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8q24 Risk Alleles and Prostate Cancer in African-Barbadian Men

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Abstract

BACKGROUND—African American men (AA) exhibit a disproportionate share of prostate cancer (PRCA) incidence, morbidity and mortality. Several genetic association studies have implicated select 8q24 loci in PRCA risk in AA. The objective of this investigation is to evaluate the association between previously reported 8q24 risk alleles and PRCA in African-Barbadian (AB) men known to have high rates of PRCA.

METHODS—Ten previously reported candidate tag SNPs were genotyped and/or imputed in the 8q24 region in 532 AB men with PRCA and 513 AB controls from the Prostate Cancer in a Black Population (PCBP) study.

RESULTS—Rs2124036 was significant in AB men, (OR = 2.7, 95% CI (1.3–5.3), P=0.005, Empirical (max(T), corrected for multiple testing) P = 0.03) for the homozygous C/C genotype. Only a single SNP from this region remained statistically significant in our analysis of our AB population. These results may indicate the presence of a founder effect or due to the chosen SNPs not tagging an ancestral haplotype bearing the 8q24 risk allele(s) in this population or could reflect inadequate power to detect an association. We conducted a meta-analysis including our AB population along with two additional African Caribbean populations from Tobago and Jamaica for SNPs rs16901979 and rs1447295. Meta-analysis results were most significant for rs16901979 A allele (Z score 2.73; p=0.006) with a summary OR= 1.31 (95% CI: 1.09–1.58).

CONCLUSIONS—Additional studies are needed to provide deeper genotype coverage to further interrogate the 8q24 region to understand its contribution to PRCA in this population.

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Introduction

African American men (AA) maintain a disproportionate burden of prostate cancer (PRCA) incidence, treatment failures and mortality (1–3). Recently several genetic association studies have implicated loci surrounding 8q24 as a potential region of PRCA risk in AA (4–14) while other studies have not corroborated these findings after correcting for local admixture within the 8q24 region(6). To elucidate the genetic determinants for cancer patterns in AA and address the noted inconsistencies, it is useful to study populations across the African Diaspora (15). African-Barbadians (AB) share a common West African heredity with AA but have lower rates of admixture, thus potentially enhancing the discovery of ancestrally-related genetic factors (16–18). AB men among other African Caribbean populations are known to have high rates of PRCA incidence and mortality. A recent study found that although PRCA risks are lower for AB compared to AA, the mortality rates were higher for AB than for their AA counterparts (mortality rates in AB ranged from 63.2 to 101.6 per 100,000 compared to 51.1 to 78.8 per 100,000 among AA) (19,20) thus representing a unique group that may assist in disentangling some of the key genetic determinants of PRCA common in populations of African origin.

In this candidate region investigation, we studied 10 previously reported SNPs in the 8q24 region in 532 AB men diagnosed with PRCA and 513 AB controls (N=1,045) who participated in the Prostate Cancer in a Black Population (PCBP) study. The purpose of this investigation was to determine whether any of the previously reported risk alleles were associated with PRCA in this Afro-Caribbean population. All study participants provided informed consent and all protocols conformed to the Declaration of Helsinki.

Materials and Methods

The PCBP is a population-based case-control study conducted between July 2002 and January 2011, which included 1,007 newly-diagnosed and histologically confirmed men with PRCA and 1,005 male controls free of PRCA at the time of their study visit. Controls were randomly selected from a national database and frequency age-matched to the cases by 5-year age groups. Among the study participants, 963 cases and 941 controls self-reported their race as AB and a subset of consecutive samples collected through January 2009 (532 cases and 513 controls; n=1,045) were genotyped for the present investigation(21).

Standardized protocols were used in the collection of demographic and lifestyle data, anthropometric measurements, medical and family history information and blood samples (to measure PSA, HbA1c and to test for genetic variants) (21).

Genotypes

Genomic DNA was isolated from buffy coats using the PUREGENE DNA Isolation system from Gentra (Qiagen®). DNA was resuspended in TE buffer and quantified by spectrophotometry. Genomic DNA quality control was assessed by UV spectrophotometry, restriction digest and PCR analysis of individual genomic DNA samples. Samples failing two rounds of quality control were re-precipitated to remove potential impurities left over from initial DNA isolation followed by reassessment of quality control. A sample of the

DNA was used for whole genome amplification in order to increase the amount of DNA available. Ten known genetic variants on chromosome 8q24 were genotyped on 858 samples using the SequenomMassARRAY™ genotyping platform with iPLEX™ chemistry according to manufacturer's recommendations. 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 assays were performed to amplify 5–10 ng of genomic DNA by polymerase chain reaction (PCR). 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 0.625μM for low mass primers and 1.25 μM for high mass primers. Reactions were diluted with 16 μl of H_2O and fragments were purified with resin, spotted onto SequenomSpectroCHIP™ microarrays and scanned by MALDI-TOF mass spectrometry. Individual SNP genotype calls were generated using Sequenom™ TYPER 4.0 software, which automatically calls allele specific peaks according to their expected masses. Duplicate controls were used for each DNA plate as well as each SequenomSpectroCHIP™ microarrays.

A portion of our AB cohort (N=458; 234 cases and 224 controls) was selected for additional genotyping (GWAS and imputed GWAS) as part of a replication phase of a separate collaborative PRCA study (7). The complete methods for this additional genotyping and imputation are described elsewhere (7). These genome-wide results were underpowered and thus did not reveal any significant genome-wide results (see supplemental Figure) but were useful to increase the power of our 8q24 candidate loci study since 187 samples (64 cases and 123 controls) with GWAS and imputed genotypes were not previously included in the candidate region study.

Briefly, the GWAS sample was genotyped using Illumina Infinium Human1M-Duo on 458 samples, 271 of which were also previously genotyped for the 10 candidate SNPs (see above). Eight of our 10 candidate SNPs were genotyped using the Infinium chipset and genotypes for the other two SNPs were imputed in these individuals. We confirmed that the 271 individuals who had genotypes for 8 candidate loci from both platforms gave concordant genotypic results. For the imputation of the two candidate SNPs not on the Infinium chip, post quality control Illumina Infinium genotypes, phased with haplotype data from the founders of the CEU and YRI HapMap phase 2 samples (22) were used to infer linkage disequilibrium patterns. Genome-wide imputation was performed using IMPUTE2(23) with a threshold of Rsq < 0.3 to filter out poor quality SNPs from the analysis.

All in all, a total of 1,045 individuals (858 with 10 genotyped SNPs from SequenomSpectroCHIP™ and an additional 187 with 8 genotyped SNPs from Infinium Human 1M-Duo assay and 2 imputed SNPs (rs16901979 and rs7818556) were available for analyses.

Statistical Analyses

Power calculations were performed using the QUANTO program (24,25) and the CaTs program (26). With a total sample size of 1,045 (AB cases + AB controls), we estimated the

minimum detectable genotype relative risk (GRR) for carriers of one or two copies of a susceptibility allele (with 90% power at significance levels of p=0.05, 0.01 and 0.00001) given different allele frequencies and different population prevalence of disease (27). Based on SEER data from AA across age groups, prevalence of PRCA ranges between 5 and 10%(1). Using these values, the power calculations suggest that this study has adequate power to detect associations of alleles with GRR in the range of 1.28 to 1.63 for p= 0.05 (1.3–1.8 for p= 0.01, as long as the allele frequency is between 5 and 50% and the mode of inheritance is either log-additive or dominant). Even for rare dominant or log-additive risk alleles with only 1% frequency, we have enough power to detect them if the GRR is at least 2.5. For a recessive risk allele, power will only be adequate for common risk alleles.

The PLINK (28) program was used to perform quality control of the genotype data, identifying and dropping any samples with low genotype call rates (> 0.2 missing genotypes), SNPs with very low genotyping rates (< 0.1), and any SNPs that failed tests for Hardy-Weinberg equilibrium ($p \leq 0.001$). A set of 53 ancestry-informative SNPs distributed across the genome were analyzed with the STRUCTURE (17) and EIGENSTRAT (29) programs to detect population stratification and to confirm race given by self-report. Of the total 1,045 subjects genotyped, 532 cases and 513 controls were confirmed to be AB. Four covariates previously associated with risk of PRCA (21,30): age, waist-hip ratio (WHR), PSA, and family history were added to the analysis in order to adjust for any effects on PRCA risk. The dataset was also subdivided and analyzed based on family-history of PRCA as an ordinal variable.

Haploview (31) was used to calculate estimates of linkage disequilibrium (LD) between the marker loci, and to test for association of genotypes and haplotypes to disease status. Upon completion of haplotype structure analysis, genotypic association tests were performed for all individual SNPs and for haplotypes using PLINK (28). All association testing results were corrected for multiple testing using max(T) permutation testing in PLINK (28) which is the family-wise error rate and corrected for multiple testing. This permutation procedure preserves the correlational structure between the SNPs, thus providing a more accurate correction compared to a Bonferroni correction assuming all these tests are independent. The included Figure shows the intermarker LD (measured as R^2) between the SNPs tested here.

A subsequent meta-analysis of the 8q24 region was performed using African Caribbean (AC) populations from Barbados, Jamaica and Tobago(32,33). The allelic odds ratio (OR) and confidence intervals were calculated using the Mantel-Haenszel method using the “rmeta” package in R (34); the fixed effects (Mantel-Haenszel ; “meta.MH”) and random (DerSimonian-Laird ; “meta.DSL”) effects options were selected. In both conditions, Woolf’s test was used to test for heterogeneity. Another program called METAL(35) was also utilized as an alternative meta-analysis method for comparison.

Results

The association analyses included 1,019 AB men (511 PRCA cases and 508 controls) after quality control steps. Principal components analysis of AB samples showed no evidence of population stratification thus there was no need for adjustment. All 10 candidate SNPs

included in the interrogation of the 8q24 region passed our quality control testing and were included in the analysis. This list of candidate SNPs (spanning regions 1–4 on 8q24) and the distribution of minor allele frequencies among cases and controls are presented in Table I. After correcting for multiple tests, no candidate SNPs showed statistically significant differences in allele frequency between cases and controls.

In the genotypic association tests, rs2124036 was found to be statistically significant (P = 0.005, OR = 2.7, 95% CI (1.3–5.3), max(T) adjusted P = 0.03) when comparing the homozygous C/C genotype to the reference (G/G homozygous) group, while none of the other tested SNP genotypes revealed any significant associations with PRCA after correction for multiple testing. Table II summarizes association test results for the 10 SNPs. Of note, the unadjusted OR for the heterozygous genotype A/C of rs16901979 was nominally significant (OR = 1.4, 95% CI (1.1–1.9), P =0.02). However this finding did not remain significant after multiple testing correction (max(T) adjusted P = 0.51). Although previously published associations were not replicated in our AB samples, it is important to note that these 10 SNPs in ABs demonstrate similar direction and magnitude of effect as in previous reports (6,8,11,36–45). We also conducted a meta-analysis of all three AC populations (AB, Tobago and Jamaica) for the two SNPs that were tested in all three samples, rs16901979 and rs1447295 (hereafter called the “in common SNPs”), since it is possible that our non-significant association results were due to inadequate power. Results from a fixed-effects meta-analysis model using METAL (35) were only significant for rs16901979 A allele (Z score 2.7; p=0.005). METAL results for rs1447295 A allele resulted in a Z score of 1.4; p=0.16. Additionally, a random effects (DerSimonian-Laird) meta-analysis in R (Table IVA) revealed a summary OR= 1.21 (95% CI: 1.01–1.46) for rs16901979; Woolf’s test for heterogeneity: X^2(2) = 0.87 (p= 0.65); estimated random effects variance: 0 for rs16901979. Random effects analysis for rs1447295 demonstrated a summary OR = 1.02 (95% CI: 0.79–1.32); Woolf’s test for heterogeneity: X^2(2) = 3.18 (p=0.20); estimated random effects variance: 0.02. These results suggested that lack of power may explain the failure to detect significant PRCA 8q24 associations at these SNPs in the individual AC samples (Table IVA and IVB).

Table III shows the allele frequencies and ORs for a set of four 8q24 SNPs genotyped in our AB sample and the 2 other aforementioned AC samples (in Tobago and Jamaica). The results indicate that the G risk allele frequency for rs7008482 is similar in Barbados and Jamaica (0.9 and 0.88, respectively) as is the A risk allele for rs16901979 (0.51 and 0.5, respectively). Additionally, the frequencies of these alleles were also similar in cases and controls in both Barbados and Jamaica. The A risk allele frequency for rs1447295 among cases in Barbados (0.35) appeared to be between the frequency reported in Tobago (0.33) and Jamaica (0.39) and a similar frequency pattern was noted among controls residing in the 3 Caribbean islands.

Additional analyses, stratifying by the presence or absence of family history, did not change the results (data not shown). Furthermore, haplotype analyses did not reveal any significantly associated haplotypes after correction for multiple testing and adjustment for the given covariates (age, WHR, PSA, and family history) did not improve the significance of the overall results.

Discussion

This work represents the largest cohort of African Caribbean males for the validation of PRCA associated variants in the 8q24 region. Although 8q24 is one of the most validated regions on the genome for harboring genetic variants found to be associated with PRCA risk in populations of African origin (5,6,9,11,12,32,33,36,39,40,44–51), confirmation of these signals in this population are limited. The present investigation evaluated 10 previously interrogated SNPs within the 8q24 region and did not find a strong association between PRCA and any of the selected markers among AB men who participated in the PCBP study.

PRCA susceptibility loci have been identified on 8q24 in various groups (8,10,13,36,39,45), including AA (8,11,36,37,39,40,44) and other populations of African origin (32,33). However, PRCA genetic association studies of chromosome 8q24 in African-Caribbean populations have been somewhat inconsistent. A recent study in Tobago (33) genotyped three candidate SNPs (rs1447295, rs16901979 and rs6983267) within the 8q24 region in 354 PRCA cases and 438 controls. The findings indicated that SNP rs16901979 was found to be associated with a significantly increased risk of PRCA (OR = 1.41, 95% CI (1.02 to 1.95); p = 0.04) with risk further increasing for men with early onset PRCA (OR = 2.37, 95% CI (1.40 to 3.99); p = 0.001) (33). The two other SNPs evaluated in that study (rs1447295 and rs6983267) were not found to be associated with PRCA risk in that AC population. It should be noted that the results from the Tobago study were not corrected for multiple testing.

A second study, including men from the Caribbean (Jamaica), as well as West Africa (Nigeria and Cameroon), also evaluated the association between PRCA risk and 10 selected SNPs in the 8q24 region (32). Although rs6983561, rs7008482 and rs16901979 were significantly associated with PRCA risk among men from Nigeria and Cameroon, none of the markers was associated with PRCA risk in the Jamaican samples. These findings are consistent with our investigation in which only one of the markers evaluated was found to be associated with PRCA in AB men after correcting for multiple testing.

Interestingly, the MAFs for two previously reported SNPs, rs16901979 and rs1447295, tended to be higher in the AC controls compared to both AA and European-American (EA) men(33,52). The average (range) of MAFs among AA and EA controls for the A risk allele frequency of rs16901979 are 0.43 (range 0.41 to 0.46) and 0.03 (range 0.02 to 0.03) respectively (38–40) compared to 0.47 in the AB control population (0.5 in the Jamaican control population and 0.46 in the Tobagonian control population for rs16901979). The range of the A risk allele of rs16901979 in AC controls is 0.46 to 0.7. Similarly, the average (range) of MAFs for the A allele of rs1447295 are 0.31 (range 0.31 to 0.32) and 0.09 (range of 0.08 to 0.1) for AA and EA controls respectively (6,36,38–40), while the frequency is 0.34 among AB controls from the PCBP. The MAFs for the A risk allele of rs1447295 are 0.31 and 0.37 respectively for Jamaican and Tobagonian AC controls (range 0.31 to 0.55). The noted differences in MAFs between EAs and men of African origin may assist in explaining the significant health disparity in the morbidity and mortality of PRCA that exists in populations of African descent. Furthermore, the somewhat higher allele frequencies found in AA controls compared to AB controls in several other 8q24 risk alleles (*i.e.* rs12547950, rs7008482, rs780321, rs4427136, rs2302793 and rs11780763)(40) may further

explain why none of the previously implicated markers on 8q24 were found to be significantly associated with PRCA in some AC populations.

Another possible explanation for the inconsistent findings in different populations may be the presence of a founder effect in which fewer PRCA risk alleles are in strong linkage disequilibrium with the selected 8q24 variants in AC compared to other populations of African descent. Furthermore, additional markers, yet undiscovered, may be more highly associated with PRCA risk in AC men than other groups. As such, further interrogation of 8q24 and other regions throughout the genome are necessary to elucidate those loci that may influence the risk of PRCA development in AC and other populations of African origin.

Conclusions

Prostate cancer disproportionately affects AA and it is believed that genetic determinants in general, and loci in the 8q24 region in particular, may play a role in explaining some of the disparities that exist in Westernized African populations compared to other groups. Surprisingly, findings from the PCBP, a large, nationwide case-control study of previous PRCA-associated tag SNPs in 8q24 conducted in Barbados, West Indies, found one significant association signal (genotypic test for rs2124036) among 10 SNPs previously reported to be associated with PRCA in other populations of African origin. Although a lack of adequate power remains a plausible explanation for a non-robust 8q24 replication, our results highlight the possibility of genetic differences in PRCA determinants not only between African-derived and non-African descendants but also within populations with shared Western African ancestry. The results from our meta-analysis of three AC populations (Barbados, Tobago and Jamaica) for 2 SNPs genotyped in all 3 samples (greatest significance for rs16901979 A allele) added power to our analyses and led to detection of significant PRCA association with rs16901979, another SNP within the chromosome 8q24 region. Additional studies with larger samples of AC men are needed to further investigate this region (through deeper sequencing) and to discover other PRCA-associated alleles that may be unique to this African-derived population. The exploration of genetic determinants of PRCA will aid in understanding the etiology of this disease and will assist in narrowing the divide between the morbidity and mortality that currently exists between men of African descent and other groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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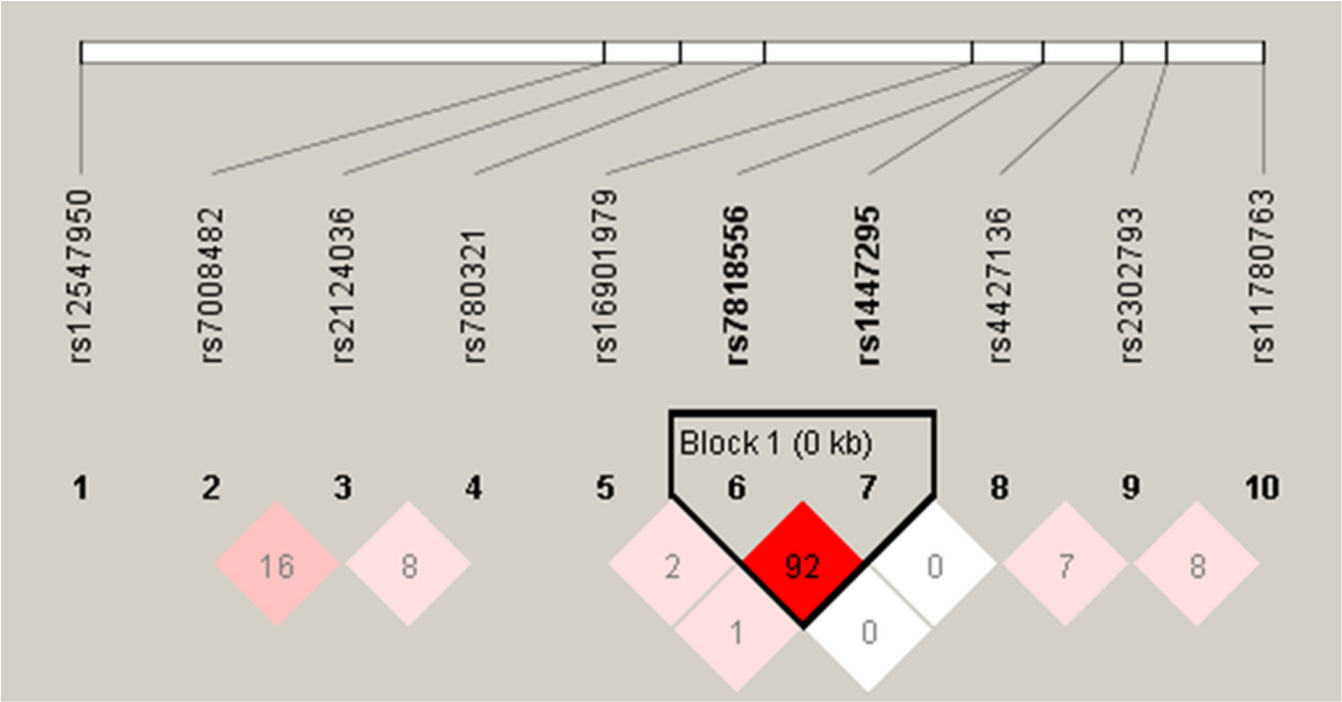

Figure 1.

Haploview image for chromosome 8q24 from the PRCA association study of 10 SNPs. Note that the residual r2 pairwise linkage disequilibrium (LD) values from Haploview displayed above are multiplied times a factor of 100.

Table I

Distribution of Minor Allele Frequencies (MAF) for 8q24 SNPs Genotyped in PCBP Cases and Controls

SNP	Region	Position*	MAF	Cases	Controls	Estimated Power (Average GRR=1.55*)	Minimum GRR for 80% Power*
rs12547950	Near 4	123616097	G	0.31	0.32	99	1.31
rs7008482	4	126267630	T	0.10	0.18	91	1.46
rs2124036	Between 2 and 4	126648134	T	0.16	0.21	97	1.38
rs780321	Between 2 and 4	127083695	C	0.22	0.24	99	1.34
rs16901979	2	128124916	A	0.50	0.47	99	1.31
rs7818556	1	128484399	G	0.37	0.35	99	1.30
rs1447295	1	128485038	A	0.35	0.34	99	1.31
rs4427136	Near 1	128879839	G	0.22	0.24	99	1.34
rs2302793	Near 1	129108697	A	0.11	0.12	92	1.44
rs11780763	Near 1	129596286	T	0.09	0.10	88	1.48

*Log-additive model, 5% disease prevalence, p <0.05

*GRCh37/hg 19 (February 2009)

Table II

Association of 8q24 Alleles and Genotypes with Prostate Cancer Risk in PCBP

SNP	Tested Allele or Genotype	Cases (N=532)	Controls (N=513)	OR (95% CI)	P-value	Permuted P-value (n=5000)
rs12547950	A	706	690	1.0 (0.9–1.2)	0.70	1
	A/A	238	228	1.1 (0.7–1.7)	0.79	1
	G/A	232	234	1.0 (0.6–1.6)	0.98	
	G/G	45	47	1.0		
rs7008482	G	921	898	1.2 (0.9–1.5)	0.29	0.94
	G/G	423	402	2.1 (0.8–5.5)	0.15	0.74
	G/T	93	96	1.9 (0.7–5.4)	0.20	
	T/T	6	12	1.0		
rs2124036	**C**	**854**	**797**	**1.4 (1.1–1.7)**	**0.01**	**0.05**
	C/C	**356**	**320**	**2.7 (1.3–5.3)**	**0.01**	**0.03**
	C/T	144	159	2.2 (1.1–4.4)	0.03	
	T/T	12	29	1.0		
rs780321	T	797	765	1.2 (0.9–1.4)	0.19	0.82
	T/T	311	293	1.5 (0.9–2.6)	0.14	0.72
	T/C	175	179	1.4 (0.8–2.4)	0.26	
	C/C	25	34	1.0		
rs16901979	A	520	474	1.2 (1.0–1.4)	0.07	0.43
	A/A	127	120	1.4 (1.0–1.9)	0.08	0.51
	A/C	270	236	1.4 (1.1–1.9)	0.02	
	C/C	123	154	1.0		
rs7818556	G	378	358	1.1 (0.9–1.3)	0.46	0.99
	G/G	71	68	1.1 (0.7–1.6)	0.62	1
	G/A	239	222	1.1 (0.8–1.5)	0.33	
	A/A	221	221	1.0		
rs1447295	A	360	347	1.0 (0.87–1.2)	0.67	1
	A/A	68	66	1.1 (0.7–1.6)	0.77	1

SNP	Tested Allele or Genotype	Cases (N=532)	Controls (N=513)	OR (95% CI)	P-value	Permuted P-value (n=5000)
	A/C	224	215	1.1 (0.8–1.4)	0.64	
	C/C	223	226	1.0		
rs4427136	A	804	772	1.1 (0.9–1.4)	0.25	0.89
	A/A	319	298	1.3 (0.8–2.3)	0.29	0.95
	A/G	172	176	1.2 (0.7–2.1)	0.50	
	G/G	27	34	1.0		
rs2302793	A	107	127	0.8 (0.6–1.1)	0.19	0.81
	A/A	8	6	1.3 (0.4–3.7)	0.67	1
	G/A	91	115	0.8 (0.6–1.0)	0.07	
	G/G	409	388	1.0		
rs11780763	G	926	915	1.0 (0.8–1.4)	0.88	1
	G/G	418	414	1.7 (0.4–7.1)	0.48	1
	G/T	90	87	1.7 (0.4–7.4)	0.47	
	T/T	3	7	1.0		

Table 3

Comparison of 8q24 PC Risk Alleles in 3 African Caribbean Populations

SNP	Region	Position*	Allele	Frequency in Cases	Frequency in Controls	OR	95% CI	P-value
Barbados								
rs7008482	4	126267630	G	0.9	0.88	1.9	0.7–5.4	0.2
rs16901979	2	128124916	A	0.51	0.47	1.4	1.1–1.9	**0.02**
rs6983267	3	128413305	N/A	N/A	N/A	N/A	N/A	N/A
rs1447295	1	128485038	A	0.35	0.34	1.1	0.82–1.4	0.6
Jamaica (Murphy 2012)								
rs7008482	4	126267630	G	0.88	0.88	0.9	0.5–1.8	0.98
rs16901979	2	128124916	A	0.5	0.5	1	0.6–1.4	0.93
rs6983267	3	128413305	G	0.91	0.89	1.1	0.6–2.5	0.68
rs1447295	1	128485038	A	0.39	0.31	1.4	0.9–2.1	0.14
Tobago (Okobia 2011)								
rs7008482	4	126267630	N/A	N/A	N/A	N/A	N/A	N/A
rs16901979	2	128124916	A	0.53	0.46	1.41	1.02–1.95	**0.03**
rs6983267	3	128413305	T	0.05	0.06	0.83	0.53–1.29	0.4
rs1447295	1	128485038	A	0.33	0.37	0.83	0.62–1.10	0.19

*GRCh37/hg19 (February 2009)

Table 4

A Meta-analyses Results in Common 8q24 Risk Alleles in African Caribbean Populations			
Random effects (DerSimonian-Laird)			
Population	**OR**	**(95% CI)**	**Heterogeneity (P-value); Estimated Variance**
rs16901979			
Barbados	1.18	(0.90–1.55)	
Jamaica (Murphy 2012)	1.00	(0.58– 1.71)	
Tobago (Okobia 2011)	1.32	(0.99–1.76)	
Summary	**1.21**	**(1.01–1.46)**	**0.87 (0.6462); 0**
rs1447295			
Barbados	1.09	(0.82–1.45)	
Jamaica (Murphy 2012)	1.43	(0.81–2.52)	
Tobago (Okobia 2011)	0.84	(0.63–1.13)	
Summary	**1.02**	**(0.79–1.32)**	**3.18 (0.2043); 0.02**

B Meta-analyses Results in Common 8q24 Risk Alleles in African Caribbean Populations			
Fixed effects (Mantel-Haenszel)			
Population	**OR**	**(95% CI)**	**Heterogeneity (P-value)**
rs16901979			
Barbados	1.18	(0.90–1.55)	
Jamaica (Murphy 2012)	1.00	(0.58– 1.71)	
Tobago (Okobia 2011)	1.32	(0.99–1.76)	
Summary	**1.21**	**(1.01–1.46)**	**0.87 (0.65)**
rs1447295			
Barbados	1.09	(0.82–1.45)	
Jamaica (Murphy 2012)	1.43	(0.81–2.52)	
Tobago (Okobia 2011)	0.84	(0.63–1.13)	
Summary	**1**	**(0.83–1.22)**	**3.18 (0.20)**