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BRIEF COMMUNICATION

Two Novel Susceptibility Loci for Prostate Cancer in Men of African Ancestry

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Abstract

Prostate cancer incidence is 1.6-fold higher in African Americans than in other populations. The risk factors that drive this disparity are unknown and potentially consist of social, environmental, and genetic influences. To investigate the genetic basis of prostate cancer in men of African ancestry, we performed a genome-wide association meta-analysis using two-sided statistical tests in 10 202 case subjects and 10 810 control subjects. We identified novel signals on chromosomes 13q34 and 22q12, with the risk-associated alleles found only in men of African ancestry (13q34: rs75823044, risk allele frequency = 2.2%, odds ratio [OR] = 1.55, 95% confidence interval [CI] = 1.37 to 1.76, $P = 6.10 \times 10^{-12}$; 22q12.1: rs78554043, risk allele frequency = 1.5%, OR = 1.62, 95% CI = 1.39 to 1.89, $P = 7.50 \times 10^{-10}$). At 13q34, the signal is located 5' of the gene *IRS2* and 3' of a long noncoding RNA, while at 22q12 the candidate functional allele is a missense variant in the *CHEK2* gene. These findings provide further support for the role of ancestry-specific germline variation in contributing to population differences in prostate cancer risk.

The incidence of prostate cancer (PCa) in African American men is 1.6-fold higher than in other racial/ethnic populations (1), remaining one of the most important health disparities globally. Reasons for this disparity likely involve a multitude of factors,

including social and environmental factors and inherited susceptibility. Genome-wide association studies (GWAS) have identified more than 100 common risk alleles for PCa (2–7), including the susceptibility region on chromosome 8q24, which harbors

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Table 1. Association results for prostate cancer risk variants at 13q34 and 22q12.1 in men of African ancestry

SNP ID chr. position*	Nearby genes	Allele†	AAPC			Ghana			Kaiser/ProHealth			ELLIPSE OncoArray			Meta-analysis		
			OR (95% CI)	P‡	RAF§	OR (95% CI)	P‡	RAF§	OR (95% CI)	P‡	RAF§	OR (95% CI)	P‡	RAF§	OR (95% CI)	P‡	
rs75823044 13q34	IRS2	T/C	1.47 (1.22 to 1.76)	3.73×10^{-5}	0.022	2.66 (1.59 to 4.47)	2.04×10^{-4}	0.029	1.27 (0.80 to 2.00)	.31	0.021	1.60 (1.31 to 1.96)	4.84×10^{-6}	0.020	1.55 (1.37 to 1.76)	6.10×10^{-12}	
rs78554043 22q12.1	CHEK2	C/G	1.60 (1.27 to 2.00)	5.02×10^{-5}	0.015	2.45 (1.33 to 4.52)	.004	0.019	1.17 (0.69 to 1.99)	.55	0.017	1.66 (1.30 to 2.13)	5.98×10^{-5}	0.013	1.62 (1.39 to 1.89)	7.50×10^{-10}	
28,374,943																	

*Genome build 37/HG19, chr. = chromosome; CI = confidence interval; OR = odds ratio; RAF = risk allele frequency.

†Risk allele/reference allele.

‡Allele dosage effects were tested through a 1-degree of freedom Wald trend test. All P values are two-sided.

§Risk allele frequency in controls.

multiple variants that have been suggested to contribute to racial/ethnic differences in PCa risk (8,9).

To search for additional PCa risk variants in men of African ancestry that may contribute to their greater disease incidence, we combined genetic association results from the African Ancestry Prostate Cancer GWAS Consortium (AAPC; 4853 case subjects and 4678 control subjects) (9), the Ghana Prostate Study (474 case subjects and 458 control subjects) (10), the Kaiser/ProHealth Prostate Cancer Study (601 case subjects and 1650 control subjects) (11), and the ELLIPSE/PRACTICAL OncoArray Consortium (4274 case subjects and 4024 control subjects) (Supplementary Table 1, available online). Subjects provided written informed consent to participate in the study. The protocol and consent documents were approved by the institutional review boards at each of the participating institutions. A total of 17.8 million genotyped and imputed single nucleotide polymorphisms (SNPs) and insertion/deletion variants with frequencies of 1% or more were tested for an association with PCa risk. For each SNP, per-allele odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression, and we tested for allele dosage effects through a 1-degree of freedom Wald trend test. All statistical tests were two-sided. Results from each study were combined through a meta-analysis of 10202 case subjects and 10810 control subjects (Supplementary Methods, available online). The cut-point for genome-wide statistical significance was a P value of less than 5.00×10^{-8} .

Only minor evidence of inflation in the test statistic was observed following adjustment for global genetic ancestry ($\lambda = 1.04$). In the meta-analysis, 775 alleles achieved genome-wide statistical significance ($P < 5.00 \times 10^{-8}$). These alleles were located at the 8q24 risk region (543 alleles) and other known susceptibility regions on chromosomes 2p15(EHBP1), 2q37(MLPH), 6q22(RFX6), 8p21(NKX3-1), 10q11(MSMB), 11q13(MYEOV), 12q13(KRT8), 17q21(ZNF652), and Xp11(NUDT11/LINC01496) (Supplementary Figure 1A, available online). Outside of these regions, genome-wide statistically significant associations were also observed on chromosomes 13q34 and 22q12.1 (Table 1; Supplementary Figure 1B, available online), with the risk-associated alleles found almost exclusively in men of African ancestry. At 13q34, marker rs75823044 (2.2% frequency) was associated with an odds ratio of 1.55 (95% CI = 1.37 to 1.76, $P = 6.10 \times 10^{-12}$). This marker is located within a cluster of five moderately correlated alleles ($r^2 > 0.30$) approximately 45 kb 3' of the gene insulin receptor substrate 2 (IRS-2), a signaling protein that mediates the effect of insulin and insulin-like growth factor 1 (12), and 20 kb 5' of a long noncoding RNA (LINC00676). Of these five variants, rs151190668 (OR = 1.67, 95% CI = 1.43 to 1.96, $P = 1.70 \times 10^{-10}$) appears to be the best functional candidate because it is located in a region containing epigenetic chromatin modifications and androgen receptor and FOXA1 binding consistent with regulatory sequences (Figure 1; Supplementary Methods, available online).

At 22q12.1, the association signal was also defined by multiple low-frequency African ancestry-specific variants spanning approximately 944 kb, with rs78554043 being the most statistically significant variant (1.5% frequency, OR = 1.62, 95% CI = 1.39 to 1.89, $P = 7.50 \times 10^{-10}$) (Table 1). The variant rs78554043 is correlated ($r^2 = 1$) with a missense polymorphism (rs17886163, Ile448Ser, $P = 1.38 \times 10^{-9}$) in the CHEK2 gene (Supplementary Table 4, available online), which is a likely candidate for the underlying biologically functional allele. Although the Ile448Ser missense is characterized as “benign” by Polyphen2 and ClinVar and “tolerated” by Sifting Intolerant from Tolerant (SIFT) (Supplementary Methods, available online), it involves a

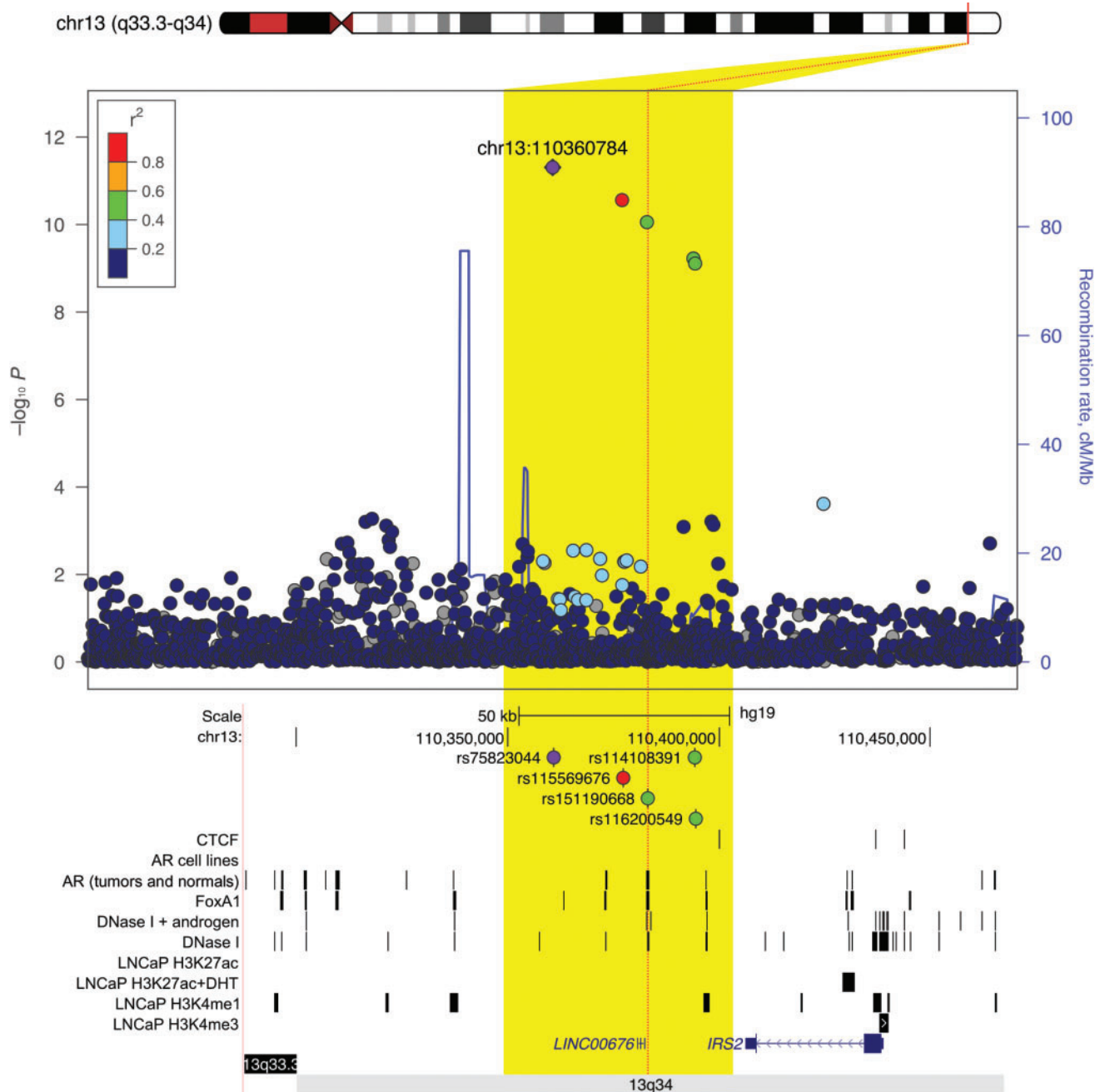


Figure 1. Regional plot of a novel genome-wide statistically significant prostate cancer risk region at chromosome 13q34. Single nucleotide polymorphisms (SNPs) are plotted by their position 110 kb on either side of the index SNP (purple diamond) on the chromosome against their association ($-\log_{10} P$) with prostate cancer risk in men of African ancestry. SNPs surrounding the index SNP are colored to indicate the local linkage disequilibrium (LD) structure using pairwise r^2 data from the African ancestry samples panel of the 1000 Genomes Project (November 2014 phase III). Below are peaks from transcription factor (TF) and histone modification ChIP-seq experiments in the same genomic window (see the Supplementary Methods, available online). All ChIP-seq in LNCaP unless otherwise indicated. AR = androgen receptor; CTCF = CCCTC-binding factor; LNCaP = Lymph Node Carcinoma of the Prostate cell line.

nonconservative nonpolar to polar change in the amino acid. While the possibility of rare regulatory variation cannot be excluded, this nonconservative change provides support for previous studies suggesting that rare/less common missense variants in *CHEK2* may be important in PCa development (13).

The risk alleles rs75823044 and rs78554043 are found almost exclusively in African ancestry populations. In the 1000 Genomes Project populations ($n = 2504$ subjects), the risk allele for rs75823044 was found in 48 of 661 African ancestry samples

(AFR), one of 85 Peruvians, and one of 96 Punjabi. For rs78554043, the risk allele was found in 30 of 661 AFR samples, one of 104 Puerto Ricans, and one of 94 Colombians (data not shown).

At 13q34 and 22q12.1, no nominally statistically significant ($P < .05$) evidence of effect heterogeneity was noted by age (above vs below the median age in case subjects plus control subjects of 64, $P \geq .27$) or disease aggressiveness (high-risk vs low-risk PCa, $P \geq .20$) (Supplementary Methods, available online). GWAS of high-risk disease (vs controls) and high- ($n = 2984$) vs

low-risk ($n = 3012$) disease (Supplementary Methods, available online) did not reveal any novel PCa loci of genome-wide statistical significance that could differentiate risk by disease aggressiveness (Supplementary Figure 1, C and D, available online). In addition, aside from 8q24 (14), admixture mapping using 220 474 genotyped SNPs in case-case and case-control comparisons of local ancestry (Supplementary Methods, available online) failed to identify any novel risk regions harboring risk alleles that are highly differentiated in frequency between men of African and European ancestry (data not shown) (Supplementary Figure 2A, available online).

The most statistically significant PCa risk association genome wide was observed with a novel triallelic (A/T/G) variant at 8q24, with the T allele found in approximately 12% of case subjects and approximately 6% of control subjects (rs72725854 at position 128,074,815 located in “region 2”) (8). The risk allele (T) is only found in populations of African ancestry with a per-allele odds ratio of 2.33 (95% CI = 2.16 to 2.50, $P = 1.08 \times 10^{-109}$) (Supplementary Figure 2B, available online) and is in linkage disequilibrium with African ancestry-specific risk alleles rs114798100 (4%, OR = 2.43, 95% CI = 2.21 to 2.66, $P = 4.07 \times 10^{-81}$) and rs111906932 (2%, OR = 1.92, 95% CI = 1.70 to 2.16, $P = 1.44 \times 10^{-26}$) (8,9). These SNPs are not correlated ($r^2 = 0$ for rs114798100 and rs111906932) but define all observed haplotypes with the risk allele T of rs72725854, and thus describe the same association signal. In stepwise models, four additional variants were found to capture risk ($P < 10^{-5}$) across the 8q24 locus (127.8–128.8Mb) in men of African ancestry (Supplementary Table 2, available online).

Of the 100 reported PCa risk loci, 94 variants are polymorphic with an MAF of 0.05 or greater, 81 are directionally consistent with previous results in other populations (OR > 1), and 47 are nominally statistically significant associations ($P < .05$) in men of African ancestry (data not shown). Based on a polygenic risk score (Supplementary Methods, available online) comprising these risk variants as well as novel variants at 13q34 and 22q12.1 and variants shown to capture risk at 8q24 in men of African ancestry ($n = 5$), the 10% of men with the highest polygenic risk scores have a 3-fold (95% CI = 2.52 to 3.63) of PCa compared with men with “average risk” (polygenic risk scores in the 25th to 75th percentiles) (Supplementary Table 3, available online), which is comparable with that observed for the top 10% of the risk score distribution in men of European ancestry (OR = 2.93, 95% CI = 2.75 to 3.12) (2). Estimates for the top 1% of the polygenic risk scores in each population are 4.23 and 5.65, respectively.

A main limitation of this study is suboptimal statistical power (<80%) to detect modest effects (OR < 1.22) at genome-wide levels of statistical significance for common alleles with minor allele frequencies of less than 10%, particularly in analyses stratified by disease aggressiveness. Another limitation is the lack of understanding regarding the biological mechanisms through which genetic variation in these susceptibility regions influences risk.

Our findings substantiate the importance of conducting large-scale genetic studies in diverse populations for the discovery of novel risk loci that are ancestry specific (15). Further discovery efforts and fine-mapping of known loci will be needed to better understand the contribution of germline variation to PCa in men of African ancestry.

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Notes

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