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8q24 risk alleles in West African and Caribbean men

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Abstract

BACKGROUND—Multiple genetic studies have confirmed associations of 8q24 variants with susceptibility to prostate cancer (CaP). However, the magnitude of risk conferred in men living in west Africa is unknown.

METHODS—Here we determine the prevalence of 8q24 risk alleles and test for association with CaP risk alleles in west African descent populations from rural Nigeria, Cameroon, and the Caribbean island of Jamaica. Ten 8q24 SNPs were genotyped in histologically-confirmed CaP cases (n=308) and clinically evaluated controls (n=469). In addition, unrelated individuals from Sierra Leone (n=380) were genotyped for comparison of allele frequency comparisons.

RESULTS—SNPs rs6983561, rs7008482, and rs16901979 were significantly associated with CaP risk in west Africans (P<0.03). No associations with CaP were observed in our Caribbean samples. Risk alleles for rs6983267, rs7008482, and rs7000448 were highly prevalent (>84%) in West Africa. We also reveal that the A-risk allele for the ‘African-specific’ SNP bd11934905 was not observed in 1,886 chromosomes from three west African ethnic groups suggesting that this allele may not be common across west Africa, but is geographically restricted to specific ethnic group(s).

CONCLUSIONS—We provide evidence of association of 8q24 SNPs with prostate cancer risk in men from Nigeria and Cameroon. Our study is the first to reveal genetic risk due to 8q24 variants (in particular, region 2) with CaP within two west Africa countries. Most importantly, in light of the disparate burden of CaP in African Americans, our findings support the need for larger genetic

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Electronic-Database Information

National Center for Biotechnology Information’s dbSNP is available at <http://www.ncbi.nlm.nih.gov/dbSNP>.

Haplotype Map (HapMap) database for SNP and allele frequency information is available at <http://www.hapmap.org>.

studies in west African descent populations to validate and discern function of susceptibility loci in the 8q24 region.

Keywords

8q24; west Africans; Caribbean; prostate cancer; genetic risk

INTRODUCTION

Recent genome-wide association, linkage, and admixture scan analyses have associated various chromosome 8q24 sequence variants with susceptibility to prostate, colorectal, and breast cancer (1–8). Several single-nucleotide polymorphisms (SNPs) from different 8q24 regions impart modest risk of prostate cancer (CaP) in European men (1,2,6–8). A recent GWAS, two admixture mapping scans, and multiple association studies revealed significantly increased risk of CaP due to 8q24 risk alleles in African American (AA) men (2,5,9–15). Several of the 8q24 risk alleles in European American (EA) men seem to be different than those of AA men (5,11). SEER data also highlights that the increased risk of CaP in AA men abates over time. AA men diagnosed at < 55 years of age have a 2.27-fold higher rate than EA men, but the ratio decreases to 1.48-fold for men diagnosed at > 75 years of age (16). Genetic variation at 8q24 may explain part of this increased incidence at an earlier age.

AA men have the highest prevalence of prostate cancer in the world, which represents a significant health disparity relative to US men of European ancestry (17). Studies comparing AAs with other US ethnic groups have clarified the increased risk of prostate cancer, but do not address the biologic etiology of this disparity. It is becoming increasingly clear that men of west African (WA) ancestry, including AAs and Blacks in the Caribbean, face higher rates of prostate cancer and worse cancer specific survival (18). Pca incidence and morbidity is increasing in west Africa (19,20), and according WHO 2010 Global Status Report on noncommunicative diseases, mortality from noncommunicative diseases will be more than the mortality from infectious diseases in sub-Saharan Africa by 2030. However, not many CaP research projects have been conducted in west Africa (21) and only a few genetic studies on risk (22,23). Conducting epidemiologic studies with men from different countries that are genetically-related may elucidate both genetic and environmental risk factors for prostate cancer in AAs. However, there is limited data on prostate cancer epidemiology from West Africa and the Caribbean Islands.

Understanding the prevalence of 8q24 risk alleles in WA men may help explain the increased impact of prostate cancer on African American men. The frequency of these 8q24 alleles and their magnitude of risk for prostate cancer in men of West African (WA) ancestry are largely unknown. In African Americans, the most consistently replicated risk allele in the 8q24 region is the A-allele of SNP bd11934905 (2,14,24). SNP bd11934905 has the largest effect size in the 8q24 region (OR>4) and its prevalence in AAs controls is ~1%. This SNP was discovered by resequencing region 2 of 8q24 in HapMap samples consisting of unrelated European Americans (n=54), West Africans (Yoruba) (n=57), and Japanese (n=39) samples. The A allele was termed ‘African-specific’ after it was observed only among the Yoruba west Africans at a frequency of 4% (2,24).

Here we examine genetic variation for ten 8q24 SNPs in 1,157 prostate cancer cases, controls, and population samples from four countries in west Africa and the Caribbean. These populations can provide insight on the spectrum of allelic diversity in men of west African descent and help elucidate a potential role of increased frequency of 8q24 risk alleles in WA men as a contributor to the CaP disparity between African Americans and

other US ethnic groups. Given the known genetic heterogeneity of African populations we tested for heterogeneity of SNP effects.

MATERIALS AND METHODS

Subjects

From 1999–2003, we performed two rural population-based studies of CaP in WA men from Edo State, Nigeria and Yaounde, Cameroon. Details on the study populations are provided in Ukoli et al. (25) and Angwafo et al (26). The WA men in this study identified themselves as Bini (Nigerian) or Bamileke (Cameroon) ethnicity. In total there were 212 CaP cases and 351 controls.

The third clinical population consisted of 214 men of African descent, who resided on the Caribbean island of Jamaica (96 CaP cases and 118 controls). Jamaican men were recruited during the year 2000 from the University Hospital of the West Indies in Kingston, Jamaica (27). Each case subject was diagnosed with histologically-confirmed prostate adenocarcinoma by a pathologist. Men free of prostate cancer were recruited from prostate cancer screening programs on the island as well.

All men underwent clinical interviews, prostate specific antigen (PSA) measurement and digital rectal examinations (DRE). All men also had blood drawn for DNA extraction. The WA cases had histological CaP based on surgical resection (radical prostatectomy or transurethral resection) performed for symptomatic, often advanced stage CaP since CaP screening is not performed in most of WA. The controls were men who had PSA < 4.0 and a normal DRE. In order to compare 8q24 allele frequencies across west Africa we included a set of population-based samples consisting of self-reported Mende and Temne men from Sierra Leone (N= 380) (28). These Sierra Leone samples were used only to examine allele frequencies and were not included in the case-control association analyses.

SNP genotyping

We selected ten SNPs from four 8q24 chromosomal regions that have been reported to be associated with CaP (2,5,7,11,15,29). SNPs were genotyped using the Sequenom MassARRAY™ platform and iPLEX™ chemistry. Briefly, iPLEX™ assays were designed utilizing the Sequenom Assay Design software, allowing for single base extension (SBE) designs used for multiplexing. PCR and SBE primer sequences are available upon request. Multiplex polymerase chain reactions (PCR) were performed to amplify 5–10 nanograms (ng) of genomic DNA. PCR reactions were treated with shrimp alkaline phosphatase (SAP) to neutralize unincorporated dNTPs. Subsequently, a post-PCR single base extension reaction was performed for each multiplex reaction using concentrations of 0.625 micromolar (μM) for low mass primers and 1.25 μM for high mass primers. Reactions were diluted with 16 microliters (μl) of H₂O and fragments were purified with resin, spotted onto Sequenom SpectroCHIP™ microarrays and scanned by MALDI-TOF mass spectrometry. Individual SNP genotype calls were generated using Sequenom TYPER™ software, which automatically calls allele specific peaks according to their expected masses. SNP data quality was high, genotyping success rate was >98.9% for the SNPs. Blinded duplicate test samples and two water samples (PCR-negative controls) were included in each 96-well plate. The rate of concordant results between duplicate samples was more than 99%.

Statistical Analyses

We tested the ten 8q24 SNPs for association with prostate cancer by performing conditional logistic regression using the program PLINK (30). In order to help determine if our associations were valid we performed permutation tests. Empirical p-values, which

corrected for multiple tests, were generated by 10,000 permutations of the trait values in the sample using the Max (T) procedure. For all analyses, genetic effects were adjusted for age and PSA levels (at time of diagnosis for case subjects and at time of ascertainment for controls). We controlled for PSA in our analyses because it is known that WA men are most often diagnosed after presenting for prostate-related symptoms due to the lack of PSA screening in west Africa, thus significantly higher mean PSA levels are observed at diagnosis for west African men (20,25,26,31). For association testing using the Caribbean samples we also included individual west African genetic ancestry estimates using 105 ancestry informative markers to control for admixture stratification (32).

RESULTS

Comparison of population characteristics revealed that significantly higher mean PSA levels were observed among the west African samples (Table 1). Additionally, the WA men were significantly older than the Caribbean CaP cases and controls ($P=0.001$). No significant differences were observed for age between cases and controls within each population except for the Nigerians who had slightly older controls than CaP cases (Table 1).

After genotyping the ten SNPs in our samples, two SNPs were excluded from further analyses due to being monomorphic in our west African populations. Surprisingly, the risk allele (A) for the African-specific SNP, bd11934905 (region 2) (2,33) was not observed at all in over 943 individuals (1,886 chromosomes) from Cameroon, Nigerian and Sierra Leone. We did observe the bd11934905 A allele in one CaP patient from Jamaica but not in any of the controls ($n=118$). In addition, for the WA and Caribbean samples, the risk allele (T) for rs7000448 was monomorphic (100%). We tested genotype frequencies for the eight remaining SNPs for significant departure from Hardy Weinberg (HW) proportions independently in the cases and controls. For each population, all genotypes were in Hardy-Weinberg equilibrium. Allele frequencies in cases and controls for the SNPs are detailed in Table 2. Several of the 8q24 risk alleles are highly prevalent in the WA groups. For instance, SNPs rs6983267, rs7008482, and rs7000448 had a frequency $>84\%$ across the sampled populations of WA descent. The G allele of the region 3 SNP rs6983267 was quite common in WA, approaching fixation (98%) in the Nigerian controls.

Allele frequencies were relatively consistent across the WA populations and several SNPs exhibited significant differences (univariate analyses) in frequencies between cases and controls within several of the groups (Table 2). Most of these associations were robust and when adjustments for age and PSA were made they were still significant (Table 3). The odds ratio for the region 4 SNP, rs7008482 was 2.3 (95% CI = 1.2 – 4.1) in the WA samples. In addition, two region 2 SNPs (rs6983561 and rs16901979) were associated with CaP in the WA pooled samples ($P=0.03$). The odds ratios were 0.6 (95% CI=0.5–0.9) and 1.6 (95% CI=1.1–2.0) for rs6983561 and rs16901979, respectively. No SNP associations were observed in the Jamaican population. In the total pooled sample, the two region 2 SNPs were significant, rs6983561 (OR=0.8; 95% CI=0.6–0.9; $P=0.04$) and rs16901979 (OR=1.3; 95% CI=1.0–1.6; $P=0.05$).

No evidence of heterogeneity of allelic effects was observed across these African descent populations (Table 3).

DISCUSSION

Multiple independent genetic variants on chromosome region 8q24 have been implicated in CaP risk (2,5–7,15,29,34). Our study of 1,157 men is the first genetic association study for 8q24 CaP risk loci in WA descent from Nigeria, Cameroon, and Jamaica. We genotyped 10

markers from each of the four previously reported regions of risk at 8q24. Results from previously published association studies have shown the strongest associations with rs6983561 (region 2), rs16901979 (region 2), rs6983267 (region 3), and rs1447295 (region 1). Our study replicates the findings of association with CaP for the two region 2 SNPs rs6983561 and rs16901979 and the region 4 SNP rs7008482.

Region 2 (128.14–128.28 Mb) is a gene desert ~140kb in length and has been consistently shown to be the strongest 8q24 region of CaP risk in AAs. Gudmundsson et al. (35) observed that SNP rs16901979 was significantly associated with prostate cancer risk, with an odd ratio (OR) of 1.6 in individuals of European descent and 1.3 in AAs. The frequency of the A-risk allele for rs16901979 is uncommon (2% – 4%) in the European population but our study reveals prevalence as high as 60% in west African populations. We observed an association with the rs16901979 A-allele (odds ratio per allele=1.6, $P=0.03$) among west Africans. Haiman et al. also observed strong association with CaP risk in this region around rs16901979 for three additional SNPs rs13254738, rs6983561 and bd11934905, with the most significant SNP being rs6983561 ($P=7.9\times10^{-19}$) and the largest OR of 2.45 at bd11934905 in AAs (2). The association of CaP risk with 8q24 region 2 around rs16901979 was further confirmed by several follow-up studies and a GWAS in AAs (5,10,12–14,36–39). Here we confirmed the inverse association of A-allele of rs6983561 with CaP risk (OR=0.6; 95%CI=0.5–0.9, $P=0.03$) in WA men.

We were unable to test the bd11934905 SNP for association with CaP in west Africans because it was monomorphic. It appears that the risk allele is even rarer in our sampled west Africans than what we and others have shown in AAs. We observed the A-risk allele in only one CaP case from Jamaica and did not observe the allele once in any of our three WA populations from Sierra Leone, Cameroon, or Nigeria (total of 1,886 chromosomes). This was unexpected given that the A-allele was found at 4% in a small number (N=57) of Yoruba, Nigerian HAPMAP samples. Thus, it is likely that the bd11934905 A-allele is regionally and/or ethnically specific to the Yoruba population. Although we had a significant number of Nigerian samples from the Bini ethnic group, we did not genotype any Yoruban samples. If our findings are correct, the bd11934905 A-allele in AAs may tag an ancestral risk haplotype of Yoruba ancestry. However, since none of these known prostate cancer risk variants in 8q24 region 2 align to a known gene, the main challenge continues to be elucidating the biological mechanism of the associated region in the development of prostate cancer.

The region 1 SNP, rs1447295, was not associated with increased CaP risk in our WA population. The rs1447295 A-allele was more frequent in WA men (43%) relative to other populations (34% in African Americans and ~12% in Europeans) (1). Strong and replicable association with rs1447295 are seen among samples of European ancestry (40–43). However, among African Americans, significance was achieved ($P=0.011$) only for early onset cases (age <65) (40). Several other studies fail to show a significant association at region 1 in African Americans (11,35,38). When we stratified based on age < 65 yrs, we still did not observe evidence of a positive association for rs1447295 with prostate cancer risk in our WA descent populations.

In our previous study of genetic ancestry and CaP in AAs, genotyping of ancestry informative markers and additional 8q24 SNPs provided evidence of a strong effect from west African ancestry along 126.8 Mb of 8q24 influencing CaP risk. SNP rs7008482 revealed a highly significant association with disease even after correction for age, and local and global individual ancestry (5). In that study, rs7008482 represented a new region of independent risk (region 4), which is mapped to 8q24.13, ~2.2 Mb proximal to rs1447295 region at 8q24.21. SNP rs7008482 lies within an intronic region of the *NSMCE2* (also

called *MMS21*) gene, which has been shown to be involved in DNA replication, recombination, and repair (44). Several studies in African Americans replicated the finding for rs7008482 (10,39). Recently, a CaP GWAS in AAs (3,425 CaP cases and 3,290 AA male controls) did not replicate the rs7008482 finding (12). However, in this study of WA men we revealed that rs7008482 was the most significantly associated risk allele among those tested. The lack of consensus across studies may be due to heterogeneity in west African ancestry along that region of 8q24 among AAs given that the association of rs7008482 with CaP in AAs is strongly influenced by genetic ancestry along that region (5).

The lack of significant associations for the other published risk alleles, such as the region 3 SNP rs6983267, may be due to the relatively small sample size of our study. We note however, a recent study of 8q24 risk variants in Afro-Caribbean Tobago men by Okobia et al. (45). They tested for the association of three 8q24 SNPs, rs16901979, rs1447298, and rs6983267 with Pca risk. Similarly, in their study, only rs16901979 was significantly associated with CaP risk. Given the relatively high frequency for many of these 8q24 risk alleles among the WA men a larger sample size is required in order to rule out significance. WA men have a much higher prevalence of 8q24 risk alleles than other populations of European and Asian ancestry. Our study provides justification for further genetic investigations, with larger patient sample sizes from west Africa, to facilitate the identification of causal alleles. As CaP disproportionately affects men of west African descent, the discovery of causal risk alleles and their function could have important implications for early detection of CaP in this high-risk population.

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Table 1

Clinical characteristics of prostate cancer cases and controls

Country of Origin/Characteristic	Cases	Controls	P
Nigeria			
Number of participants	110	218	
Age, years (mean (SD))	74.6 (12.9)	77.1 (9.7)	0.050
PSA in ngml-1 (mean(SD)) ^a	109.6 (25.8)	1.5 (1.7)	<0.001
Cameroon			
Number of participants	102	133	
Age, years (mean (SD))	70.1 (11.5)	71.5 (11.1)	0.453
PSA in ngml-1 (mean(SD)) ^a	183.2 (261.1)	1.41 (2.5)	<0.001
Jamaica			
Number of participants	96	118	
Age, years (mean (SD))	65.4 (11.4)	64.7 (10.0)	0.633
PSA in ngml-1 (mean(SD)) ^a	14.5 (9.7)	1.3 (1.2)	<0.001
Total African descent clinical samples			
Number of participants	308	469	
Age, years (mean (SD))	70.0 (11.7)	71.1 (10.4)	0.170
PSA in ngml-1 (mean(SD)) ^a	146.2 (240.7)	2.0 (1.9)	<0.001
Sierra Leone population controls			
Number of participants	--	380	

Table 2

8q24 SNP allele frequency in Pca cases/controls

Region ^a	SNP ID	Position	Allele	Cameroon	Nigeria	WA Pooled	Jamaica	Total	SL	AA ^b	EA ^b
				102/133	110/218	212/351	96/118	308/469	380	601	401
4	rs16900305	126142853	A	0.13/0.09	0.10/0.09	0.11/0.09	0.10/0.08	0.11/0.09	0.12	0.18	0.00
4	rs7008482	126336812	G	0.92/0.84 ^{**}	0.93/0.85 ^{**}	0.92/0.87 [*]	0.88/0.88	0.91/0.87	0.99	0.83	0.17
2	rs6983561	128176062	A	0.30/0.41 [*]	0.38/0.45	0.35/0.44 [*]	0.45/0.50	0.38/0.46 [*]	0.48	0.57	0.96
2	rs16901979	128194098	A	0.64/0.57	0.60/0.50 [*]	0.61/0.52 [*]	0.50/0.50	0.58/0.52	0.50	0.42	0.02
2	bd11934905	128200991	A	0.00/0.00	0.00/0.00	0.00/0.00	0.01/0.00	0.002/0.00	0.00	0.01	0.00
3	rs10505477	128476625	C	0.13/0.14	0.06/0.10	0.09/0.11	0.14/0.17	0.11/0.13	0.14	0.17	0.42
3	rs6983267	128482487	G	0.95/0.97	0.95/0.98 [*]	0.95/0.98 [*]	0.91/0.89	0.93/0.96	0.95	0.93	0.46
3	rs7000448	128510352	T	1.00/1.00	1.00/1.00	1.00/1.00	1.00/1.00	1.00/1.00	1.00	0.74	0.35
1	rs1447295	128554220	A	0.36/0.39	0.39/0.45	0.38/0.43	0.39/0.31	0.38/0.40	0.35	0.31	0.11
1	rs10090154	128601319	T	0.19/0.29	0.19/0.20	0.19/0.23	0.20/0.15	0.19/0.21	0.25	0.16	0.09

^aRisk regions as defined by (5).

^bFrequency of the SNPs in African Americans (AA) and European American (EA) controls (5,14).

WA = west African; SL = Sierra Leone population controls.

* P < 0.05 from univariate regression analyses.

** P < 0.001 from univariate regression analyses.

Table 3
Association of 8q24 alleles with Prostate Cancer Risk in the African Diaspora

SNP #	Allele	OR (95% CI) ^a P					P _{het}
		Cameroon	Nigeria	WA Pooled	Jamaica	Total	
rs16900305	A	1.4 (0.7–3.0) 0.29	1.1 (0.6–2.1) 0.71	1.3 (0.8–2.0) 0.33	1.4 (0.7–2.8) 0.36	1.2 (0.2–0.9) 0.25	0.55
rs7008482	G	2.3 (1.2–5.4) 0.003	2.3 (1.2–5.9) 8.9×10⁻⁵	2.3 (1.2–5.1) 0.03	0.9 (0.5–1.8) 0.98	0.7 (0.5–1.0) 0.30	0.87
rs6983561	A	0.6 (0.4–0.9) 0.05	0.7 (0.5–1.1) 0.12	0.6 (0.5–0.9) 0.03	0.8 (0.5–1.2) 0.32	0.8 (0.6–0.9) 0.04	0.46
rs16901979	A	1.4 (0.8–2.5) 0.19	1.4 (1.1–2.0) 0.03	1.6 (1.1–2.0) 0.03	1.0 (0.6–1.4) 0.93	1.3 (1.0–1.6) 0.05	0.63
bd11934905	A	-	-	-	-	-	-
rs10505477	C	0.9 (0.5–1.8) 0.70	0.6 (0.3–1.3) 0.18	0.7 (0.4–1.2) 0.24	0.8 (0.4–1.4) 0.43	0.8 (0.6–1.2) 0.25	0.90
rs6983267	G	0.6 (0.2–2.0) 0.83	0.4 (0.1–1.1) 0.06	0.5 (0.2–1.0) 0.06	1.1 (0.6–2.5) 0.68	0.6 (0.4–1.1) 0.24	0.76
rs7000448	T	-	-	-	-	-	-
rs1447295	A	0.9 (0.5–1.4) 0.63	0.7 (0.5–1.1) 0.85	0.8 (0.6–1.1) 0.29	1.4 (0.9–2.1) 0.14	0.9 (0.7–1.2) 0.55	0.82
rs10090154	T	0.6 (0.3–1.0) 0.08	0.8 (0.6–1.4) 0.64	0.8 (0.5–1.1) 0.19	1.5 (0.9–2.6) 0.14	0.9 (0.7–1.2) 0.47	0.51

^a ORs were adjusted for age and PSA levels in all samples and genome-wide west African ancestry in the Jamaican samples.

^b P_{het} = P value for heterogeneity of allelic effects across African descent groups (2 df test).