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ORIGINAL INVESTIGATION

Associations of prostate cancer risk variants with disease aggressiveness: results of the NCI-SPORE Genetics Working Group analysis of 18,343 cases

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Abstract Genetic studies have identified single nucleotide polymorphisms (SNPs) associated with the risk of prostate cancer (PC). It remains unclear whether such genetic variants are associated with disease aggressiveness. The NCI-SPORE Genetics Working Group retrospectively collected clinicopathologic information and genotype data for 36 SNPs which at the time had been validated to be associated with PC risk from 25,674 cases with PC. Cases were grouped according to race, Gleason score (Gleason $\leq$6, 7, $\geq$8) and aggressiveness (non-aggressive, intermediate, and aggressive disease). Statistical analyses were used to compare the frequency of the SNPs between different disease cohorts. After adjusting for multiple testing, only PC-risk SNP rs2735839 (G) was significantly and inversely associated with aggressive (OR = 0.77; 95 % CI 0.69–0.87) and high-grade disease (OR = 0.77; 95 % CI 0.68–0.86) in European men. Similar associations with aggressive

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(OR = 0.72; 95 % CI 0.58–0.89) and high-grade disease (OR = 0.69; 95 % CI 0.54–0.87) were documented in African-American subjects. The G allele of rs2735839 was associated with disease aggressiveness even at low PSA levels (<4.0 ng/mL) in both European and African-American men. Our results provide further support that a PC-risk SNP rs2735839 near the KLK3 gene on chromosome 19q13 may be associated with aggressive and high-grade PC. Future prospectively designed, case-case GWAS are needed to identify additional SNPs associated with PC aggressiveness.

Introduction

Current serum prostate-specific antigen (PSA)-based screening practices cannot reliably distinguish between men with indolent disease versus those with life-threatening disease. In this regard, PSA-based screening has been associated with an "over-diagnosis" of prostate cancer (PC), with some men possibly being diagnosed and treated for a seemingly indolent tumor that may never have been detected nor caused symptoms (Andriole et al. 2009; Schroder et al. 2009). Accordingly, there is an urgent need for new biomarkers that can better differentiate tumor behavior and clinical outcome.

Genome-wide association studies (GWAS) of PC patients and controls have identified approximately 100 different single nucleotide polymorphisms (SNPs) associated with the overall risk of being diagnosed with PC (Al Olama et al. 2014; Amundadottir et al. 2006; Choudhury et al. 2012; Eeles et al. 2008b, 2013; Gudmundsson et al. 2007a, b, 2008, 2009; Haiman et al. 2007; Thomas et al. 2008; Yeager et al. 2007). Most of these initial discovery studies have compared men with non-aggressive or moderately aggressive tumors to controls without known PC. Although some of these studies have been performed or validated in different racial populations (Cook et al. 2014; Freedman et al. 2006; Haiman et al. 2011; Han et al. 2014; Wang et al. 2012; Zheng et al. 2010), the great majority have been limited to men of European ancestry (Ishak and Giri 2011). Thus, while the results advance the knowledge of genetic factors associated with PC risk, in general, they have not been focused on clinically significant disease nor directed towards ethnic groups at greatest risk of dying of PC, such as men of African ancestry.

Some of the initial discovery GWAS attempted to evaluate the associations between specific PC-risk SNPs and various aspects of disease aggressiveness (e.g., Gleason score). However, these studies were generally performed as post hoc analyses and involved heterogeneous definitions of disease aggressiveness. In addition, most of these analyses compared the frequency of genetic variants in men with high-grade disease to controls and men with low-grade disease to controls. Only a relatively small proportion of GWAS in PC has been designed to evaluate the associations between genetic variants and clinically significant outcomes (e.g., disease aggressiveness) as their primary outcome measure. Xu et al. (2010) reported that the minor allele of single nucleotide polymorphism (SNP), rs4054823 on chromosome 17p12 was present at a significantly greater frequency in men with Gleason score ≥8 tumors and higher-stage disease (≥pT3b). Lin et al. (2011) used a candidate gene approach to identify a panel of 5 SNPs associated with PC-specific mortality. However, other studies have not found robust associations with PC-specific mortality (Penney et al. 2010). Other research

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groups have reported associations between individual SNPs on chromosomes 3p12, 8q24, 10q11, 15q13 and 19q13 and the pathology features characteristic of aggressive PC (Ahn et al. 2011; Bensen et al. 2013; FitzGerald et al. 2011). A meta-analysis aimed at determining whether genetic variants were associated with adverse pathology features reported that SNP rs11672691 showed associations with more aggressive tumors (Amin Al Olama et al. 2013). Additionally, results from other GWAS and linkage analyses have reported risk loci associated with aggressive disease amongst familial cases (Casey et al. 2006; Chang et al. 2005; Gudmundsson et al. 2008; Kirkland et al. 2010; Liu et al. 2011; Nam et al. 2011; Nurminen et al. 2011; Schaid et al. 2006, 2007; Slager et al. 2006; Stanford et al. 2006; Witte et al. 2000). In addition, Shui et al. reported that 8 SNPs were associated with lethal PC (Shui et al. 2014). The results of these studies are limited by the relatively small cohorts of PC patients of European ancestry studied, the heterogeneous definitions of aggressive disease used, reliance upon clinical (versus surgical) grading and staging of tumors, and lack of validation in diverse racial populations. Validation is essential to provide generalizability of results, especially since most of the genetic variants have only modest effects on disease risk and aggressiveness (OR 1.1–1.3).

The National Cancer Institute Prostate Cancer Genetics Working Group (GWG) was assembled to conduct a case-case association study of aggressive and non-aggressive PC (Catalona et al. 2011) using a panel of the then 36 validated SNPs associated with PC risk. In order to eliminate some of the variability in definitions of disease aggressiveness, only PC cases with complete information on disease aggressiveness and clinical follow-up were included in the analyses. Herein, we report our findings from a retrospective evaluation of more than 18,000 men with PC, including >8,000 men with aggressive disease, 5,000 men with non-aggressive disease, and >1,800 African-American men.

Materials and methods

Study samples

Nineteen PC research groups participated in this study and contributed clinical and genotype data (Supplemental Table 1). All institutions provided de-identified genotype and clinical information regarding pathologic tumor staging and grading to a central data-coordinating center (Northwestern University). The genotypes of 36 SNPs previously validated to be associated with PC risk were collected from a total of 25,674 cases with PC, including 23,278 men of self-reported European ancestry, 2,129 of African ancestry, and 267 of unknown ancestry. This panel of SNPs was chosen for evaluation because at the time of the 2010 NCI-SPORE GWG Conference, it included the most comprehensive list of validated PC-risk SNPs. While information was collected on all 36 SNPs, there were varying numbers of SNPs available for analysis from each site (Supplemental Table 1). Details on the methodologies for genotyping at each individual institution are presented in Supplemental Table 2.

For men treated with surgery for PC, the pathology tumor grade and stage were used in the analysis. For men who underwent non-surgical treatments, the clinical stage and biopsy Gleason score were used. In addition, biochemical (PSA) evidence of tumor recurrence status and PC-specific mortality was documented for both cohorts of men. For the purposes of the present study, disease aggressiveness was defined in two ways: First, “aggressive disease” was indicated by PC-specific death, or distant metastasis, or lymph node involvement, or seminal vesicle invasion, or extracapsular tumor extension or Gleason score $\geq$8. “Non-aggressive” disease was defined strictly as Gleason $\leq$6 and clinically localized and organ-confined disease. For men who underwent radiation therapy,

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their clinical stage and grade were used to define organ-confined disease. "Intermediate disease" was defined as non-lethal with either Gleason 7 disease or biochemical recurrence. All cohorts required documentation of at least 3 years follow-up from the time of diagnosis and/or treatment, no high-risk pathology features, metastases or PC-specific mortality. A second overlapping definition of "aggressive disease" was based solely on the Gleason grade of the tumor. For this analysis, high-, intermediate- and low-grade tumors were defined by Gleason scores $\geq$8, 7, and $\leq$6, respectively. Because there was incomplete data on the primary and secondary Gleason patterns, analyses that separated Gleason scores 3 + 4 and 4 + 3 could not be performed.

Exclusion criteria

Men were excluded from the analysis if they did not have documentation of pathology Gleason score for men undergoing prostatectomy (n = 48, 0.2 %), clinical Gleason score for men undergoing radiation therapy (147, 0.6 %), data on PSA (n = 1,481, 5.8 %), staging (n = 3,408, 13.3 %), and/or clinical follow-up information (n = 4,878, 19.0 %). Men were also excluded if they did not have documentation of either European or African-American ancestry (n = 267, 1.0 %).

Statistical analyses

Sensitivity analyses were performed comparing the genotypes of men fulfilling and those not meeting inclusion criteria. With the exception of one SNP, there were no differences between the included and excluded groups. However, the allele counts of SNP rs16902094 on chromosome 8q24 were significantly different between excluded and included groups of men of European ancestry. This difference was eliminated after adjusting for length of clinical follow-up, i.e., when outcomes were compared among patients who had similar follow-up intervals.

Analyses were performed for the entire cohort and separately by self-reported race (European and African-American). The reference allele used for all analyses was defined by the allele previously associated with PC risk. We used logistic regression analysis to test for the association between the allele counts for each individual SNP and the presence of PC within the included cohorts. Alleles were coded in a log-additive manner, whereby the counts reflected the number of previously associated alleles. For some analyses, we stratified cases into those with aggressive, intermediate, or non-aggressive disease, and we treated these case groups as ordinal outcomes. The institutional site was documented to adjust for possible differences in genotyping methodology. As such, institutional site was included in the logistic regression model as a covariate using Northwestern University and the referent site.

Multinomial logistic regression analysis was used to examine the association between allele counts (again for the previously reported PC-risk allele) and tumor aggressiveness as well as the potential association between allele counts and Gleason score. The Bonferroni correction was used to adjust for multiple testing.

Results

A total of 18,343 men (16,515 of European ancestry and 1,828 of African ancestry) met inclusion criteria. The clinical and pathology features of these men are shown (Table 1). Of the Caucasian men, 49.8, 21.6 and 28.6 % had aggressive, intermediate and non-aggressive disease, respectively. Similarly, 39.4, 34.2 and 26.4 % men of African heritage were categorized as having aggressive, intermediate or non-aggressive disease, respectively. The numbers of men genotyped for each of the 36 SNPs are shown in Table 1 and Supplemental Table 3.

After adjusting for multiple testing, case-case logistic analyses comparing the genotypes of the entire cohort with aggressive, intermediate and non-aggressive disease showed that only the minor allele (G) of rs2735839 (G) near *KLK3* (encoding PSA) on chromosome 19q13 remained significantly (and inversely) associated with aggressive disease ($P = 9.343 \times 10^{-8}$; Table 2). Similarly, after correction for multiple testing, only the same SNP was significantly (and inversely) associated with the presence of aggressive disease in the European ($P = 1.042 \times 10^{-5}$) and African-American ($P = 2.0 \times 10^{-4}$; Table 2) cohorts

We also compared the allele count frequencies in men of European ancestry with high (Gleason score $\geq$8), intermediate (Gleason score =7), and low-grade disease (Gleason score $\leq$6). After correction for multiple testing, only the minor allele (G) of rs2735839 near KLK3 on 19q13 remained significantly (and inversely) associated with high-grade disease in the entire cohort ($P = 1.389 \times 10^{-8}$). Again, after correction for multiple testing, only the same SNP retained its significance within European ($P = 1.862 \times 10^{-5}$) and African-American men ($P = 4.667 \times 10^{-4}$; Table 3).

To determine whether the association between rs2735839 and high-risk and high-grade disease was due to a PSA screening bias, we performed subset analyses using various PSA cutoffs (Table 4). There was a significant and inverse association between rs2735839 and aggressive disease at nearly every PSA cutoff in both cohorts of European and African-American men.

Table 1 Demographic and clinicopathologic information

	Overall		Non-aggressive		Intermediate aggressive		Aggressive	
	N	%	*N*	%	*N*	%	*N*	%
N	18,343	100	5,213	28.4	4,188	22.8	8,942	48.8
Median age at diagnosis	61	(34–93)	60	(34–84)	60	(35–79.7)	63	(36–93)
Mean age at diagnosis	61.3	8.1	59.8	7.7	59.9	7.6	62.9	8.2
<55	3,636	19.8	1,260	24.2	1,025	24.5	1,351	15.1
55–64	8,183	44.6	2,563	49.2	2,007	47.9	3,613	40.4
GW65-74	5,054	27.6	1,246	23.9	1,037	24.8	2,771	31
>74	969	5.3	144	2.8	119	2.8	706	7.9
Unknown	501	2.7	0	0	0	0	501	5.6
Race								
European ancestry	16,515	90	4,731	90.8	3,563	85.1	8,221	91.9
African-American ancestry	1,828	10	482	9.2	625	14.9	721	8.1
Median PSA level	6.3	(0–5,300)	5.2	(0–20)	5.3	(0.1–20)	9.4	(0–5,300)
PSA level								
<2.5	1,052	5.7	544	10.4	302	7.2	206	2.3
2.5–4	1,892	10.3	791	15.2	612	14.6	489	5.5
4–10	9,376	51.1	3,161	60.6	2,752	65.7	3,463	38.7
10–20	2,533	13.8	597	11.5	499	11.9	1,437	16.1
>20	2,403	13.1	0	0	0	0	2,403	26.9
Unknown	1,087	5.9	120	2.3	23	0.6	944	10.6
Clinical stage								
T1c	7,727	42.1	2,694	51.7	2,786	66.5	2,247	25.1
T2–T3	3,542	19.3	769	14.7	986	23.5	1,787	20
Unknown	7,074	38.6	1,750	33.6	416	9.9	4,908	54.9
Pathologic stage								
T1–T2	10,266	56	4,663	89.4	3,569	85.2	2,034	22.8
T3–T4	5,001	27.3	0	0	0	0	5,001	55.9
Unknown	3,076	16.8	550	10.6	619	14.8	1,907	21.3
Clinical Gleason score								
≤6	1,041	37.5	497	100	212	39.3	340	19.6
7	663	24	0	0	328	60.7	327	18.9
8–10	1,064	38.5	0	0	0	0	1,064	61.5
Pathologic Gleason score								
≤6	7,729	50.9	4,716	100	1,568	43.1	1,451	21.2
7	5,058	33.3	0	0	2,068	56.9	2,984	43.7
8–10	2,400	15.8	0	0	0	0	2,400	35.1
Unknown Gleason	388	2.1	0	0	12	0.2	376	4.2
Death from prostate cancer	986	5.4	0	0	0	0	986	11
Median follow-up time (years)	4.7	(0–29.9)	4	(0–20)	4	(0–22)	5	(0–29.9)

Discussion

Most previous studies of PC-risk alleles were not designed to identify genetic variants associated with aggressive disease because they were largely focused on men with a diagnosis of PC, irrespective of disease aggressiveness. In contrast, our study was aimed at identifying variants that are associated with PC aggressiveness rather than overall risk of PC (Helfand et al. 2010).

Previous studies have identified associations between SNPs within or near the PSA gene (*KLK3*) and high-grade tumors and adverse clinical outcomes (Bensen et al. 2013; Cramer et al. 2008; Gudmundsson et al. 2010; Lindstrom et al. 2011; Reinhardt et al. 2013; Slager et al. 2003; Xu

Table 2 Case-case study comparing the genotypes of men with aggressive to non-aggressive disease

SNP	Location	Risk allele	European ancestry		African-American ancestry	
			OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
rs721048	2p15	A	1.09 (0.98–1.20)	0.105	0.80 (0.49–1.30)	0.353
rs1465618	2p21	A	1.09 (1.00–1.20)	0.053	0.71 (0.41–1.22)	0.210
rs12621278	2q31.1	G	0.95 (0.79–1.15)	0.656	0.51 (0.09–2.84)	0.436
rs2660753	3p12.1	T	0.92 (0.84–1.00)	0.071	0.83 (0.68–1.01)	0.047
rs10934853	3q21	A	1.03 (0.94–1.13)	0.507	0.79 (0.26–2.35)	0.617
rs12500426	4q22.3	A	1.02 (0.94–1.10)	0.649	1.15 (0.67–1.96)	0.816
rs17021918	4q22.3	T	1.03 (0.94–1.14)	0.555	1.00 (0.57–1.77)	0.997
rs7679673	4q24	A	1.04 (0.96–1.13)	0.378	1.28 (0.84–1.96)	0.238
rs2736098	5p15	A	1.10 (0.88–1.37)	0.249	1.82 (0.62–5.33)	0.285
rs401681	5p16 (TERT)	C	0.89 (0.77–1.02)	0.120	1.12 (0.42–2.99)	0.724
rs9364554	6q25.3 (SLC22A3)	T	1.03 (0.95–1.12)	0.436	0.86 (0.58–1.27)	0.429
rs10486567	7p15.2 (JAZF1)	G	0.94 (0.87–1.01)	0.060	0.92 (0.74–1.15)	0.436
rs6465657	7q21.3 (LMTK2)	C	0.95 (0.90–1.01)	0.155	0.91 (0.50–1.66)	0.733
rs1512268	8p21.2	A	1.03 (0.95–1.11)	0.569	1.07 (0.70–1.62)	0.785
rs16901979	8q24	A	1.15 (1.00–1.32)	0.051	1.12 (0.90–1.40)	0.355
rs16902094	8q24	G	1.02 (0.92–1.14)	0.643	1.22 (0.24–6.31)	0.836
rs445114	8q24	T	0.98 (0.89–1.08)	0.714	1.46 (0.53–4.02)	0.558
rs6983267	8q24	G	1.00 (0.94–1.06)	0.832	1.23 (0.84–1.78)	0.234
rs1447295	8q24	A	1.02 (0.94–1.11)	0.621	0.87 (0.71–1.08)	0.249
rs10086908	8q24	C	1.07 (0.97–1.18)	0.187	0.73 (0.20–2.63)	0.693
rs1571801	9q33.2	A	0.97 (0.90–1.03)	0.304	1.14 (0.86–1.51)	0.380
rs10993994	10q11 (MSMB)	T	0.96 (0.91–1.02)	0.180	0.85 (0.69–1.03)	0.116
rs4962416	10q26.13	C	0.92 (0.84–1.00)	0.052	0.98 (0.76–1.27)	0.805
rs7127900	11p15.5	A	0.92 (0.84–1.01)	0.108	0.78 (0.51–1.20)	0.287
rs11228565	11q13	A	1.01 (0.91–1.13)	0.774	1.30 (0.16–10.90)	0.733
rs10896450	11q13	G	0.95 (0.82–1.09)	0.450	0.62 (0.24–1.58)	0.376
rs12418451	11q13.3	A	1.00 (0.90–1.11)	0.936	0.77 (0.08–7.75)	0.761
rs4054823	17p12	T	1.09 (1.00–1.19)	0.088	–	
rs11649743	17q12	G	0.99 (0.91–1.07)	0.755	0.96 (0.62–1.49)	0.898
rs4430796	17q12	A	1.00 (0.95–1.06)	0.948	1.05 (0.86–1.29)	0.610
rs1859962	17q24	G	0.99 (0.94–1.05)	0.803	1.06 (0.86–1.31)	0.493
rs8102476	19q13	C	1.07 (0.98–1.16)	0.097	0.93 (0.33–2.62)	0.958
rs2735839	19q13.3 (KLK2/KLK3)	G	0.77 (0.69–0.87)	1.042×10^{-5}	0.72 (0.58–0.89)	2.0×10^{-4}
rs9623117	22q13.1	C	1.00 (0.93–1.09)	0.994	1.00 (0.17–6.01)	0.648
rs5759167	22q13.2	T	0.96 (0.88–1.04)	0.294	1.35 (0.70–2.59)	0.536
rs5945572	Xp11	A	0.93 (0.83–1.04)	0.270	0.94 (0.68–1.30)	0.687

The OR (95 % CI) was calculated from multinomial logistic regression analyses using a saturated model comparing aggressive and non-aggressive disease. The *P* value is derived from a cumulative logit model comparing aggressive, intermediate and non-aggressive disease

et al. 2008). For example, using cohorts of European and Ashkenazi Jewish ancestry, two studies found that SNP rs2735839 near *KLK3* was associated with PC-specific mortality (Gallagher et al. 2010; Pomerantz et al. 2011). In addition, SNP rs2735839 near the *KLK3* (PSA) gene has been previously evaluated in men of European and African-American ancestry for its association with clinicopathologic features of prostate tumors (Bensen et al. 2013; He et al. 2014; Kader et al. 2009; Lindstrom et al. 2011; Nobata et al. 2012; Pomerantz et al. 2011; Xu et al. 2008). Taken together, the G allele has been associated with PC risk and increased serum PSA levels, but also with significantly lower disease aggressiveness (Bensen et al. 2013). However, results have been inconsistent. In the present study of large cohorts of both European and African-American men, this SNP was present at significantly

Table 3 Analysis of genotype association with Gleason score

SNP	Location	Risk allele	European ancestry		African-American ancestry	
			OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
rs721048	2p15	A	1.08 (0.77–1.11)	0.259	0.76 (0.41–1.41)	0.686
rs1465618	2p21	A	1.08 (0.98–1.20)	0.047	1.22 (0.72–2.07)	0.919
rs12621278	2q31.1	G	0.93 (0.73–1.17)	0.538	–	
rs2660753	3p12.1	T	0.99 (0.88–1.10)	0.510	0.95 (0.76–1.18)	0.137
rs10934853	3q21	A	0.95 (0.86–1.05)	0.454	1.94 (0.65–5.84)	0.447
rs12500426	4q22.3	A	1.01 (0.93–1.11)	0.992	1.04 (0.64–1.67)	0.395
rs17021918	4q22.3	T	1.06 (0.95–1.18)	0.122	0.91 (0.55–1.48)	0.514
rs7679673	4q24	A	1.03 (0.94–1.13)	0.310	1.17 (0.79–1.72)	0.407
rs2736098	5p15	A	1.10 (0.80–1.50)	0.578	0.87 (0.25–3.04)	0.811
rs401681	5p16 (TERT)	C	0.94 (0.82–1.07)	0.293	1.77 (0.65–4.77)	0.194
rs9364554	6q25.3 (SLC22A3)	T	0.90 (0.82–0.98)	0.114	0.96 (0.61–1.51)	0.904
rs10486567	7p15.2 (JAZF1)	G	0.89 (0.82–0.97)	0.003	0.86 (0.68–1.10)	0.091
rs6465657	7q21.3 (LMTK2)	C	0.92 (0.86–1.00)	0.014	0.80 (0.47–1.38)	0.444
rs1512268	8p21.2	A	0.97 (0.89–1.06)	0.785	0.86 (0.58–1.28)	0.776
rs16901979	8q24	A	1.18 (1.00–1.39)	0.072	1.07 (0.83–1.36)	0.836
rs16902094	8q24	G	1.02 (0.89–1.16)	0.709	0.89 (0.18–4.36)	0.695
rs445114	8q24	T	0.96 (0.86–1.07)	0.330	1.28 (0.46–3.55)	0.764
rs6983267	8q24	G	0.94 (0.88–1.00)	0.076	1.16 (0.76–1.79)	0.209
rs1447295	8q24	A	1.04 (0.93–1.15)	0.104	1.05 (0.82–1.33)	0.548
rs10086908	8q24	C	1.06 (0.94–1.18)	0.439	0.94 (0.34–2.61)	0.960
rs1571801	9q33.2	A	0.98 (0.91–1.07)	0.951	1.41 (1.04–1.91)	0.198
rs10993994	10q11 (MSMB)	T	0.94 (0.88–1.01)	0.127	0.89 (0.71–1.11)	0.289
rs4962416	10q26.13	C	0.95 (0.86–1.04)	0.348	1.04 (0.77–1.40)	0.863
rs7127900	11p15.5	A	0.82 (0.73–0.92)	0.002	1.12 (0.75–1.67)	0.816
rs11228565	11q13	A	1.05 (0.92–1.19)	0.765	4.49 (0.78–26.00)	0.054
rs10896450	11q13	G	0.98 (0.84–1.16)	0.829	0.76 (0.28–2.09)	0.708
rs12418451	11q13.3	A	0.98 (0.85–1.13)	0.869	0.83 (0.22–3.16)	0.868
rs4054823	17p12	T	1.03 (0.94–1.14)	0.352	4.72 (1.24–17.89)	0.025
rs11649743	17q12	G	0.95 (0.86–1.05)	0.096	1.05 (0.63–1.75)	0.684
rs4430796	17q12	A	1.05 (0.98–1.13)	0.513	0.94 (0.74–1.19)	0.956
rs1859962	17q24	G	0.95 (0.88–1.02)	0.093	0.97 (0.77–1.22)	0.297
rs8102476	19q13	C	1.00 (0.91–1.10)	0.717	1.53 (0.53–4.41)	0.477
rs2735839	19q13.3 (KLK2/KLK3)	G	0.77 (0.68–0.86)	1.862×10^{-5}	0.69 (0.54–0.87)	4.667×10^{-4}
rs9623117	22q13.1	C	0.96 (0.87–1.07)	0.746	1.74 (0.72–4.19)	0.117
rs5759167	22q13.2	T	0.98 (0.89–1.07)	0.599	0.99 (0.54–1.80)	0.267
rs5945572	Xp11	A	0.87 (0.77–0.99)	0.128	1.17 (0.82–1.68)	0.655

The OR (95 % CI) was calculated from multinomial logistic regression analyses using a saturated model comparing high-grade and low-grade disease. The *P* value is derived from a cumulative logit model comparing high-, intermediate- and low-grade disease

Table 4 Subgroup analysis based upon PSA level comparing the association between SNP rs2735839 and high-risk disease

	SNP	Location	Risk allele	European ancestry		African-American ancestry	
				OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
PSA $\leq$ 20.0 ng/ml	rs2735839	19q13.3 (KLK2/KLK3)	G	0.73 (0.64–0.83)	1.622×10^{-5}	0.76 (0.59–0.98)	0.019
PSA $\leq$ 10.0 ng/ml	rs2735839	19q13.3 (KLK2/KLK3)	G	0.68 (0.59–0.79)	1.302×10^{-5}	0.82 (0.61–1.10)	0.067
PSA $\leq$ 4.0 ng/ml	rs2735839	19q13.3 (KLK2/KLK3)	G	0.70 (0.52–0.94)	0.0092	N/A	N/A

Of note, there were not enough African-African men with very low PSA values to make meaningful comparisons

different frequencies amongst men with aggressive and high-grade disease compared to those with non-aggressive or low-grade disease. Since this genetic variant lies within the *KLK3* gene, it is not surprising that variants within or around this gene could influence PC aggressiveness (Gudmundsson et al. 2009, 2010; He et al. 2014; Hsu et al. 2009; Kader et al. 2009; Lange et al. 2012; Pal et al. 2007; Penney et al. 2011; Schaid et al. 2007; Xu et al. 2008). Although the mechanism (s) of this association are unclear, it is possible that it may reflect, at least in part, a PSA detection bias (e.g., G allele of rs2735839 is associated with lower PSA expression and a delay in PC diagnosis). However, a PSA detection bias may not be sufficient to explain all of the current findings. For example, data from non-PSA-screened cohorts (Eeles et al. 2008a) and from men with low PSA values (Table 4) and functional studies (Lai et al. 2007) support the possibility of other potential roles for this locus, including PSA production, and the intrinsic risk of PC overall and of aggressive disease. Regardless, this SNP is associated with disease aggressiveness. Specifically, in men of European ancestry, this SNP was associated with disease aggressiveness amongst men with relatively low PSA values <4 ng/mL (Table 4). Because the clinical and pathology features were used to define the groups, we were not able to determine whether this allele adds independent prognostic information. Therefore, additional studies aimed at fully evaluating its clinical utility are needed.

Previous studies using a case–control study design have suggested associations between PC-risk SNPs and aggressive disease. In contrast, the results of the present study support only an association with SNP rs2735839. This association remained whether we defined aggressive disease using Gleason score alone or whether a more comprehensive definition (PC-specific death, distant metastasis, lymph node involvement, seminal vesicle invasion, extracapsular tumor extension) was employed (Tables 2 and 3). Taken together, our results provide rationale for a need for case-case study designs.

It is well established that men of African descent are at significantly increased risk of PC, with a greater proportion being diagnosed at an earlier age with aggressive disease (Moul 2000; Zeliadt et al. 2003). Specifically, African- American men have a 50 % higher incidence and more than a 240 % higher mortality rate of PC than Caucasian men (Hsing and Chokkalingam 2006) (Taksler et al. 2012). Unfortunately, the majority of genetic studies have not included large cohorts of African-American men. The present study is strengthened by the fact that it highlights both similarities and differences between African-American and European men. For example, there were many more SNPs that were marginally associated with high-risk and high-grade disease in the European compared to African-American men (Tables 2 and 3). As stated above, this is likely related to the mechanisms of their initial discovery in Caucasian cohorts (Han et al. 2014). Other nearby or related SNPs may also be associated with aggressive disease in African-Americans, and more studies within this population are needed. Interestingly, both racial populations showed an association between the aggressive phenotype and the minor allele of rs2735839 (G). This suggests a robustness of the association in other racial populations as well as a common genetic mechanism for PC aggressiveness.

Our study has several strengths, including its involvement of large cohorts with aggressive prostate tumors. This allowed the identification of PC-risk SNPs with at least marginally significant associations with aggressive disease. These small relative risks of aggressive disease are somewhat expected given similar associations between these SNPs and overall disease risk. However, based upon the fact that these SNPs are common within the general population and have a low penetrance, we cannot exclude the possibility of false positive results. Additionally, we used a widely validated subset of PC-risk variants in the present study. This relatively limited subset of 36 SNPs allowed us to evaluate more fully the SNPs in a new context without having the same statistical constraints as many GWAS studies that involve millions of other SNPs. However, this same subset also limited the scope of our results, as it did not permit the identification of other more recently validated risk SNPs or novel genetic variations that may better predict PC aggressiveness. Furthermore, we did not have genotype data on all 36 SNPs in all patients included in the study. This limited the statistical power. Therefore, future case-case GWAS involving large cohorts of men with complete genotype data are needed. In addition, future complementary case–control studies evaluating these same SNPs would be needed to better define the direction and magnitude of the associations with aggressive disease. Additionally, although our study population represents one of the largest cohorts of men with African-American ancestry, the statistical power remains limited, and the results require replication in larger, independent datasets. It should be noted that there may have been a selection bias present since the proportion of African-American men with aggressive disease included in the cohort was significantly less than among European-Americans. Furthermore, our results may have been confounded by the fact that race was self-reported and lacked associated genetic information on ancestry. While our results are limited by the definition of disease aggressiveness used, it emphasizes the need for replication, as the majority of prior aggressiveness loci have failed to be replicated.

In summary, we provide further evidence that a single PC-risk SNP (rs2735839) on chromosome 19q13 may be associated with high-risk and high-grade PC. Future

prospective designed, case-case GWAS should be performed to identify additional SNPs associated with PC aggressiveness.

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