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Generalizability of Associations from Prostate Cancer GWAS in Multiple Populations

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Abstract

Genome-wide association studies have identified multiple common alleles associated with prostate cancer risk in populations of European ancestry. Testing these variants in other populations is needed to assess the generalizability of the associations, and may guide fine-mapping efforts. We examined 13 of these risk variants in a multiethnic sample of 2,768 incident prostate cancer cases and 2,359 controls from the Multiethnic Cohort (MEC; African Americans, European Americans, Latinos, Japanese Americans and Native Hawaiians). We estimated ethnic-specific and pooled odds ratios and tested for ethnic heterogeneity of effects using logistic regression. In ethnic-pooled analyses, 12 of the 13 variants were positively associated with risk, with statistically significant associations ($p<0.05$) noted with 6 variants (odds ratio, 95% confidence interval): *JAZF1*, rs10486567, 1.23(1.12–1.35); Xp11.2, rs5945572, 1.31(1.13–1.51); *HNF1B*, rs4430796, 1.15(1.06–1.25); *MSMB*, rs10993994, 1.13(1.04–1.23); 11q13.2, rs7931342, 1.13(1.03–1.23); 3p12.1, rs2660753, 1.11(1.01–1.21); *SLC22A3*, rs9364554, 1.10(1.00–1.21); *CTBP2*, rs12769019, 1.11(0.99–1.25); *HNF1B*, rs11649743, 1.10(0.99–1.22); *EHBP1*, rs721048, 1.08(0.94–1.25); *KLK2/3*, rs2735839, 1.06(0.97–1.16); 17q24.3, rs1859962, 1.04(0.96–1.13); and *LMTK2*, rs6465657, 0.99(0.89–1.09). Significant ethnic heterogeneity of effects was noted for 4 variants (*EHBP1*, $p_{het} = 3.9\times10^{-3}$; 11q13, $p_{het} = 0.023$; *HNF1B* (rs4430796), $p_{het} = 0.026$; and *KLK2/3*, $p_{het} = 2.0\times10^{-3}$). Although power was limited in some ethnic/racial groups due to variation in sample size and allele frequencies, these findings suggest that a large fraction of prostate cancer variants identified in populations of European ancestry are global markers of risk. For many of these regions, fine-mapping in non-European samples may help localize causal alleles and better determine their contribution to prostate cancer risk in the population.

Keywords

Genitourinary Cancers; Prostate; Risk Assessment; Epidemiology; Cancer in minority and underserved populations; Genetics of Risk; Outcome, and Prevention; MEC

Introduction

Genome-wide association studies (GWAS) in men of European ancestry have revealed multiple variants consistently associated with prostate cancer risk (1–5). Testing of these risk alleles across populations is an important first step to address the pan-ethnic nature of

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their associations, as differences in linkage disequilibrium (LD) and minor allele frequencies (MAF) may make it difficult to generalize the associations to populations of non-European descent. We have recently demonstrated the power that multiethnic genetic studies of common complex diseases possess, having revealed a number of common variants for prostate cancer at 8q24 that were not identified in larger comprehensive studies in populations of European ancestry (6). In the present study, we have evaluated 13 variants considered to be established risk variants for prostate cancer among men of European ancestry in association with prostate cancer risk in a large multiethnic case-control study.

Materials and Methods

Study Population

The Multiethnic Cohort Study (MEC) is a population-based prospective cohort study that was initiated between 1993 and 1996 and includes subjects from various ethnic groups – African-Americans and Latinos primarily from California (mainly Los Angeles) and Native Hawaiians, Japanese-Americans, and European Americans primarily from Hawaii (7). State driver's license files were the primary sources used to identify study subjects in Hawaii and California. Additionally, in Hawaii, state voter's registration files were used, and, in California, Health Care Financing Administration (HCFA) files were used to identify additional African American men.

All participants (n=215,251) returned a 26-page self-administered baseline questionnaire that obtained general demographic, medical and risk factor information. In the cohort, incident cancer cases are identified annually through cohort linkage to population-based cancer Surveillance, Epidemiology, and End Results (SEER) registries in Hawaii and Los Angeles County as well as to the California State cancer registry. Information on stage and grade of disease are also obtained through the SEER registries.

Blood sample collection in the MEC began in 1994 and targeted incident prostate cancer cases and a random sample of study participants to serve as controls for genetic analyses. This nested prostate cancer case-control study in the MEC consists of 2,768 invasive prostate cancer cases and 2,359 controls. This study was approved by the Institutional Review Boards at the University of Southern California and at the University of Hawaii and informed consent was obtained from all study participants.

Laboratory Assays

Genotyping for this study was performed using genomic DNA samples, and the allelic discrimination assay (8). The assay for rs4962416, which was previously reported as a risk allele near the CTBP2 gene (4), failed in genotyping so it was replaced by rs12769019 for association testing of this risk allele (pairwise r2 = 1.0 in the hapmap CEU population). We included ~5% duplicate samples to assess genotyping reproducibility. In total, the concordance was 99.9% among the replication sets. For the 13 variants, the overall genotyping call rate was 98.7%. Call rates were also similar between cases and controls for each population (largest difference was 5.5% for rs5945572 in African Americans). For each variant, we examined Hardy-Weinberg equilibrium (HWE) using a chi squared test (1 df) among the controls for each ethnic group. Three variants were nominally statistically significantly (rs2660753, European Americans, p=0.035; rs9364554, Japanese Americans, p=0.047; and rs2735839, European Americans, p=0.035). Based on the number of tests we would have expected ~3 of these tests to be significant by chance alone. Details regarding genotyping efficiency and HWE are provided in Supplemental Table 1.

Statistical Analysis

Odds ratios (OR) and 95% confidence intervals (CI) of the effect of each variant on prostate cancer risk were computed using logistic regression in ethnic-specific and ethnic-pooled analyses (SAS version 9.1, SAS Institute Inc., Cary, North Carolina). We estimated the log-additive effect of each risk allele as well as the OR for heterozygotes and homozygotes separately. All estimates are adjusted for age (quintiles) and race (in pooled analysis). In the admixed populations (African Americans, Latinos, and Native Hawaiians), we adjusted for their global proportion of European ancestry as previously described (6). First degree family history of prostate cancer (father or full brother) was also examined as a potential confounding variable, but was not included in the model because it had no effect (<2% change) on the pooled risk associations. We tested for allelic heterogeneity of effects by including an interaction term between variant and racial/ethnic group in the regression model (4 df test). We also tested for gene × gene interaction by including an interaction term for every combination of two risk alleles. We also examined genetic associations with prostate cancer risk among disease subgroups using the standard case-control approach, limiting the cases to those with a specific phenotype (‘advanced disease’) and all controls, and a case-only analysis to test for differences by disease subgroup. We defined the cancer as ‘advanced’ if high stage (regional by direct extension, regional by lymph nodes, regional by both direct extension and lymph nodes, regional NOS, or distant metastases/systemic disease), and/or high grade (low level of cell differentiation; Gleason score > 7). Non-advanced disease was defined as having both a localized stage and low grade (Gleason Score ≤ 7). We were unable to define cases as either advanced or localized if both stage and grade data were missing or if either the stage was localized or grade was low (Gleason Score ≤ 7), and information for the other variable was missing (n=207).

Results and Discussion

Cases in this study ranged in age of entry into the cohort from 44 to 78 with a mean of 64.3 (age at diagnosis ranged from 46 to 87). Controls ranged in age from 45 to 77 with a mean of 62.5. The Japanese-Americans were slightly older (mean age of entry, 64.6 years) while the Native Hawaiians were slightly younger than the other three groups (mean age of entry, 62.7 years).

Six of the variants were nominally statistically significant (p<0.05) in pooled analyses (*JAZF1*, rs10486567, OR= 1.23; (95% CI, 1.12–1.35); Xp11.2, rs5945572, 1.31(1.13–1.51); *HNF1B*, rs4430796, 1.15(1.06–1.25); *MSMB*, rs10993994, 1.13(1.04–1.23); 11q13.2, rs7931342, 1.13(1.03–1.23), and 3p12.1, rs2660753, 1.11(1.01–1.21); Table 1). These associations were similar in magnitude (RR>1.10) and in the same direction as reported in previous GWAS among men of European ancestry (1–5). The associations for each genotype class are provided in Supplemental Table 2. These 6 risk variants were common in all populations with frequencies ranging from 0.06–0.76, and frequencies ≥0.19 in the combined sample. For two variants we detected significant heterogeneity of the effect across populations (*HNF1B*, rs4430796, $p_{het} = 0.026$; 11q3.2, rs7931342, $p_{het} = 0.023$). For these variants, positive associations were noted in all populations except African Americans and Japanese, respectively, the two largest groups, suggesting that these variants are poorly linked to the causal alleles in these populations.

Non-significant positive associations were also observed in the expected direction for 6 other variants (*SLC22A3*, rs9364554, 1.10(1.00–1.21); *CTBP2*, rs12769019, 1.11(0.99–1.25); *HNF1B*, rs11649743, 1.10(0.99–1.22); *EHBP1*, rs721048, 1.08(0.94–1.25); *KLK2/3*, rs2735839, 1.06(0.97–1.16); and 17q24.3, rs1859962, 1.04(0.96–1.13)) and for most of these variants, positive associations were observed consistently across population (Table 1).

Two of these variants had frequencies <0.20 in the combined sample with ethnic-specific frequencies <0.05 in some populations. We noted significant ethnic heterogeneity in the associations for *EHBP1* (rs721048, $p_{het} = 3.9 \times 10^{-3}$) and *KLK2/3* (rs2735839, $p_{het} = 2.0 \times 10^{-3}$), (Table 1) and no evidence of an association with variant rs6465657 in *LMTK2*, (OR=0.99; 95% CI: 0.89–1.09). Interestingly, the *KLK2/3* variant was inversely associated with risk in African Americans.

The original GWAS found effect sizes of 1.10–1.25 per allele with frequencies of the risk alleles ranging from 0.10–0.85 (1–5). A replication study of seven of these alleles by the PRACTICAL Consortium found per allele effect sizes ranging from 1.08 to 1.30 (9). In our study, a lack of power due to smaller sample size and/or low MAFs in some populations (and thus in the combined sample) was likely to contribute to some of the variants not reaching statistical significance. We had relatively limited power (50–65%) to detect statistically significant pooled effects of 1.10–1.12 for variants with frequencies as low as 0.20. Power was improved (≥81%) for effects ≥1.20 and risk alleles with frequencies ≥0.10 in the combined sample.

We detected 6 significant gene × gene interactions; however, it is difficult to determine whether any of these are true effects, since this analysis included 78 tests and we would have expected ~4 significant interactions by chance alone. The most significant interaction ($p=9.0 \times 10^{-3}$) was between rs4430796 (*HNF1B*) and rs1859962 (17q24) which are both located on the same chromosome, albeit in distant areas.

We also examined allelic associations by disease subgroup (advanced vs. non-advanced; Table 2 and Supplemental Tables 3 and 4) and tested for differences in case-case analyses. None of the differences in prostate cancer risk between advanced and non-advanced subgroups were statistically significant.

While the majority of the risk variants examined in this study were positively associated with risk in the pooled analysis, the lack of consistent effects in all populations for some markers suggests that, for these associations, the underlying causal variant may not be of appreciable frequency in all populations and/or differences in LD may be obscuring effects in some populations. One example where this is likely to be case is rs4430796 (*HNF1B*) where we noted no evidence of an association in African Americans (OR = 0.99, 95% CI 0.84–1.16). The ethnic heterogeneity observed for some markers may also be due to interactions with other genetic risk factors and environmental exposures that vary in frequency across populations, which we plan to explore in future analyses.

Our previous studies on 8q24 and prostate cancer provide strong support for the hypothesis that the higher incidence of prostate cancer in African American men, compared to men in other racial and ethnic populations, is due to common risk variants that are more common in men of African descent (6). It is interesting to note that only three of the variants examined in this study were more common in African Americans than in the other racial/ethnic groups (Table 1). Fine-mapping of these candidate prostate cancer risk loci in a multiethnic sample will be important in order to identify the strongest markers of risk in each population and hopefully will help us to better understand the excess risk of prostate cancer in African Americans.

Among the alleles examined, very little is known about the genes involved and/or the potential biological mechanisms underlying their association with prostate cancer risk. None of the risk variants examined in this study are located in exons. Decreased serum levels of the protein product of *MSMB*, Prostate Secretory Protein of 94 amino acids, has been associated with increased prostate cancer risk (10). *MSMB* may be a tumor suppressor and altering its expression could play an important role in tumorigenesis. *HNF1B*, a transcription factor, is involved in nephrogenesis, and heterozygous mutations in *HNF1B* are known to cause maturity-onset diabetes of the young (MODY5) (11,12). *HNF1B* is located on chromosome 17q12 where two independent risk alleles for prostate cancer have been detected in non-coding sequence (2,5). *KLK3* encodes the PSA protein, which raises the question as to whether the previously reported relationship is causal or an artifact of differential selection of cases and controls based on PSA levels (13,14). Controls were unselected with regard to PSA level in the present study. A statistically significant positive association was found with the *KLK3* SNP for subjects of European and Japanese ancestry, whereas a significant inverse association was found in African Americans. This may suggest that either the variant is not causal, and/or that distinct mechanisms are at play in these populations. In addition to the already established 8q24 region, the variants at both 3p12 and 11q13 lie in gene deserts, with the closest annotated genes being ~70 kb and ~67 kb away, respectively.

In conclusion, we have confirmed that the majority of associations noted with prostate cancer risk variants from GWAS in European populations can be generalized to other populations. Moreover, they appear to act independentlly. Deep resequencing and fine-mapping of these regions in samples from multiple populations is now recommended, specifically for loci that display significant ethnic heterogeneity, to both define the full spectrum of risk alleles in the population, as well as further localize the causal alleles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Frequencies of risk alleles and associations with prostate cancer risk in the MEC.

			OR(95% CI)[a] Risk Allele Frequency							
SNP	**Chr. Gene**	**Allele Tested**	**African Americans 860 ca/575 co**	**European Americans 468 ca/419 co**	**Latinos 603 ca/572 co**	**Japanese Americans 725 ca/684 co**	**Native Hawaiians 112 ca/109 co**	**Pooled 2768 ca/2,359 co**	**P value**	**P_{het}[b]**
rs721048	2p15 EHBP1	A	0.86(0.59–1.26) 0.05	0.87(0.67–1.12) 0.19	1.49(1.19–1.87) 0.14	1.05(0.71–1.56) 0.04	0.52(0.24–1.12) 0.09	1.08(0.94–1.25) 0.09	0.26	3.9×10^{-3}
rs2660753	3p12.1	T	0.97(0.83–1.14) 0.46	1.06(0.81–1.39) 0.13	1.15(0.94–1.40) 0.20	1.30(1.09–1.55) 0.24	0.94(0.56–1.57) 0.18	1.11(1.01–1.21) 0.26	0.034	0.16
rs9364554	6q25.3 SLC22A3	T	1.10(0.82–1.48) 0.07	1.06(0.86–1.30) 0.27	1.15(0.95–1.39) 0.21	1.09(0.93–1.29) 0.34	1.07(0.69–1.68) 0.22	1.10(1.00–1.21) 0.22	0.062	0.99
rs10486567	7p15.2 JAZF1	G	1.18(1.00–1.40) 0.70	1.50(1.19–1.89) 0.74	1.19(1.00–1.40) 0.53	1.14(0.88–1.48) 0.09	1.25(0.83–1.89) 0.36	1.23(1.12–1.35) 0.47	2.1×10^{-5}	0.48
rs6465657	7q21.3 LMTK2	C	0.91(0.72–1.14) 0.85	1.08(0.89–1.31) 0.45	0.94(0.78–1.12) 0.70	1.04(0.82–1.33) 0.90	0.98(0.65–1.49) 0.67	0.99(0.89–1.09) 0.75	0.80	0.77
rs10993994	10q11.23 MSMB	T	1.05(0.90–1.24) 0.59	1.15(0.96–1.39) 0.42	1.06(0.90–1.25) 0.37	1.26(1.08–1.46) 0.45	1.10(0.75–1.61) 0.64	1.13(1.04–1.23) 0.47	3.1×10^{-3}	0.52
rs12769019	10q26.13 CTBP2	G	1.20(0.98–1.47) 0.16	1.12(0.90–1.39) 0.26	1.00(0.83–1.21) 0.24	1.43(0.75–2.76) 0.01	1.42 (0.68–2.95) 0.07	1.11(0.99–1.25) 0.15	0.062	0.60
rs7931342	11q13.2	G	1.12(0.93–1.35) 0.76	1.28(1.05–1.55) 0.51	1.27(1.07–1.51) 0.37	0.87(0.73–1.05) 0.23	1.19(0.79–1.80) 0.48	1.13(1.03–1.23) 0.45	8.4×10^{-3}	0.023
rs11649743	17q12 HNF1B	G	1.04(0.79–1.38) 0.91	1.05(0.82–1.35) 0.82	1.29(1.04–1.61) 0.82	1.08(0.91–1.27) 0.70	0.96(0.65–1.41) 0.62	1.10(0.99–1.22) 0.80	0.067	0.58
rs4430796	17q12 HNF1B	A	0.99(0.84–1.16) 0.35	1.44(1.18–1.74) 0.48	1.26(1.07–1.50) 0.57	1.04(0.89–1.22) 0.64	1.23(0.79–1.90) 0.70	1.15(1.06–1.25) 0.53	9.1×10^{-4}	0.026
rs1859962	17q24.3	G	1.01(0.86–1.19) 0.32	1.00(0.83–1.20) 0.51	1.10(0.93–1.30) 0.60	1.06(0.89–1.25) 0.26	1.03(0.69–1.52) 0.56	1.04(0.96–1.13) 0.42	0.35	0.95
rs2735839	19q13 KLK2/3	G	0.80(0.67–0.95) 0.71	1.33(1.02–1.75) 0.84	1.15(0.94–1.40) 0.77	1.21(1.03–1.41) 0.58	0.91(0.61–1.35) 0.51	1.06(0.97–1.16) 0.70	0.20	2.0×10^{-3}
rs5945572	Xp11.22 NUDT10/11	A	1.34(1.05–1.71) 0.26	1.25(0.95–1.66) 0.35	1.32(0.98–1.77) 0.17	1.25(0.86–1.82) 0.08	1.65(0.61–4.46) 0.06	1.31(1.13–1.51) 0.19	2.6×10^{-4}	0.98

[a] ORs adjusted for age (quintiles), genome-wide European ancestry (African Americans, Latinos and Native Hawaiians) and age-ethnicity strata (pooled analysis).

[b] P_{het} = p value for heterogeneity of allelic effects across ethnic groups (4 df test)

Table 2

Frequency of Risk Allele and Association with Prostate Cancer by Disease Subgroup and Case-only testing.

			OR(95% CI)[a] Risk Allele Frequency	OR(95% CI)[a] Risk Allele Frequency	
SNP	**Chr. Gene**	**Allele Tested**	**Advanced Cases 961 ca/2359 co**	**Non-Advanced Cases 1600 ca/2359 co**	**P_{het}[b]**
rs721048	2p15 EHBP1	A	1.00(0.82–1.21) 0.09	1.11(0.94–1.30) 0.09	0.33
rs2660753	3p12.1	T	1.15(1.01–1.30) 0.26	1.06(0.96–1.19) 0.26	0.26
rs9364554	6q25.3 SLC22A3	T	1.06(0.93–1.21) 0.22	1.12(0.99–1.25) 0.22	0.53
rs10486567	7p15.2 JAZF1	G	1.13(0.99–1.29) 0.47	1.31(1.17–1.46) 0.47	0.088
rs6465657	7q21.3 LMTK2	C	0.95(0.83–1.08) 0.75	1.04(0.93–1.17) 0.75	0.17
rs10993994	10q11.23 MSMB	T	1.07(0.96–1.20) 0.47	1.16(1.06–1.27) 0.47	0.19
rs12769019	10q26.13 CTBP2	G	1.16(1.00–1.36) 0.15	1.08(0.94–1.23) 0.15	0.36
rs7931342	11q13.2	G	1.17(1.04–1.32) 0.45	1.10(1.00–1.22) 0.45	0.37
rs11649743	17q12 HNF1B	G	1.14(0.99–1.32) 0.80	1.10(0.98–1.25) 0.80	0.69
rs4430796	17q12 HNF1B	A	1.16(1.03–1.30) 0.53	1.15(1.05–1.27) 0.53	0.88
rs1859962	17q24.3	G	1.00(0.89–1.12) 0.42	1.07(0.97–1.18) 0.42	0.27
rs2735839	19q13 KLK2/3	G	1.03(0.91–1.17) 0.70	1.09(0.98–1.21) 0.70	0.33
rs5945572	Xp11.22 NUDT10/11	A	1.27(1.04–1.55) 0.19	1.31(1.11–1.54) 0.19	0.84

[a] ORs adjusted for age(quintiles)-ethnicity strata, and genome-wide European ancestry (African Americans, Latinos and Native Hawaiians)

[b] P_{het} = p value for heterogeneity (advanced vs. non-advanced)