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BRIEF COMMUNICATION

Prostate Cancer Susceptibility in Men of African Ancestry at 8q24

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† In Memoriam.

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Abstract

The 8q24 region harbors multiple risk variants for distinct cancers, including >8 for prostate cancer. In this study, we conducted fine mapping of the 8q24 risk region (127.8–128.8 Mb) in search of novel associations with common and rare variation in 4853 prostate cancer case patients and 4678 control subjects of African ancestry. All statistical tests were two-sided. We identified three independent associations at P values of less than 5.00×10^{-8} , all of which were replicated in studies from Ghana and Uganda (combined sample = 5869 case patients, 5615 control subjects; rs114798100: risk allele frequency [RAF] = 0.04, per-allele odds ratio [OR] = 2.31, 95% confidence interval [CI] = 2.04 to 2.61, $P = 2.38 \times 10^{-40}$; rs72725879: RAF = 0.33, OR = 1.37, 95% CI = 1.30 to 1.45, $P = 3.04 \times 10^{-27}$; and rs111906932: RAF = 0.03, OR = 1.79, 95% CI = 1.53 to 2.08, $P = 1.39 \times 10^{-13}$). Risk variants rs114798100 and rs111906923 are only found in men of African ancestry, with rs111906923 representing a novel association signal. The three variants are located within or near a number of prostate cancer-associated long noncoding RNAs (lncRNAs), including PRNCR1, PCAT1, and PCAT2. These findings highlight ancestry-specific risk variation and implicate prostate-specific lncRNAs at the 8q24 prostate cancer susceptibility region.

Genetic variation at 8q24 is a major contributor to prostate cancer (PCa) susceptibility globally (1–4). African ancestry has been found to be over-represented in this region in African American men with PCa, which suggests that underlying risk variants may be more common in men of African than European ancestry (5). Rare, ancestry-specific alleles have been revealed in African and European ancestry populations, highlighting allelic heterogeneity in the overall contribution of this region to PCa risk (2,6). However, the biological mechanism(s) underlying the PCa risk associations is not entirely clear, with studies implicating both MYC and long noncoding RNAs (lncRNAs) in this region (7–9).

Given the importance of this region in men of African ancestry, we conducted a comprehensive investigation of common and rare variation across the 8q24 region (127.8–128.8 Mb) in 4853 case patients and 4678 control subjects from the African Ancestry Prostate Cancer GWAS Consortium (AAPC) (Supplementary Table 1 and Supplementary Note, available online) (10). Genotyping was conducted using the Illumina Infinium 1M-Duo with imputation to a cosmopolitan reference panel from the 1000 Genomes Project (1KGP, March 2012) (Supplementary Methods, available online). For each SNP, per-allele odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression. We tested for allele dosage effects through a 1 degree of freedom Wald trend test. Multivariable logistic regression was utilized to identify independent risk variants across the 8q24 locus (127.8–128.8 Mb) by conditioning on the most statistically significant SNPs in a stepwise fashion. All statistical tests were two-sided.

We identified 199 variants at 8q24 associated with PCa risk ($P < 5.00 \times 10^{-8}$), all located between 127.894 and 128.233 Mb (spanning a region previously described as ‘region 2’ [2]) (Figure 1; Supplementary Table 2, available online). Associations with 10 of the 14 known risk variants at 8q24 were replicated at P values of less than .05 (Supplementary Table 3, available online). Through forward selection (Supplementary Table 3 and Supplementary Figure 1, available online), we identified three independent association signals at P values of less than 5.00×10^{-8} (Table 1). The most statistically significant association was with a low frequency SNP (risk allele frequency [RAF] = 0.04), rs114798100 (conditional OR = 2.07, 95% CI = 1.80 to 2.38, $P = 2.98 \times 10^{-24}$,

imputation info score = 0.93), which is only found in populations of African ancestry (Table 1) and is correlated with a known African-specific risk variant rs116041037 ($r^2 = 0.63$, AFR 1KGP) (2). A second nearby signal captured by rs72725879 (conditional OR = 1.27, 95% CI = 1.19 to 1.36, $P = 2.77 \times 10^{-13}$, imputation info score = 0.95) (Table 1) is more common in populations of African (RAF = 0.33) than European (RAF = 0.19, EUR 1KGP) ancestry and is most common in Asian populations (RAF = 0.66, ASN 1KGP); variant rs72725879 is the strongest risk signal across the 8q24 region in Japanese men (8). A third and novel signal was defined by variant rs111906932 (conditional OR = 1.75, 95% CI = 1.47 to 2.07, $P = 1.52 \times 10^{-10}$, imputation info score = 0.88) (Table 1). Like rs114798100, the signal captured by rs111906932 is uncommon and only found in African ancestry populations (RAF = 0.03). The correlation for genotyped and imputed variants for these three variants was greater than 0.90 (Supplementary Table 4, available online). Subsequent conditional analyses revealed four additional variants with suggestive independent associations (conditional $P < 10^{-4}$) (Table 1). Of previously reported risk variants at 8q24, only rs6983267 ($P = .0091$, imputation info score = 0.93) and rs7000448 ($P = .0091$, imputation info score = 1.00) (Supplementary Table 3, available online) remained nominally statistically significant after conditioning on the seven markers described above. None of these markers was statistically significantly associated with disease aggressiveness (data not shown).

The associations with rs114798100 (OR = 1.93, 95% CI = 1.23 to 3.03, $P = 4.30 \times 10^{-3}$), rs72725879 (OR = 1.30, 95% CI = 1.04 to 1.63, $P = 2.02 \times 10^{-2}$), and rs111906932 (OR = 2.04, 95% CI = 1.34 to 3.11, $P = 9.36 \times 10^{-4}$) were replicated in the Ghana Prostate Study (GPS; 474 case patients, 458 control subjects) (11) and in a study from Uganda (UGPCS; 542 case patients, 479 control subjects; rs114798100: OR = 2.54, 95% CI = 1.75 to 3.69, $P = 9.84 \times 10^{-7}$; rs72725879: OR = 1.37, 95% CI = 1.14 to 1.65, $P = 9.00 \times 10^{-4}$; and rs111906932: OR = 2.51, 95% CI = 1.22 to 5.15, $P = 1.24 \times 10^{-2}$) (Supplementary Table 5, available online). The associations with these variants were highly statistically significant in a meta-analysis of AAPC, GPS, and UGPCS (5869 case patients, 5615 control subjects; rs114798100: OR = 2.31, 95% CI = 2.04 to 2.61, $P = 2.38 \times 10^{-40}$; rs72725879: OR = 1.37, 95% CI = 1.30 to 1.45, $P = 3.04 \times 10^{-27}$; and rs111906932: OR = 1.79, 95% CI = 1.53 to 2.08, $P = 1.39 \times 10^{-13}$).

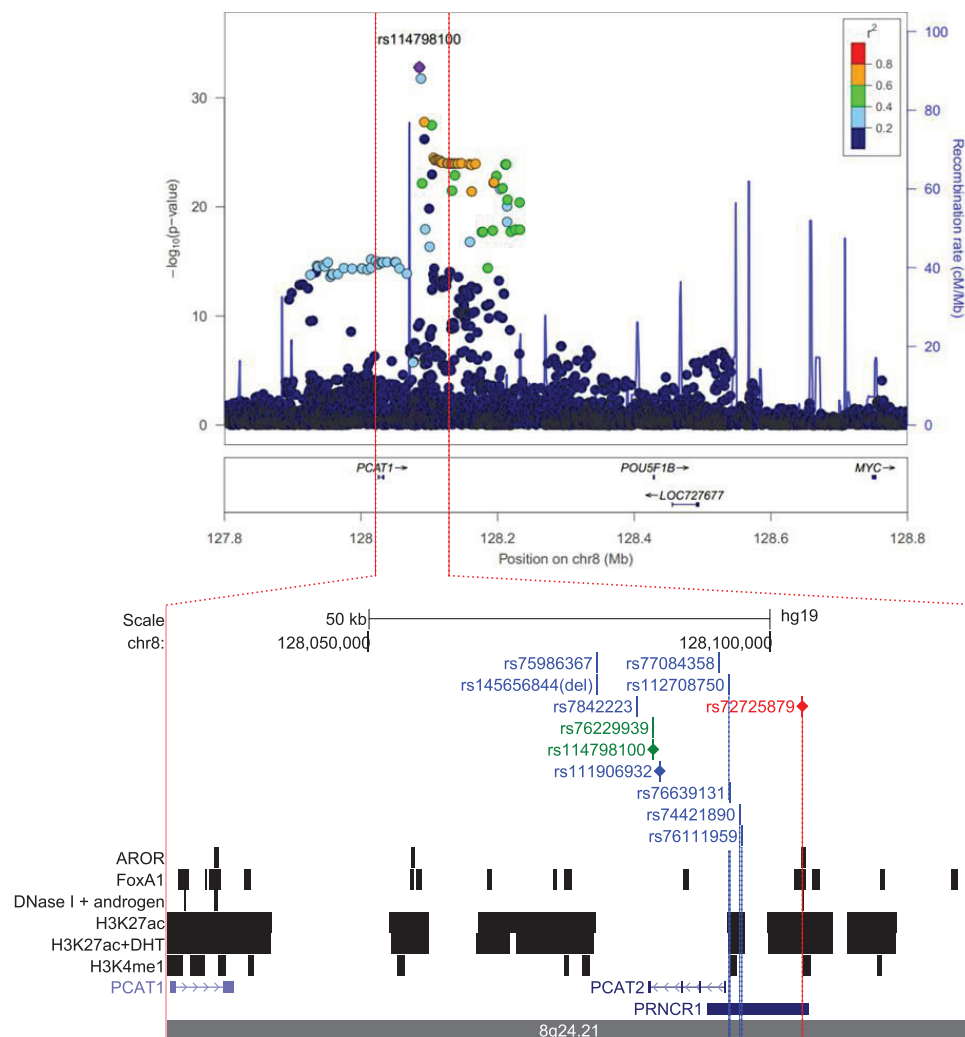


Figure 1. Regional association plot of the 8q24 risk region in men of African ancestry. Single-nucleotide polymorphisms (SNPs) are plotted by position (x-axis) and $-\log_{10}$ P value (y-axis). The most associated SNP (purple diamond) is rs114798100, and the surrounding SNPs are colored to indicate pairwise correlation in African ancestry populations (AFR panel in 1000 Genomes). Below shows the overlap of the three most associated variants in 'region 2' as well as variants correlated at $r^2 \geq 0.7$ with rs114798100 (green), rs72725879 (red) and rs111906932 (blue) (Supplementary Table 7, available online) and functional annotations from DNaseI, histone modification, and ChIP-seq experiments in LNCaP (Supplementary Table 8 and Supplementary Methods, available online). All statistical tests were two-sided.

Table 1. Prostate cancer risk variants at 8q24 in men of African ancestry

SNP	Position*	Alleles, RAF†	OR (95% CI)‡,§	P ,§	Conditional OR (95% CI)‡,¶	Conditional P ,¶
rs7816007#	128012359	A/G, 0.80/0.74	1.21 (1.12 to 1.30)	1.73×10^{-6}	1.20 (1.11 to 1.30)	3.71×10^{-6}
rs114798100#	128085434	G/A, 0.04/0	2.32 (2.02 to 2.66)	1.61×10^{-33}	2.07 (1.80 to 2.38)	2.98×10^{-24}
rs111906932#	128086204	A/G, 0.03/0	1.72 (1.45 to 2.03)	4.32×10^{-10}	1.75 (1.47 to 2.07)	1.52×10^{-10}
rs72725879#	128103969	T/C, 0.33/0.19	1.38 (1.29 to 1.47)	1.07×10^{-23}	1.27 (1.19 to 1.36)	2.77×10^{-13}
rs2445605	128161944	C/T, 0.90/0.96	1.30 (1.18 to 1.44)	3.67×10^{-7}	1.24 (1.11 to 1.37)	5.97×10^{-5}
rs7824868	128524414	T/C, 0.04/0.11	1.43 (1.25 to 1.64)	2.62×10^{-7}	1.40 (1.22 to 1.61)	2.57×10^{-6}
rs11784480#	128762529	T/A, 0.77/0.48	1.18 (1.09 to 1.28)	8.17×10^{-5}	1.19 (1.10 to 1.30)	3.61×10^{-5}

* Base-pair position in hg19 (GRCh37). CI = confidence interval; OR = odds ratio; RAF = risk allele frequency in control subjects of African/European (EUR 1KGP) ancestry populations; SNP = single-nucleotide polymorphism.

† Risk allele/reference allele.

‡ Odds ratio with reference allele as the reference category.

§ Adjusted for age, study, global ancestry (the first 10 principal components), and local ancestry.

¶ P value from two-sided Wald test with 1 degree of freedom.

|| Additionally adjusted for all variants in this table.

Imputed; imputation quality score range = 0.82–0.98.

An analysis of targeted sequencing data (~15× mean coverage) of the 8q24 risk locus (127.8–128.8Mb) was also conducted in 1644 case patients and 1459 control subjects to investigate

rarer variation that may have been missed through imputation (Supplementary Methods and Supplementary Figure 2, available online). None of the 4186 variants identified in 'region 2',

including 2604 with a frequency of less than 1%, could explain the associations observed with the three risk variants in this region (data not shown).

In African American men, 8q24 was initially highlighted by an admixture signal (identified in a subset of the AAPC samples) (5). Here we find that the three most statistically significant risk variants (rs114798100, rs72725879, and rs111906932), being more prevalent in men of African than European ancestry, can account for the rise in local African ancestry in the region in African American men with PCa (OR per African chromosome at 8q24 = 1.16, 95% CI = 1.07 to 1.26, $P = 3.76 \times 10^{-4}$; OR adjusted for the three risk variants = 1.03, 95% CI = 0.94 to 1.12, $P = .57$) (Table 1; Supplementary Table 6, available online).

These findings provide further evidence of rare, ancestry-specific variants in region 2 of 8q24 that have substantial effects on risk (ORs per allele = 1.8–2.9) (6). Effect size heterogeneity is also a hallmark of risk variants at 8q24, as exemplified by rs72725879 with an odds ratio of 1.75 (95% CI = 1.57 to 1.95) in Japanese men (8) and 1.38 (95% CI = 1.29 to 1.47) in men of African Ancestry. Such heterogeneity exists even after sequencing in these populations and implies an impact of genetic background or differences in linkage disequilibrium structure between these markers and one or more functional variants in the region. The number, location, and frequency of risk alleles at 8q24 also vary between populations. For example, rs6983561 in region 2 (1KGP RAF = 0.49 AFR, 0.21 ASN, and 0.03 EUR) is no longer associated with risk at P values of less than 10^{-3} when adjusting for rs114798100 and rs72725879 (Supplementary Table 3, available online); however, rs6983561 remains an independent signal in Japanese and European men (12,13). Likewise, rs1016343, which is common in all populations (RAF > 0.15), is the strongest signal in region 2 (aside from rs188140481) in European men but is not found as an independent signal in Asian (12) or African populations ($P = .21$) (Supplementary Table 3, available online) (12,14). Together, these observations suggest a complex relationship between the underlying functional alleles at 8q24.

The most statistically significantly associated risk variants in region 2 are located near a number of PCa-associated lncRNAs, including PRNCR1, PCAT1, and PCAT2 (Figure 1). PRNCR1 has been shown to be overexpressed in aggressive PCa and to influence androgen receptor-mediated gene activation (15). PCAT1 has been implicated in the regulation of double-strand break repair through the repression of BRCA2 (16,17). Nearby lncRNAs have also been implicated at the prostate/colorectal cancer 8q24 risk locus rs6983267 (in region 3) (9). Based on epigenetic annotations in PCa cell lines (Supplementary Methods, available online), rs72725879 was found to lie within an H3K27Ac-marked enhancer overlapping a FOXA1 ChIP-seq peak while four SNPs correlated with rs111906932 were found in putative enhancers within the PRNCR1 transcript (Figure 1; Supplementary Tables 7 and 8, available online). These data therefore implicate lncRNAs and/or enhancers of unknown target genes involved in PCa etiology at 8q24. To ascertain possible functions of lncRNAs, their knockdown (siRNA) or overexpression in prostate cells can be followed by phenotypic assays. To identify the targets of enhancers, experiments such as 1) CRISPR-cas9-mediated genome editing to either knock out or replace alleles; 2) chromatin interaction assays that identify physical proximity between the locations of the risk variants and functional target regions; and 3) eQTL or ELMER (18) associations will be required to assess whether and how the alleles highlighted in this study are functional. Such functional follow-up may yield insight into the mechanism(s) underlying the risk associations in this region.

There are several limitations to this study. Compared with other ongoing efforts in European populations, the sample size in men of African ancestry still remains small, so there may be other less common, low-risk alleles in the region that we did not have power to detect. We performed targeted sequencing to investigate rarer alleles in the region; however, large sections were missed because of repetitive sequence. Efforts that combine studies across multiple racial/ethnic populations will be required to understand the complex genetic architecture of this region on PCa risk.

With the identification of a second risk variant for PCa at 8q24 that is only found in men of African ancestry, these findings strongly reinforce the importance of rarer genetic variation in this region, which may contribute, in part, to their greater risk of PCa.

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