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ORIGINAL INVESTIGATION

Results from a prostate cancer admixture mapping study in African-American men

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Abstract There are considerable racial disparities in prostate cancer risk, with a 60% higher incidence rate among African-American (AA) men compared with European-American (EA) men, and a 2.4-fold higher mortality rate in AA men than in EA men. Recently, studies have implicated several African-ancestry associated prostate cancer susceptibility loci on chromosome 8q24. In the current study, we performed admixture mapping in AA men from two independent case–control studies of prostate cancer to confirm the 8q24 ancestry association and also identify other genomic regions that may harbor prostate cancer susceptibility genes. A total of 482 cases and 261 controls were genotyped for 1,509 ancestry informative markers across the genome. The mean estimated individual admixture proportions were 20% European and 80% African. The most significant observed increase in European ancestry occurred at rs2141360 on chromosome 7q31 in both the case-only ($P = 0.0000035$) and case–control analyses. The most significant observed increase in African ancestry across the genome occurred at a locus on chromosome 5q35 identified by SNPs rs7729084 (case-only analysis $P = 0.002$), and rs12474977 (case–control analysis $P = 0.004$), which are separated by 646 kb and were adjacent to one another on the panel. On chromosome 8, rs4367565 was associated with the greatest excess African ancestry in both the case-only and case–control analyses (case-only and case–control $P = 0.02$), confirming previously reported African-ancestry associations with chromosome 8q24. In conclusion, we confirmed ancestry associations on 8q24, and identified additional ancestry-associated regions potentially harboring prostate cancer susceptibility loci.

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Introduction

Prostate cancer (MIM #176807) is the most common cancer among American men, affecting one in six of the male population. The American Cancer Society estimates that about 186,300 men in the United States will be diagnosed with prostate cancer in 2008 and about 28,660 men will die of this disease. Prostate cancer is the second leading cause of cancer death in men. There are considerable racial disparities

in prostate cancer risk, with a 60% higher incidence rate among African-American (AA) men compared with White men, and a 2.4-fold higher mortality rate in AA men than in White men (Jemal et al. 2008). In addition to AA race, established risk factors for prostate cancer include age and family history. It is estimated that highly penetrant inherited prostate cancer susceptibility genes contribute to approximately 5% of all prostate cancer cases, but they play a more significant role in early-onset disease. Family history studies support the role of genes in cancer risk, with an estimated 4.5-fold increase in risk among men with an affected brother, and an estimated 2.3-fold increase in risk in men with an affected father (Cerhan et al. 1999).

Multiple genome-wide linkage scans for prostate cancer genes have yielded few consistent results (Easton et al. 2003; Schaid 2004). A recently published report from a genome-wide admixture mapping study of prostate cancer in 1,597 AA men detected a susceptibility region on chromosome 8q24 (Freedman et al. 2006). Multiple follow-up studies using both admixture and traditional mapping methods have confirmed linkage to this region (Ghoussaini et al. 2008; Gudmundsson et al. 2007; Haiman et al. 2007; Robbins et al. 2007; Schumacher et al. 2007; Suuriniemi et al. 2007; Wang et al. 2007; Yeager et al. 2007), and three out of four loci in this region have been shown to be independently associated with prostate cancer risk in AA populations (Haiman et al. 2007). In the current study, our objective was to confirm the 8q24 ancestry association and identify other genomic regions associated with prostate cancer susceptibility using admixture mapping methods in AA prostate cancer cases and controls.

Materials and methods

Study subjects

Subjects included in this project are from two independent sources. The first was a case–control study of prostate cancer, gene–environment interaction in prostate cancer (GECAP) (Rybicki et al. 2006). All cases were diagnosed with adenocarcinoma of the prostate within 2 years of the date of enrollment, either of Caucasian or AA race, less than 75 years of age, living in the metropolitan Detroit tri-county area, and used Henry Ford Health System (HFHS) for their primary care. Controls were randomly selected from the same HFHS population base from which cases were drawn and frequency matched to cases on race and 5-year age stratum for a 3:1 case:control ratio; there were more cases than controls because the GECAP study was designed primarily for case-only analyses. From the original study population, AA cases and controls were included in the admixture analyses. The second source of subjects was men who participated in one of three case–control studies at Howard University (HU). The HU population consists of unrelated AA men affected and unaffected with prostate cancer, previously described by Robbins et al. (2007). All affected men were histologically diagnosed with adenocarcinoma of the prostate. Subjects were recruited over 4 years in the Washington, DC area from a Howard University Hospital urology practice and/or from ongoing free prostate cancer screening programs at the Howard University Cancer Center. Clinical evaluations, including PSA levels, were determined for all prostate cancer cases and all controls. Included in these studies were AA men 40–90 years of age. All healthy unaffected volunteers had PSA levels <2.5 ng/ml and normal DREs.

For all study participants, standardized demographic and medical history were collected, and all DNA used for genotyping was extracted from blood samples drawn at the time of interview by a trained phlebotomist. All study subjects provided informed, signed consent, and study protocols were approved by institutional Internal Review Boards.

Genotyping

Primers for a panel of 1,509 SNPs informative for West African versus European ancestry for use on the Illumina Bead Station platform were provided by one of the authors (David Reich). After removing SNPs with poor genotype call rates (n = 188), 1321 SNPs were available for analysis. Earlier versions of this panel were used in the Freedman et al. (2006) prostate cancer admixture mapping study, and the panel genotyped is now available as a standard product from Illumina (http://www.illumina.com/pages.ilmn?ID=235). For quality control in our study, DNA samples from 30 Centre d'Etude du Polymorphisme Humain (CEPH) individuals were included so that their genotype results could be compared with those publicly available through HapMap. Concordance was excellent for the markers we used for analysis.

Admixture mapping

Data were analyzed using the ADMIXMAP statistical program, http://homepages.ed.ac.uk/pmckeigu/admixmap/ (Hoggart et al. 2003, 2004). ADMIXMAP uses a hybrid of Bayesian and traditional modeling to compare observed versus expected ancestry across the genome. Both case-only and case–control approaches were implemented. All models were adjusted for age at diagnosis for cases and age at study entry for controls. We report Z scores and associated P values for the case-only analyses. The Z score is a test statistic for association with ancestry at each locus, based on comparing the observed and expected proportions of gene copies at each locus. In our models, a positive Z-score

indicates excess African ancestry, and a negative *Z*-score indicates excess European ancestry. Prior allele frequencies for the African and European ancestral populations were provided by David Reich based on genotypes from the West African and European populations previously reported in Smith et al. (2004) and in the International HapMap project (http://www.hapmap.org/). Analyses were performed in the entire sample, stratified by age, and stratified by prostate cancer aggressiveness within the HFHS samples. We defined aggressive prostate cancer as Gleason sum ≥4 + 3 or stage ≥T3 (regional or distant).

Results

Of the 776 samples genotyped, a total of 482 cases and 261 controls were eligible for inclusion in the analyses. 33 samples (4.4%) were excluded because they failed one of the standard data quality checks described in previous reports (Freedman et al. 2006; Reich et al. 2005). Briefly, samples were removed if they had a much lower genotyping completeness than other samples used in the analysis based on an empirical inspection of the distribution, if they were duplicates or first degree relatives of other samples in the analysis, if they had greater than about 85% European origin from our analysis, or if they had one parent of entirely European origin. The mean estimated individual admixture proportions after removal of the outlier samples were 20% European and 80% African. Patient characteristics overall and by study site are described in Table 1. Equal number of cases were derived from each source, and a greater proportion of the controls came from HU. Cases from HU were significantly older than cases from HFHS, and controls from HU were significantly younger than controls from HFHS. Median PSA in the HFHS cases was significantly lower than the median PSA in the HU cases, and there was no difference between the two sites with respect to median PSA in the controls.

The age-adjusted genome-wide *z*-scores for the case-only analyses are presented in Fig. 1, and information about markers at local peaks with $|Z| > 3.0$ is summarized in Table 2. In general, results from the case–control analyses did not differ greatly from those obtained using the more powerful case-only approach; therefore, only case-only results are presented unless discrepancies in inferences from the two methods occurred. The greatest observed increase in ancestry occurred at marker rs2141360 on chromosome 7 (Fig. 2a), where excess European ancestry was observed (case-only $P = 0.0000036$). The greatest observed increase in *African* ancestry across the genome occurred at rs7729084 on chromosome 5q35 in the case-only analysis ($P = 0.0016$; Fig. 2b), and at marker rs12474977 in the case–control analysis ($P = 0.0039$). Note that marker rs12474977 is 646 kb centromeric to marker rs7729084, and the two markers were adjacent to each other on the panel. The marker on chromosome 8 that was associated with the greatest excess African ancestry in both the case-only (Fig. 2c) and case–control analyses was rs4367565 (case-only and case–control $P < 0.02$).

When subjects were stratified by age (<60 or ≥60), both age categories supported an association with rs2141360 on chromosome 7q31 (Table 2). Conversely, support for rs4367565 on chromosome 8q24 was greater in men in the older age group than in the younger age group ($Z = 2.063$, $P = 0.039$ vs. $Z = 1.513$, $P = 0.13$). Overall, the greatest ancestry association observed in the men <age 60 was at rs6724395 on chromosome 2p14, in a region of excess European ancestry ($Z = -4.195$, $P = 0.000027$). The greatest excess African ancestry in men <age 60 occurred at rs692842, approximately 1.9 Mb from the peak on chromosome 5 in the unstratified sample. Among men ≥age 60, the greatest excess European ancestry was observed at

Table 1 Participant characteristics, overall and by study site

	All sites	Henry Ford health system	Howard University	*P* value
Total				
Cases	482	241	241	
Controls	261	92	169	
Mean age				
Cases	63.8	61.5	66.1	<0.0001[a]
Controls	58.2	60.9	56.7	0.0004[a]
Median PSA				
Cases	6.0	5.6	7.8	0.0007[b]
Controls	0.9	0.8	0.9	0.6787[b]

[a] *t* test comparing HFHS and HU

[b] Mann–Whitney *U* test comparing HFHS and HU

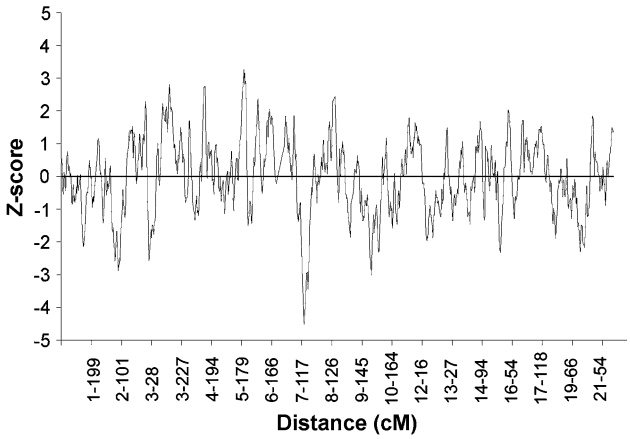

Fig. 1 Genome-wide admixture mapping results in 482 men with prostate cancer, adjusted for age

Table 2 Summary of SNPs at regional ancestry association peaks with $|Z| > 3.0$

Locus name	Location[a]	Position[b]	Excess ancestral population	Entire sample		Age <60		Age ≥60	
				Z score	*P* value	*Z* score	*P* value	*Z* score	*P* value
rs6724395	2p14	69799822	European	−2.666	0.0077	−4.195	0.000027	−0.381	0.7029
rs7729084	5q35.2	174314186	African	3.164	0.0016	2.704	0.0068	2.221	0.0263
rs692843	5q35.2	176188252	African	3.058	0.0022	3.116	0.0018	2.036	0.0418
rs2141360	7q31.31	120847409	European	−4.636	0.0000035	−3.172	0.0015	−3.311	0.0009
rs683493	7q31.33	125592537	European	−4.516	0.0000063	−3.338	0.0008	−2.994	0.0028
rs4623785	10p13	12784342	European	−3.116	0.0018	−1.523	0.1279	−2.551	0.0107

[a] dbSNP build 129

[b] HG18 genome build

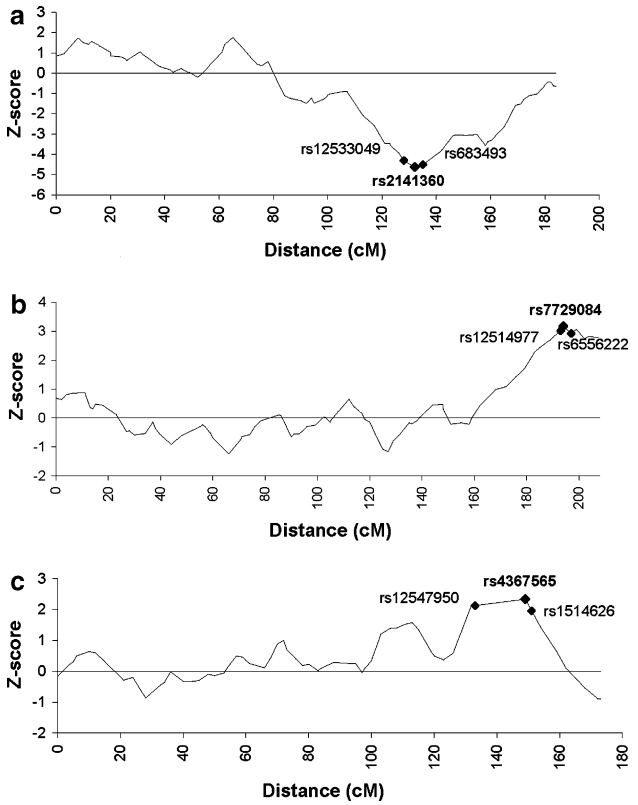

Fig. 2 Admixture mapping results from select chromosomes in 482 African-American men with prostate cancer, adjusted for age: **a** chromosome 7, **b** chromosome 5, **c** chromosome 8

rs2141360 on chromosome 7q31 ($Z = -3.311$, $P = 0.00090$); note that this is also where a regional peak in the entire sample occurred. In this same subsample, the greatest excess African ancestry was observed at rs9288952 on chromosome 3 ($Z = 3.208$, $P = 0.0013$).

Within the HFHS subjects, we were able to stratify on prostate cancer aggressiveness in 238 cases with available clinical information. In the 134 men with aggressive disease, the strongest ancestry association was at the same marker on chromosome 7q31.31 ($Z = -4.782$, $P = 0.0000017$); however, no association with this marker was observed in the 104 men with non-aggressive disease ($Z = -1.561$, $P = 0.12$; data not shown).

Discussion

Results from the current study confirm the African ancestry association with the region on chromosome 8q (supporting data; Fig. 1) detected by Freedman et al. (2006), with greatest excess African ancestry on chromosome 8 at rs4367565 ($Z = 2.37$, $P = 0.018$). This finding is also consistent with several other confirmatory studies (Ghoussaini et al. 2008; Gudmundsson et al. 2007; Haiman et al. 2007; Robbins et al. 2007; Schumacher et al. 2007; Suuriniemi et al. 2007; Wang et al. 2007; Yeager et al. 2007). Robbins et al. (2007) report the greatest association at rs7008482 ($P = 0.00050$), which is flanked in our study by rs12547950 ($Z = 2.13$, $P = 0.033$) ~2.7 Mb centromeric and the local peak at rs437565, 5.3 Mb telomeric.

Additionally, ancestry associations with regions on chromosomes 7 and 5 were detected in our study population. Of note, our best evidence for genome-wide ancestry association overall and within the aggressive cancer group resides in a region on chromosome 7q31.31 which contains the *PODXL* (Podocalyxin-Like, MIM *607679) gene. Association between this region and high Gleason grade was first identified by Witte et al. (2000) at 7q32.3, with a peak ~2 cM centromeric to D7S1804, and evidence for this association was strengthened by the 2003 expanded study (Witte et al. 2003). Subsequently, association with high Gleason score was confirmed in a German population (Paiss et al. 2003) and by an allelic imbalance study (Neville et al. 2002). The *PODXL* gene, located within this region, was implicated in aggressive prostate cancer risk by Casey et al. (2006), and the variant most associated with prostate cancer was very rare in the Yoruban population (<1%). A second candidate gene in this region is *DOCK4* (dedicator of cytokinesis 4, MIM *602632) which is involved in regulating intercellular junctions and cell

migration, and also has been shown to harbor a missense mutation in prostate cancer cells resulting in defective Rap1 activation (Yajnik et al. 2003).

The greatest association with African ancestry occurred on 5q35 at marker rs7729084. This region also demonstrated the greatest association with African Ancestry on chromosome 5, albeit not statistically significant, in the Freedman study (2006). Witte et al. (2000) first observed linkage to a ~26 cM region on 5q31.3-33.3 associated with high Gleason score, with peak linkage occurring halfway between D5S1480 and D5S820 ($P = 0.0004$); this region is slightly centromeric to the 5q35.2 region observed to have excess African ancestry in our sample. Association between this region on chromosome 5 and Gleason grade has been confirmed by several other genome-wide linkage scans (Goddard et al. 2001; Schaid et al. 2007; Slager et al. 2006), including a follow-up study by Witte et al. (2003).

While we are encouraged by the consistency between our results and multiple confirmatory findings on chromosome 8 (Ghoussaini et al. 2008; Gudmundsson et al. 2007; Haiman et al. 2007; Robbins et al. 2007; Schumacher et al. 2007; Suuriniemi et al. 2007; Wang et al. 2007; Yeager et al. 2007) including one that included the HU samples also used in our study (Robbins et al. 2007), the study is limited by a relatively small sample size to detect loci with smaller effects, particularly after stratifying by age and disease aggressiveness. Of the 22 SNPs included in the Robbins paper, 16 (including all that achieved statistical significance) fell between two flanking markers (rs12547950 and rs4367565) in our paper. Z scores of the HFHS samples and HU samples were very similar at these flanking markers: 2.20 and 1.30 at rs12547950 and 1.58 and 2.09 at rs4367565, respectively. When the HU samples were excluded from the analyses, the peak on chromosome 8 in the HFHS samples is at rs6994682 ($Z = 2.52$), approximately 30 cM centromeric to the combined peak rs4367565. We were unable to examine the specific prostate-cancer associated regions identified within this genomic locus (Haiman et al. 2007; Robbins et al. 2007) because of inadequate SNP density. A final limitation was that the ADMIXMAP program does not yet have the capacity to examine the X chromosome reliably. Previously published ADMIXMAP power calculations established that a Z score of 4.27 with a corresponding P value of 10^{-5} is the threshold for statistical significance (Hoggart et al. 2004). We were not able to achieve this level of power for the loci on chromosomes 8 and 5. However, the locus on chromosome 7 far exceeded this criterion level of genome-wide significance.

In conclusion, we confirmed the previous African ancestry associations with a genomic locus on 8q24, and identified a possible second locus on chromosome 7q31 associated with excess European ancestry in this region. Fine mapping with a higher density of ancestry informative marker density in this region is needed to narrow the defined locus and better target future candidate gene studies.

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