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ORIGINAL ARTICLE

Prostate Cancer

Region 2 of 8q24 is associated with the risk of aggressive prostate cancer in Caribbean men of African descent from Guadeloupe (French West Indies)

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Multiple regions of the genome have been associated with the risk of prostate cancer in Caucasians, particularly including several polymorphisms located at 8q24. Region 2 of 8q24 has been repeatedly found to be associated with the risk of prostate cancer among men of African descent, although one study performed in the Caribbean island of Jamaica did not report this finding. In this study, the single nucleotide polymorphism rs16901979, located in region 2 of 8q24, was genotyped in 498 cases of histologically confirmed prostate cancer and 541 controls from the French Caribbean islands of Guadeloupe, where the population is largely of African descent. The AA genotype and the A allele at rs16901979 were associated with elevated risks of prostate cancer (odds ratios [ORs] = 1.84, 95% confidence interval [95% CI] = 1.26–2.69, *P* = 0.002 and OR = 1.36, 95% CI = 1.13–1.64, *P* = 0.001, respectively). Following stratification of the patients by disease aggressiveness, as defined by the Gleason score, the pooled genotypes AC + AA were associated with a higher risk of a Gleason score ≥7 at diagnosis (OR = 1.79, 95% CI = 1.17–2.73, *P* = 0.007). In summary, the A allele at rs16901979 was associated with the risk of prostate cancer in the Caribbean population of Guadeloupe, confirming its involvement in populations of African descent. Moreover, our study provides the first evidence of an association between this variant and the risk of aggressive prostate cancer.

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INTRODUCTION

Over the last few years, several genome-wide association studies have been performed on patients with prostate cancer and controls of Caucasian origin. These studies identified more than 70 loci or regions associated with the risk of prostate cancer.[1] Notably, at least five different regions on the long arm of chromosome 8 at 8q24 have been implicated.[2] These 8q24 loci were also studied in various populations of African descent, which have a higher incidence of prostate cancer and a higher associated mortality rate than Caucasian men. Among these loci, markers in region 2 of 8q24 were consistently found to be associated with prostate cancer susceptibility in men of African ancestry;[3,4] in particular, the polymorphism rs16901979 is associated with a higher risk of prostate cancer in African-American men,[5–11] Afro-Caribbean men (on Tobago island),[12] and West African men (Nigerians).[13] However, no association was reported between this single nucleotide polymorphism (SNP) and the risk of prostate cancer in men in Cameroon (Africa) or Jamaica (an Afro-Caribbean population).[13] This discrepancy may be attributable to heterogeneity in African ancestry and/or the relatively small samples included in the studies. To further assess the potential association between the polymorphism rs16901979 and the risk of prostate cancer in Afro-Caribbean men, we analyzed a larger sample of men living in Guadeloupe (French West Indies), a Caribbean population of predominantly West African ancestry.

MATERIALS AND METHODS

Study population

Subjects were recruited as part of a population-based case–control study in Guadeloupe (French West Indies), as previously described.[14] Briefly, consecutive patients who had histologically confirmed prostate cancer and attended public or private urological clinics participated in the study. Overall, the study population included 80% of new cases of prostate cancer in the Guadeloupe archipelago during the study period. Controls were recruited from the group of men who participated in a free systematic health screening program open to the general population during the same period. Each year, a random population sample was selected in accordance with the sex and age

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distribution of the general population and invited to participate. The rate of participation exceeded 95% for both cases and controls. For both groups, inclusion criteria were as follows: no history of (or current) hormone treatment, including treatment with 5-α reductase inhibitors, and at least one parent born on a Caribbean island with a population recognized as being predominantly of African descent. Additional inclusion criteria for controls were normal findings upon digital rectal examination and a total plasma prostate-specific antigen concentration no higher than the 75th percentile of that of the appropriate age group of African-American men without clinical evidence of prostate cancer.[15]

Information was collected from both patients and controls concerning demographic characteristics, place of birth, parents' place of birth, use of medication, and family history of prostate cancer. Participants were also asked to provide a blood sample. DNA was extracted from leucocytes using a standardized protocol. Eligible cases (n = 498) and controls (n = 537) had a DNA sample available at the time of genotyping. Their ages ranged from 40 to 94 years (**Table 1**). The clinical characteristics of the prostate cancer cases are also described in **Table 1**. The study was approved by the Guadeloupean Ethics Committee for studies involving human subjects and written informed consent was obtained from each participant.

Single nucleotide polymorphism genotyping

Genotyping was performed by the 5′ nuclease PCR method, using commercially available TaqMan® assays (Applied Biosystems, Foster City, CA, USA). Briefly, the final volume for PCR was 10 µl, which contained 10 ng DNA, 0.25 µl 40× Assay Mix, and 5 µl TaqMan® Universal PCR master mix (Applied Biosystems, Foster City, CA, USA). A first step at 92°C for 10 min was followed by 90 cycles of 92°C for 15 s and 60°C for 1 min. After PCR, end-point fluorescence was measured, and allelic discrimination was carried out using the ABI 7000 Sequence Detector (Applied Biosystems).

Statistical analyses

Genotypes were tested for consistency with the expected genotype frequencies under Hardy–Weinberg equilibrium in the control population. For the analysis of aggressiveness, the prostate cancer patients were stratified by the aggressiveness of their cancers, as defined by the Gleason score. Specifically, low aggressiveness was defined as a Gleason score <7 and high aggressiveness was defined as a Gleason score ≥7. A case-only analysis was performed. Odds ratios (ORs), as a measure of risk, and 95% confidence intervals (95% CIs) were estimated from logistic regression models with adjustment for age and Caribbean origin. $P < 0.05$ were considered as statistically significant. All statistical tests were two-tailed and were carried out using StatView version 5.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS AND DISCUSSION

We successfully determined the SNP rs16901979 genotype of 489 prostate cancer cases and 534 controls (**Table 1**). The genotype frequencies for healthy controls were in Hardy–Weinberg equilibrium. The frequency of the A allele in the control population (40%) was not different from the frequencies reported for African-Americans (42.5%[5] and 42%[6,10]) and was statistically lower than the frequencies reported for West Africans (57% among Cameroonian controls and 50% among Nigerian controls).[13]

The AA genotype and the A allele at rs16901979 were associated with elevated risks of prostate cancer (OR = 1.84, 95% CI = 1.26–2.69, P = 0.002 and OR = 1.36, 95% CI = 1.13–1.64, P = 0.001, respectively) (**Table 2**). This finding is in agreement with the study by Okobia *et al.*[12] of African-Caribbean men from Tobago, which found a significant association between this AA genotype and the risk of prostate cancer

Table 1: Characteristics of the cases and controls

	Cases (n=489)	*Controls (n=534)*
Age, year		
Median	66.3	60.0
Mean	66.5	60.5
Interquartile range	11.5	11.2
PSA (ng ml^{-1})		
Median	8.7	0.8
Mean	34.9	1.1
Interquartile range	7.9	0.9
Origin, *n* (%)		
French West Indies (Guadeloupe or Martinique)	473 (96.7)	490 (91.8)
Other Caribbean islands (Haiti or Dominica)	16 (3.3)	44 (8.2)
Clinical stage at diagnosis[a], *n* (%)		
T1c or T2 and N0 and M0	414 (91.6)	-
T3 or T4, or N+ or M+	38 (8.4)	-
Gleason score at diagnosis[b], *n* (%)		
4–6	252 (53.6)	-
7	174 (36.9)	-
8–10	45 (9.5)	-

[a]Data on 37 patients were missing; [b]Data on 18 patients were missing.
PSA: prostate-specific antigen

Table 2: Associations between rs16901979 variants and the risk of prostate cancer

Variant	*Cases/controls*[a]	*OR*[b]	*95% CI*[c]	*P*
CC genotype	143/192	1 (reference)		
AC genotype	239/253	1.34	1.00–1.81	0.05
AA genotype	107/89	1.84	1.26–2.69	0.002
C allele	0.54/0.60	1 (reference)		
A allele	0.46/0.40	1.36	1.13–1.64	0.001

[a]Number for the genotypes, frequency for the alleles; [b]OR adjusted for age and Caribbean origin; [c]95% CI. CI: confidence interval; OR: odds ratio

(OR = 1.57, 95% CI = 1.06–2.32, P = 0.02). In contrast, Murphy *et al.*[13] reported no association between this variant and the risk of prostate cancer in the population of the Caribbean island of Jamaica. The discrepancies between these three studies cannot be explained by the differences between the frequencies of the A allele in the three Caribbean populations: 42% among the controls from Guadeloupe (this study), 46% among those from Tobago,[12] and 50% among the Jamaican controls.[13] Thus, the A allele was statistically less frequent in controls from Guadeloupe than in controls from Tobago and Jamaica. By contrast, no difference was found between the controls from Tobago and Jamaica. Yet, despite the similar allele frequencies in Tobago and Jamaica, the significant association with prostate cancer risk in Tobago was not observed in Jamaica. The lack of an observed association in the population from Jamaica may be a consequence of the small numbers of cases (n = 96) and controls (n = 118) included the noted study.

Even if the frequency of the A allele at rs16901979 differs greatly according to the origin of the population, it appears that this variant is largely associated with the risk of prostate cancer. Indeed, it has now been implicated in populations of Caucasian,[5,16–18] African,[5–12] and even Asian[19,20] origin.

In this study, our comparison of prostate cancer cases with low and high aggressiveness (Gleason score <7 *vs* ≥7) revealed that the pooled genotypes AC + AA were associated with a higher risk of a Gleason score ≥7 at diagnosis (OR = 1.79, 95% CI = 1.17–2.73,

Table 3: Association between rs16901979 variants and risk of prostate cancer stratified by disease aggressiveness (as defined by the Gleason score)

Genotype	*Low/high aggressiveness*[a]	*OR*[b]	*95% CI*[c]	*P*
CC	85/50	1 (reference)		
AA+AC	167/169	1.79	1.17–2.73	0.007

[a]Number of patients with low or high disease aggressiveness as defined by the Gleason score (low: Gleason score<7 and high: Gleason score≥7); [b]OR adjusted for age and Caribbean origin; [c]95% CI. CI: confidence interval; OR: odds ratio

$P = 0.007$) (**Table 3**). This is the first report of an association between the SNP rs16901979 and the risk of more aggressive prostate cancer in a population of African ancestry. However, another polymorphism in region 2 of 8q24, broad11934905, has similarly been shown to be associated with an increase in nonorgan confined disease and early biochemical recurrence after radical prostatectomy in African-American men.[21] In addition, rs16901979 is associated with the risk of advanced disease in men of European[16] and Asian[22] origin. However, other studies did not find any statistically significant difference between aggressive and nonaggressive cases in men of either European or African ancestry.[3,7,23] Bensen *et al.*[24] recently performed a large case-only study of 1536 candidate SNPs in 1066 African-American men and 1087 European men. They showed that the polymorphisms rs13254738 and rs1456305 in region 2 of 8q24 were associated with prostate cancer aggressiveness in African-American men and that rs6993569 in the same region was associated with prostate cancer aggressiveness in European men. They suggested that the apparent inconstancies between the two populations might reflect ethnic differences in the linkage disequilibrium structure of this region. Nevertheless, this study of a large series of African-American and Caucasian patients provided further evidence that region 2 of 8q24 is important in prostate cancer aggressiveness. In agreement with these results, linkage analyses performed by the International Consortium of Prostate Cancer Genetics found LOD scores ($\log_{10}$ of the ORs) over 3.0 at 8q24 in families with multiple cases and more aggressive disease.[25]

CONCLUSIONS

We found that the A allele at rs16901979 was associated with the risk of prostate cancer in the population of the Caribbean archipelago of Guadeloupe. Our findings confirm the involvement of the A allele at rs16901979 in populations of African descent, irrespective of their locations or their migration stories (the United States, the Caribbean Islands, and West Africa). Furthermore, we report a positive association between this variant and the risk of aggressive prostate cancer.

AUTHOR CONTRIBUTIONS

GCT, LM, and OC conceived, designed, and supervised the study. GCT and LM performed the statistical analyses and drafted the manuscript. GCT, LM, MR, CG, and PB participated in data acquisition and management. All authors read and approved the manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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REFERENCES

1 Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, *et al*. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet* 2013; 45: 385–91, 391e1.
2 Al Olama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J, *et al*. Multiple loci on 8q24 associated with prostate cancer susceptibility. *Nat Genet* 2009; 41: 1058–60.
3 Salinas CA, Kwon E, Carlson CS, Koopmeiners JS, Feng Z, *et al*. Multiple independent genetic variants in the 8q24 region are associated with prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 1203–13.
4 Hooker S, Hernandez W, Chen H, Robbins C, Torres JB, *et al*. Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African Americans. *Prostate* 2010; 70: 270–5.
5 Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, *et al*. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 2007; 39: 631–7.
6 Robbins C, Torres JB, Hooker S, Bonilla C, Hernandez W, *et al*. Confirmation study of prostate cancer risk variants at 8q24 in African Americans identifies a novel risk locus. *Genome Res* 2007; 17: 1717–22.
7 Xu J, Kibel AS, Hu JJ, Turner AR, Pruett K, *et al*. Prostate cancer risk associated loci in African Americans. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2145–9.
8 Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, *et al*. Multiple regions within 8q24 independently affect risk for prostate cancer. *Nat Genet* 2007; 39: 638–44.
9 Benford ML, VanCleave TT, Lavender NA, Kittles RA, Kidd LR. 8q24 sequence variants in relation to prostate cancer risk among men of African descent: a case-control study. *BMC Cancer* 2010; 10: 334.
10 Wang Y, Ray AM, Johnson EK, Zuhlke KA, Cooney KA, *et al*. Evidence for an association between prostate cancer and chromosome 8q24 and 10q11 genetic variants in African American men: the Flint Men's Health Study. *Prostate* 2011; 71: 225–31.
11 Chang BL, Spangler E, Gallagher S, Haiman CA, Henderson B, *et al*. Validation of genome-wide prostate cancer associations in men of African descent. *Cancer Epidemiol Biomarkers Prev* 2011; 20: 23–32.
12 Okobia MN, Zmuda JM, Ferrell RE, Patrick AL, Bunker CH. Chromosome 8q24 variants are associated with prostate cancer risk in a high risk population of African ancestry. *Prostate* 2011; 71: 1054–63.
13 Murphy AB, Ukoli F, Freeman V, Bennett F, Aiken W, *et al*. 8q24 risk alleles in West African and Caribbean men. *Prostate* 2012; 72: 1366–73.
14 Multigner L, Ndong JR, Giusti A, Romana M, Delacroix-Maillard H, *et al*. Chlordecone exposure and risk of prostate cancer. *J Clin Oncol* 2010; 28: 3457–62.
15 Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, *et al*. Age-specific reference ranges for prostate-specific antigen in black men. *N Engl J Med* 1996; 335: 304–10.
16 Cheng I, Plummer SJ, Jorgenson E, Liu X, Rybicki BA, *et al*. 8q24 and prostate cancer: association with advanced disease and meta-analysis. *Eur J Hum Genet* 2008; 16: 496–505.
17 Thomas G, Jacobs K, Yeager M, Kraft P, Wacholder S, *et al*. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 2008; 40: 310–5.
18 Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, *et al*. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 2008; 40: 316–21.
19 Liu F, Hsing AW, Wang X, Shao Q, Qi J, *et al*. Systematic confirmation study of reported prostate cancer risk-associated single nucleotide polymorphisms in Chinese men. *Cancer Sci* 2011; 102: 1916–20.
20 Joung JY, Park S, Yoon H, Lee SJ, Park WS, *et al*. Association of common variations of 8q24 with the risk of prostate cancer in Koreans and a review of the Asian population. *BJU Int* 2012; 110: E318–25.
21 Whitman EJ, Pomerantz M, Chen Y, Chamberlin MM, Furusato B, *et al*. Prostate cancer risk allele specific for African descent associates with pathologic stage at prostatectomy. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1–8.
22 Tan YC, Zeigler-Johnson C, Mittal RD, Mandhani A, Mital B, *et al*. Common 8q24 sequence variations are associated with Asian Indian advanced prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 2431–5.
23 Pal P, Xi H, Guha S, Sun G, Helfand BT, *et al*. Common variants in 8q24 are associated with risk for prostate cancer and tumor aggressiveness in men of European ancestry. *Prostate* 2009; 69: 1548–56.
24 Bensen JT, Xu Z, Smith GJ, Mohler JL, Fontham ET, *et al*. Genetic polymorphism and prostate cancer aggressiveness: a case-only study of 1,536 GWAS and candidate SNPs in African-Americans and European-Americans. *Prostate* 2013; 73: 11–22.
25 Isaacs WB. Inherited susceptibility for aggressive prostate cancer. *Asian J Androl* 2012; 14: 415–8.