0.56 (0.48–0.65)	3.2E-13
	10% - 20%	859	332	0.56 (0.48–0.67)	3.8E-11	859	359	0.59 (0.5–0.7)	5.8E-10	1502	835	0.78 (0.69–0.89)	2.3E-04	1697	1000	0.78 (0.69–0.87)	1.6E-05
	20% - 30%	859	414	0.71 (0.6–0.83)	2.5E-05	859	435	0.71 (0.61–0.83)	2.6E-05	198	121	0.87 (0.65–1.15)	0.3	64	44	0.96 (0.61–1.51)	0.9
	30% - 40%	859	462	0.86 (0.74–1.01)	0.06	859	495	0.88 (0.75–1.02)	0.09	902	492	0.82 (0.7–0.95)	9.0E-03	759	482	0.88 (0.76–1.02)	0.10
	40% - 60%	1719	1087	REF		1719	1142	REF		1707	1205	REF		2195	1657	REF	
	60% - 70%	859	677	1.28 (1.11–1.48)	9.4E-04	859	674	1.2 (1.04–1.39)	0.02	857	565	0.95 (0.82–1.1)	0.5	581	469	1.22 (1.04–1.44)	0.02
	70% - 80%	859	755	1.46 (1.27–1.69)	1.9E-07	859	791	1.37 (1.19–1.57)	1.6E-05	1124	923	1.26 (1.1–1.43)	6.6E-04	665	457	0.9 (0.77–1.05)	0.2
	80% - 90%	859	927	1.89 (1.64–2.17)	3.0E-19	859	907	1.7 (1.48–1.95)	5.9E-14	604	541	1.4 (1.19–1.64)	3.6E-05	1217	1107	1.29 (1.14–1.45)	3.0E-05
	90% - 100%	861	1246	2.61 (2.28–2.98)	6.3E-45	861	1076	2.17 (1.89–2.48)	2.8E-29	822	1118	2.12 (1.86–2.42)	2.3E-28	499	536	1.6 (1.37–1.88)	4.9E-09
FH+ & Age Dx <60 Cases vs. Controls	0% - 10%	861	17	0.32 (0.18–0.58)	1.9E-04	861	19	0.33 (0.19–0.58)	8.8E-05	879	29	0.49 (0.3–0.79)	3.4E-03	918	39	0.59 (0.39–0.89)	0.01
	10% - 20%	859	11	0.21 (0.1–0.43)	3.1E-05	859	13	0.18 (0.08–0.38)	7.4E-06	1502	70	0.56 (0.39–0.81)	2.3E-03	1697	94	0.66 (0.49–0.91)	9.6E-03
	20% - 30%	859	26	0.55 (0.33–0.91)	019	859	37	0.63 (0.4–1)	0.05	198	9	1.01 (0.48–2.14)	0.98	64	5	1.16 (0.4–3.38)	0.8
	30% - 40%	859	42	0.79 (0.51–1.22)	0.3	859	47	0.76 (0.5–1.15)	0.2	902	53	0.84 (0.56–1.26)	0.4	759	52	0.8 (0.54–1.18)	0.3
	40% - 60%	1719	115	REF		1719	122	REF		1707	120	REF		2195	187	REF	
	60% - 70%	859	74	1.47 (1.02–2.12)	0.04	859	87	1.21 (0.85–1.72)	0.3	857	54	0.93 (0.63–1.38)	0.7	581	43	0.85 (0.54–1.34)	0.5
	70% - 80%	859	76	1.4 (0.97–2.03)	0.07	859	75	1.23 (0.86–1.75)	0.3	1124	108	1.28 (0.92–1.78)	0.15	665	61	1.24 (0.86–1.79)	0.2
	80% - 90%	859	120	2.13 (1.52–2.97)	9.1E-06	859	111	1.8 (1.3–2.5)	4.6E-04	604	68	1.45 (0.98–2.13)	0.06	1217	142	1.35 (1.01–1.79)	0.04
	90% - 100%	861	207	3.27 (2.41–4.42)	1.6E-14	861	176	2.38 (1.76–3.21)	1.4E-08	822	177	2.69 (1.98–3.64)	2.2E-10	499	65	1.72 (1.2–2.47)	2.9E-03

[a]Family history in non-familial cases and controls includes first- or second-degree relatives with prostate cancer.

Supplemental Table 9. Proportion of familial relative risk (FRR) explained by known PCa variants in men of African ancestry.

Genetic Loci	Proportion FRR (RR=2.0)	Proportion FRR (RR=2.5)	% of Total FRR
rs72725854 at 8q24	12%	9.2%	32%
5 8q24 African Ancestry Variants	18%	14%	49%
14 Known 8q24 Variants*	21%	16%	57%
Remaining 166 (non-8q24) PCa Variants	16%	12%	43%
Total 180 Known PCa Variants	38%	29%	100%

* Includes 12 8q24 variants associated with PCa in men of European ancestry, 3 of which are also associated with PCa in men of African ancestry, and 2 additional variants only associated with PCa in men of African ancestry.

Supplemental Table 10. Proportion of familial relative risk (FRR) explained by each of 180 known PCa variants in men of African ancestry.

Chr	Position	rsid	Prop FRR (RR=2.0)	Prop FRR (RR=2.5)	% of Total FRR
8	128074815 †	rs72725854	12%	9.2%	32%
8	128103969 †¥	rs72725879	4.4%	3.3%	12%
11	69002342	rs11228580	1.8%	1.4%	4.8%
8	128103979 ¥	rs5013678	0.97%	0.73%	2.6%
6	117199790	rs630045	0.94%	0.71%	2.5%
13	110360784	rs75823044	0.85%	0.64%	2.3%
8	128413305 ¥	rs6983267	0.80%	0.60%	2.1%
22	28374943	rs78554043	0.78%	0.59%	2.1%
8	128027954 †	rs7463326	0.72%	0.55%	1.9%
8	128021752 ¥	rs1487240	0.70%	0.53%	1.9%
8	23525358	rs11782388	0.64%	0.48%	1.7%
8	128520479 †¥	rs7812894	0.58%	0.44%	1.6%
2	63277843	rs58235267	0.56%	0.43%	1.5%
8	128540776 †¥	rs12549761	0.53%	0.40%	1.4%
6	160581543	rs4646284	0.51%	0.38%	1.3%
22	43500212	rs5759167	0.44%	0.33%	1.2%
5	1889346	rs199577062	0.42%	0.31%	1.1%
11	68980335	rs4620729	0.38%	0.29%	1.0%
10	51549496	rs10993994	0.37%	0.28%	0.99%
6	76495882	rs9443189	0.36%	0.27%	0.95%
17	47398244		0.34%	0.26%	0.91%
4	106064626		0.33%	0.25%	0.87%
3	87172632	rs7642887	0.33%	0.25%	0.87%
8	128342866 ¥	rs17464492	0.32%	0.24%	0.85%
7	27975919	rs67152137	0.29%	0.22%	0.78%
8	127910317 ¥	rs1914295	0.28%	0.21%	0.75%
19	51361382	rs61752561	0.27%	0.20%	0.71%
2	85767735	rs2028900	0.26%	0.20%	0.70%
11	2233574	rs7127900	0.26%	0.20%	0.69%
9	110145833		0.26%	0.19%	0.68%
X	51245276	rs11338635	0.24%	0.18%	0.63%
5	1291331	rs11414507	0.22%	0.17%	0.60%
2	20878820	rs7255	0.22%	0.16%	0.57%
10	126650696	rs11245446	0.20%	0.15%	0.53%
5	1284135	rs4449583	0.19%	0.14%	0.50%
12	133067989	rs7295014	0.15%	0.11%	0.40%
19	38735804	rs11667256	0.14%	0.11%	0.37%
5	1285974	rs7705526	0.14%	0.10%	0.36%
11	113700546	rs56969947	0.13%	0.10%	0.36%
18	60961193	rs11381388	0.13%	0.10%	0.35%
7	47486259	rs145961284	0.13%	0.09%	0.33%
3	170083629	rs61436251	0.12%	0.09%	0.33%
17	618039	rs2474694	0.12%	0.09%	0.33%
1	150772613	rs1811698	0.12%	0.09%	0.33%
13	73714290	rs7996468	0.12%	0.09%	0.33%
17	36099952	rs10908278	0.12%	0.09%	0.32%
2	242151791	rs62187431	0.12%	0.09%	0.31%
1	88210715	rs56391074	0.12%	0.09%	0.31%
20	62374389	rs1058319	0.10%	0.08%	0.28%
12	14416918	rs10845938	0.10%	0.08%	0.27%
11	102396607	rs12285347	0.10%	0.08%	0.27%
2	173318244	rs114161133	0.10%	0.07%	0.26%
7	1944537		0.09%	0.07%	0.24%
4	95544718	rs6853490	0.08%	0.06%	0.23%
2	174234547	rs34925593	0.08%	0.06%	0.22%
17	7803118	rs28441558	0.08%	0.06%	0.22%
6	41525739	rs10947980	0.08%	0.06%	0.21%
19	51360840	rs62113212	0.08%	0.06%	0.21%
12	114666202	rs10774740	0.07%	0.06%	0.19%
3	170074374	rs57508070	0.07%	0.06%	0.19%
14	69126744	rs7141529	0.07%	0.06%	0.19%

12	53268073	rs147181250	0.07%	0.05%	0.19%
X	9807589	rs4830660	0.07%	0.05%	0.19%
12	12871099	rs2066827	0.07%	0.05%	0.17%
19	41985587	rs11672691	0.07%	0.05%	0.17%
20	49509184	rs17790938	0.06%	0.05%	0.17%
12	49676010	rs10875943	0.06%	0.05%	0.17%
1	154980351	rs56103503	0.06%	0.05%	0.17%
6	11217897	rs2018336	0.06%	0.05%	0.16%
5	44328731	rs10055386	0.06%	0.05%	0.16%
7	20994491	rs12155172	0.06%	0.04%	0.15%
11	61908440	rs2277283	0.06%	0.04%	0.15%
3	113277105	rs7639565	0.05%	0.04%	0.13%
9	34049779	rs10122495	0.05%	0.03%	0.12%
17	69104938	rs7222314	0.04%	0.03%	0.12%
16	82178893	rs199737822	0.04%	0.03%	0.11%
6	153430305		0.04%	0.03%	0.10%
8	25892142	rs11135910	0.04%	0.03%	0.10%
14	37138294	rs11629412	0.04%	0.03%	0.10%
6	160181878	rs2342478	0.04%	0.03%	0.10%
1	153899900	rs34579442	0.04%	0.03%	0.10%
17	36074979	rs11649743	0.04%	0.03%	0.10%
12	90160530	rs5799921	0.04%	0.03%	0.09%
6	30098259		0.03%	0.03%	0.09%
5	133836209	rs10793821	0.03%	0.02%	0.09%
11	76260543	rs11290954	0.03%	0.02%	0.08%
6	43694598	rs4711748	0.03%	0.02%	0.08%
19	51355650	rs266863	0.03%	0.02%	0.08%
19	17214073	rs11666569	0.03%	0.02%	0.08%
1	204556990	rs55664108	0.03%	0.02%	0.08%
3	106962521	rs1283104	0.03%	0.02%	0.08%
11	7556577	rs12791447	0.03%	0.02%	0.08%
17	36047417	rs3110641	0.03%	0.02%	0.07%
6	32400939	rs3129859	0.02%	0.02%	0.07%
2	8597123	rs62106670	0.02%	0.02%	0.06%
16	57654576	rs11863709	0.02%	0.02%	0.06%
3	152004202	rs182314334	0.02%	0.02%	0.06%
9	22041998	rs17694493	0.02%	0.02%	0.06%
1	205731166	rs34848415	0.02%	0.02%	0.05%
5	172955855	rs6860868	0.02%	0.02%	0.05%
20	31347512	rs11480453	0.02%	0.02%	0.05%
18	51772473	rs8093601	0.02%	0.01%	0.05%
18	53230859	rs28607662	0.02%	0.01%	0.05%
10	854691	rs141536087	0.02%	0.01%	0.04%
3	127948958	rs34834087	0.02%	0.01%	0.04%
10	104398895	rs12764219	0.01%	0.01%	0.04%
2	202123479	rs59308963	0.01%	0.01%	0.04%
4	74349158	rs1894292	0.01%	0.01%	0.04%
5	1287194	rs2853677	0.01%	0.01%	0.04%
6	34793124	rs9469899	0.01%	0.01%	0.04%
1	150563440	rs11352831	0.01%	0.01%	0.03%
14	53409931		0.01%	0.01%	0.03%
18	73036165	rs10460109	0.01%	0.01%	0.03%
X	66865496	rs5919402	0.01%	0.01%	0.03%
3	141093285	rs7624084	0.01%	0.01%	0.03%
9	19055965	rs1048169	0.01%	0.01%	0.03%
11	7547587	rs61890184	0.01%	0.01%	0.03%
2	111893096	rs11691517	0.01%	0.01%	0.03%
20	52455205	rs6091758	0.01%	0.01%	0.03%
7	40875192	rs17621345	0.01%	0.01%	0.03%
17	30098749	rs142444269	0.01%	0.01%	0.03%
X	11482634	rs17321482	0.01%	0.01%	0.03%
10	90195149	rs1935581	0.01%	0.01%	0.02%
2	10138585		0.01%	0.01%	0.02%
18	76770820	rs9959454	0.01%	0.01%	0.02%
2	238358584	rs60079197	0.01%	0.01%	0.02%
14	71091142	rs11158871	0.01%	0.01%	0.02%

15	40922915	rs4924487	0.01%	0.01%	0.02%
22	40428706	rs6001723	0.01%	<0.01%	0.02%
22	19749525	rs1978060	0.01%	<0.01%	0.02%
10	122796182	rs1004934	0.01%	<0.01%	0.02%
10	114712154	rs7094871	0.01%	<0.01%	0.01%
6	32192331	rs3096702	0.01%	<0.01%	0.01%
7	97817321	rs11763970	0.01%	<0.01%	0.01%
5	177968915	rs4976790	0.01%	<0.01%	0.01%
14	64693912	rs58262369	0.01%	<0.01%	0.01%
2	43637998	rs7591218	<0.01%	<0.01%	0.01%
8	128114146 ¥	rs78511380	<0.01%	<0.01%	0.01%
11	47421962	rs59111863	<0.01%	<0.01%	0.01%
14	23305649	rs1004030	<0.01%	<0.01%	0.01%
12	48365265	rs4760607	<0.01%	<0.01%	0.01%
6	160779134	rs641990	<0.01%	<0.01%	0.01%
11	134266372	rs878987	<0.01%	<0.01%	0.01%
10	46082985	rs76934034	<0.01%	<0.01%	0.01%
12	65012824	rs7968403	<0.01%	<0.01%	0.01%
8	23440180	rs11135749	<0.01%	<0.01%	<0.01%
7	20414110	rs11452686	<0.01%	<0.01%	<0.01%
4	95487714	rs2452593	<0.01%	<0.01%	<0.01%
6	32988695	rs9296068	<0.01%	<0.01%	<0.01%
6	30601232	rs12665339	<0.01%	<0.01%	<0.01%
18	56746315	rs12956892	<0.01%	<0.01%	<0.01%
11	1507512	rs1881502	<0.01%	<0.01%	<0.01%
9	132576060	rs1182	<0.01%	<0.01%	<0.01%
15	66764641	rs112293876	<0.01%	<0.01%	<0.01%
20	61008583	rs11204424	<0.01%	<0.01%	<0.01%
22	43525176	rs909666	<0.01%	<0.01%	<0.01%
X	52695895	rs5943724	<0.01%	<0.01%	<0.01%
19	32167803	rs118005503	<0.01%	<0.01%	<0.01%
4	74442349	rs17804499	<0.01%	<0.01%	<0.01%
19	42700947	rs61088131	<0.01%	<0.01%	<0.01%
6	109279211	rs12209480	<0.01%	<0.01%	<0.01%
2	10756343		<0.01%	<0.01%	<0.01%
X	70142030	rs5937025	<0.01%	<0.01%	<0.01%
17	56456120	rs2680708	<0.01%	<0.01%	<0.01%
11	66951965	rs12785905	<0.01%	<0.01%	<0.01%
2	66652885*	rs74702681	0%	0%	0%
2	242135265*	rs77559646	0%	0%	0%
2	242139600*	rs77482050	0%	0%	0%
3	169093100*	rs142436749	0%	0%	0%
5	1292118*	rs71595003	0%	0%	0%
5	169172133*	rs76551843	0%	0%	0%
8	128077146 ¥*	rs77541621	0%	0%	0%
8	128103466 ¥*	rs190257175	0%	0%	0%
8	128104117 ¥*	rs183373024	0%	0%	0%
11	58919922*		0%	0%	0%
11	108143456*	rs1800057	0%	0%	0%
11	125054793*	rs138466039	0%	0%	0%
15	56385868*	rs33984059	0%	0%	0%
21	42897136*	rs145013758	0%	0%	0%
22	28888939*	rs9625483	0%	0%	0%

† 8q24 variant associated with PCa in men of African ancestry

¥ 8q24 variant associated with PCa in men of European ancestry

* Very rare or monomorphic in African ancestry populations

Supplementary Note

This work was support by NIH grants U19CA214253, R01CA165862, U19 CA148537, and K99CA246063. This work is also supported by the Achievement Rewards for College Scientists Foundation Los Angeles Founder Chapter

The AAPC studies were supported as follows:

MEC: The MEC and the genotyping in this study were supported by NIH grants CA63464, CA54281, CA1326792, CA148085 and HG004726. Cancer incidence data for the MEC and LAAPC studies have been collected by the Los Angeles Cancer Surveillance Program of the University of Southern California with Federal funds from the NCI, NIH, Department of Health and Human Services, under Contract No. N01-PC-35139, and the California Department of Health Services as part of the state-wide cancer reporting program mandated by California Health and Safety Code Section 103885, and grant number 1U58DP000807-3 from the Centers for Disease Control and Prevention.

PLCO: Genotyping of the **PLCO** samples was funded by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, NCI, NIH. The authors thank Drs. Christine Berg and Philip Prorok, Division of Cancer Prevention at the National Cancer Institute, the screening center investigators and staff of the PLCO Cancer Screening Trial for their contributions to the PLCO Cancer Screening Trial. We thank Mr. Thomas Riley, Mr. Craig Williams, Mr. Matthew Moore, and Ms. Shannon Merkle at Information Management Services, Inc., for their management of the data and Ms. Barbara O'Brien and staff at Westat, Inc. for their contributions to the PLCO Cancer

Screening Trial. We also thank the PLCO study participants for their contributions to making this study possible.

MDA: MDA was support by grants, CA68578, ES007784, DAMD W81XWH-07-1-0645, and CA140388.

LAAPC was funded by grant 99-00524V-10258 from the Cancer Research Fund, under Interagency Agreement #97-12013 (University of California contract #98-00924V) with the Department of Health Services Cancer Research Program. Cancer incidence data for the MEC and LAAPC studies have been collected by the Los Angeles Cancer Surveillance Program of the University of Southern California with Federal funds from the NCI, NIH, Department of Health and Human Services, under Contract No. N01-PC-35139, and the California Department of Health Services as part of the state-wide cancer reporting program mandated by California Health and Safety Code Section 103885, and grant number 1U58DP000807-3 from the Centers for Disease Control and Prevention

KCPCS was supported by NIH grants CA056678, CA082664 and CA092579, with additional support from the Fred Hutchinson Cancer Research Center. We thank the participants in these studies, and Ms. Suzanne Kolb for help with study management.

GECAP was supported by NIH grant ES011126.

CaP Genes was supported by CA88164 and CA127298.

IPCG was supported by the generous support from donors to The Patrick C. Walsh Hereditary Prostate Cancer Research Program at The Brady Urological Institute.

DCPC was supported by NIH grant S06GM08016 and DOD grants DAMD W81XWH-07-1-0203, DAMD W81XWH-06-1-0066 and DOD W81XWH-10-1-0532.

CPS-II is supported by the American Cancer Society.

PCBP: PCBP was supported by NHGRI contract N01HG25487 and NCI grant R01CA114379

SCPCS: SCPCS is funded by CDC grant S1135-19/19, and SCPCS sample preparation was conducted at the Epidemiology Biospecimen Core Lab that is supported in part by the Vanderbilt-Ingram Cancer Center (P30 CA68485).

SELECT is funded by Public Health Service cooperative Agreement grant CA37429 awarded by the National Cancer Institute as well as 5UM1CA182883 from the Office of Dietary Supplements at the National Institutes of Health. The authors thank the site investigators and staff and, most importantly, the participants from SELECT who donated their time to this trial.

SCCS is funded by NIH grant CA092447. SCCS sample preparation was conducted at the Epidemiology Biospecimen Core Lab that is supported in part by the Vanderbilt Ingram Cancer Center (CA68485). Data on SCCS cancer cases used in this publication were provided by the Alabama Statewide Cancer Registry; Kentucky Cancer Registry; Tennessee Department of Health, Office of Cancer Surveillance; Florida Cancer Data System; North Carolina Central Cancer Registry, North Carolina Division of Public Health; Georgia Comprehensive Cancer Registry; Louisiana Tumor Registry; Mississippi Cancer Registry; South Carolina Central Cancer Registry; Virginia Department of Health, Virginia Cancer Registry; Arkansas Department of Health, Cancer Registry. The Arkansas Central Cancer Registry is fully funded by a grant from National Program of Cancer Registries, Centers for Disease Control and Prevention (CDC). Data on SCCS cancer cases from Mississippi were collected by the Mississippi

Cancer Registry which participates in the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the CDC or the Mississippi Cancer Registry.

The ELLIPSE/PRACTICAL OncoArray studies in men of African ancestry were supported as follows:

CeRePP: The authors thank Cecile Gaffory for technical assistance.

Karuprostate: The Karuprostate study was supported by the French National Health Directorate and by the Association pour la Recherche sur les Tumeurs de la Prostate. Séverine Ferdinand.

MEC: The MEC was support by NIH grants CA63464, CA54281 and CA098758.

MIAMI (WFPCS): WFPCS was supported by a grant from the American Cancer Society (No. CNE-101119 to J.J.H.), a pilot grant from the Comprehensive Cancer Center of Wake Forest University (CA12197 to J.J.H.) and a grant from the National Research Foundation to the Wake Forest University's General Clinical Research Center (M01-RR07122). The authors are grateful to study participants. We also want to acknowledge the contributions of Frank M.Torti, MD; Robert Lee, MD; Charles J.Rosser, MD; Dean G.Assimos, MD; Elizabeth Albertson, MD; Dominck J.Carbone, MD; William Rice, MD; Francis O'Brien, MD; Ray Morrow, MD; Franklyn Millman, MD; Nadine Shelton, Joel Anderson, Shirley Cothren, Eunkyung Chang, the General Clinical Research Center, the Urology Clinic and the Internal Medicine Clinic.

MOFFITT: The Moffitt group was supported by the US National Cancer Institute (R01CA128813, PI: J.Y. Park).

NMHS: Funding for the Nashville Men's Health Study (NMHS) was provided by the National Institutes of Health Grant numbers: RO1CA121060

PLCO: Genotyping of the PLCO samples was funded by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, NCI, NIH. The authors thank Drs. Christine Berg and Philip Prorok, Division of Cancer Prevention at the National Cancer Institute, the screening center investigators and staff of the PLCO Cancer Screening Trial for their contributions to the PLCO Cancer Screening Trial. We thank Mr. Thomas Riley, Mr. Craig Williams, Mr. Matthew Moore, and Ms. Shannon Merkle at Information Management Services, Inc., for their management of the data and Ms. Barbara O'Brien and staff at Westat, Inc. for their contributions to the PLCO Cancer Screening Trial. We also thank the PLCO study participants for their contributions to making this study possible.

SFPCS: SFPCS was funded by grant 99-00527V-10182 from the California Cancer Research Fund under Interagency Agreement #97-12013 (University of California contract #98-00924V) with the Department of Health Services Cancer Research Program. Cancer incidence data used in this study have been collected by the Greater Bay Area Cancer Registry of the Cancer Prevention Institute of California under contract N01-PC-35136 with the National Cancer Institute and with support of the California Cancer Registry, a project of the Cancer Surveillance Section, California Department of Health and Human Services, under subcontract 1006128 with the Public Health Institute.

PCPT: PCPT is funded by Public Health Service grants U10CA37429 and 5UM1CA182883 from the National Cancer Institute. The authors thank the site investigators and staff and, most importantly, the participants from PCPT who donated their time to this trial.

SELECT: SELECT is funded by Public Health Service cooperative Agreement grant CA37429 awarded by the National Cancer Institute, National Institutes of Health. The authors thank the site investigators and staff and, most importantly, the participants from SELECT who donated their time to this trial.

WUGS/WUPCS: WUGS would like to thank the following for funding support: The Anthony DeNovi Fund, the Donald C. McGraw Foundation, and the St. Louis Men's Group Against Cancer.

UGANDA: The UGANDA study was support by R01CA165862.

SABOR: The SABOR research is supported by NIH/NCI Early Detection Research Network, grant U01 CA0866402-12. Also supported by the Cancer Center Support Grant to the Cancer Therapy and Research Center from the National Cancer Institute (US) P30 CA054174.

PCaP: The North Carolina - Louisiana Prostate Cancer Project (PCaP) is carried out as a collaborative study supported by the Department of Defense contract DAMD 17-03-2-0052. The authors thank the staff, advisory committees and research subjects participating in the PCaP study for their important contributions. We would also like to acknowledge the UNC BioSpecimen Facility and the LSUHSC Pathology Lab for our DNA extractions, blood processing, storage and sample disbursement (https://genome.unc.edu/bsp).

EPICAP: The EPICAP study was supported by grants from Ligue Nationale Contre le Cancer, Ligue départementale du Val de Marne; Fondation de France; Agence Nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES). The EPICAP study group would like to thank all urologists, Antoinette Anger and Hasina Randrianasolo (study monitors), Anne-Laure Astolfi, Coline Bernard, Oriane Noyer, Marie-Hélène De Campo, Sandrine Margaroline, Louise N'Diaye, Sabine Perrier-Bonnet (Clinical Research nurses).

BioVU: The dataset(s) used for the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by institutional funding and by the National Center for Research Resources, Grant UL1 RR024975-01 (which is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06).

PROtEuS: PROtEuS was supported financially through grants from the Canadian Cancer Society [13149, 19500, 19864, 19865] and the Cancer Research Society, in partnership with the Ministère de l'enseignement supérieur, de la recherche, de la science et de la technologie du Québec, and the Fonds de la recherche du Québec - Santé. PROtEuS would like to thank its collaborators, research personnel, and urologists. We also wish to acknowledge the special contribution made by Drs. Ann Hsing and Anand Chokkalingam to the conception of the genetic component of the study.

CPDR: This research was supported by funds from the Center for Prostate Disease Research, Uniformed Services University Program, HU0001-10-2-0002 (PI: COL Inger L. Rosner, MD).

UKGPCS would also like to thank the following for funding support: The Institute of Cancer Research and The Everyman Campaign, The Prostate Cancer Research Foundation, Prostate Research Campaign UK (now Prostate Action), The Orchid Cancer Appeal, The National Cancer Research Network UK, The National Cancer Research Institute (NCRI) UK. We are grateful for support of NIHR funding to the NIHR Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. UKGPCS should also like to acknowledge the NCRN nurses, data managers and Consultants for their work in the UKGPCS study.

UM-PCGP: We appreciate the support from both the University of Michigan School of Medicine and the Duke University School of Medicine.