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African American, Ancestry, genetics, Susceptibility

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Abstract:

African American men have the highest incidence and mortality from prostate cancer in the world. Multiple reasons have been postulated to explain these findings although the definitive reasons for this are unknown. While both environmental and genetic factors may contribute to prostate cancer susceptibility, results from multiple studies consistently implicate a strong genetic component of this cancer. However, a specific gene which is consistently and reproducibly associated with prostate cancer risk in any population has not been identified. Association studies examining the frequency of common but specific genetic variants in study populations with and without a particular disease (i.e. case-control) is a powerful way to detect the influence of common genetic variants capable of affecting disease risk. While these types of studies are powerful, they are not without limitations, including the tendency to be confounded due to population stratification (a critical issue in admixed populations like African American), and the requirement for large, well matched, and well characterized study populations. While there has been extensive use of case control studies to identify genetic risk variants in Caucasian populations, corresponding studies in the African American prostate cancer population have been less extensive, typically being much smaller than the Caucasian counterparts, with little or no efforts to address the critical issue of population stratification as a confounder. It is now quite clear that unless cases are well matched to controls in terms of genetic heterogeneity in such studies, spurious associations will and undoubtedly have been observed and reported. In this study we use Ancestry Informative Markers (AIM) to match African American prostate cancer cases and controls for the purposes of performing association studies without confounding by population stratification. After this matching, we have identified and confirmed several prostate cancer susceptibility loci in this study population, on chromosomes 8 and 17. These and other ongoing studies will provide unprecedented insight into the role of inherited factors in prostate carcinogenesis in African Americans.
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INTRODUCTION

African American men have the highest incidence and mortality from prostate cancer in the world. Multiple reasons have been postulated to explain these findings including access to care, attitudes about care, socioeconomic and education differences, differences in type and aggressiveness of treatment, dietary, and genetic differences, although the definitive reasons for this are unknown. Indeed, the reasons why any prostate cancers occur are incompletely understood, and the only consistent risk factors identified for prostate cancer in addition to race are age and family history. While both environmental and genetic factors may contribute to prostate cancer susceptibility, results from multiple studies consistently implicate a strong genetic component of this cancer, with an estimated heritability of 42%, the highest among all common cancers. However, despite years of extensive effort by multiple research groups world wide, a specific gene which is consistently and reproducibly associated with prostate cancer risk in any population has not been identified. Association studies examining the frequency of common but specific genetic variants in study populations with and without a particular disease (i.e. case-control) is a powerful way to detect the influence of common genetic variants capable of affecting disease risk. While these types of studies are powerful, they are not without limitations, including the tendency to be confounded due to population stratification (a critical issue in admixed populations like African American), and the requirement for large, well matched, and well characterized study populations. While there has been extensive use of case control studies to identify genetic risk variants in Caucasian populations, corresponding studies in the African American prostate cancer population have been less extensive, typically being much smaller than the Caucasian counterparts, with little or no efforts to address the critical issue of population stratification as a confounder. It is now quite clear that unless cases are well matched to controls in terms of genetic heterogeneity in such studies, spurious associations will and undoubtedly have been observed and reported. In this study we use Ancestry Informative Markers (AIMs) to match African American prostate cancer cases and controls for the purposes of performing association studies without confounding by population stratification. We have identified and confirmed several prostate cancer susceptibility loci in these studies, on chromosomes 8 and 17. These and other ongoing studies will provide unprecedented insight into the role of inherited factors in prostate carcinogenesis in African Americans.

BODY: To date, we are currently performing the proposed analysis of AIMs in our study population. As prelude to these analyses, in a collaborative study with investigators at deCODE Genetics in Iceland, we performed an analysis of a smaller set of AIMs to evaluate genetically estimated ancestry of our case-control groups. This panel of consisted of the following 30 microsatellite markers: D1S2630, D1S2847, 1S466, D1S493, D2S166, D3S1583, D3S4011, D3S4559, D4S2460, D4S3014, D5S1967, DG5S802, D6S1037, D8S1719, D8S1746, D9S1777, D9S1839, D9S2168, D10S1698, D11S1321, D11S4206, D12S1723, 13S152, D14S588, D17S1799, D17S745, D18S464, D19S113, D20S878 and D22S1172. This panel was selected from about 2000 microsatellites genotyped in a previously described (Pritchard et al Genetics 155, 945-59, 2000) multi-ethnic cohort of 35 European Americans, 88 African Americans, 34 Chinese, and 29 Mexican Americans. Of the 2000 microsatellite markers, the selected set showed the most significant differences between European Americans, African Americans, and Asians, and also had good quality and yield. The results of this genotyping were used to match cases and controls on average genome wide African ancestry.

Genotyping this matched case control population for SNPs led to the discovery of an additional prostate cancer susceptibility locus at 8q24 (rs16901979) (Gudmundsson et al 2007). The risk allele (“A”) at this locus is present in 50% of our African American cases, compared to 42% of controls. Importantly, this locus also shows association with risk for prostate cancer in European Americans although the risk allele is much less common in this population (~3% in controls, ~6% in cases); the OR of ~1.8 for this latter population is the largest effect observed to date for any SNP. These data indicate that the same locus can affect risk of prostate cancer in multiple different ancestral populations, although the effects and risk allele frequencies may be very different. More recently, we completed genotyping of an additional 7 SNPs on chromosome 17 in our matched African American case control population (Sun et al 2008). These analyses provided the first evidence that SNPs at
17q12 are associated with risk of prostate cancer in African Americans. In this case the risk allele (T at rs4430796) is less common in African Americans than it is in European Americans.

KEY RESEARCH ACCOMPLISHMENTS:

- Our African American case control population has been genotyped for 30 AIMs
- Matching of cases and controls based on average percent African American ancestry has been accomplished
- Genotyping of 8q24 markers in this population led to the discovery of a novel prostate cancer risk variant (rs16091970) that is reproducibly associated with prostate cancer in African American men
- Genotyping of 17q12 markers in this population provided the first demonstration that rs4430796 is associated with prostate cancer risk in African American men.

REPORTABLE OUTCOMES


CONCLUSIONS

Ancestry mapping of African American prostate cancer cases and controls allows for the identification and characterization of genetic risk factors that are significantly and reproducibly associated with prostate cancer risk in this high risk population. The identification of reproducible genetic risk factors for prostate cancer in African American men will permit an estimation of the relative importance of genetics vs environment as factors responsible for disparity in prostate cancer risk and mortality.