Short Communication

Replication of the 10q11 and Xp11 Prostate Cancer Risk Variants: Results from a Utah Pedigree-Based Study

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Abstract

A recent genome-wide association study suggested seven new loci as associated with prostate cancer susceptibility. The strongest associated single nucleotide polymorphism (SNP) in each region was identified (rs2660753, rs9364554, rs6465657, rs10993994, rs7931342, rs2735839, rs5945619). We studied these seven SNPs in a replication study consisting of 169 familial prostate cancer cases selected from Utah high-risk prostate cancer pedigrees and 805 controls. We performed subset analyses for aggressive and early-onset prostate cancer. At a nominal significance level, two SNPs were found to be associated with prostate cancer: rs10993994 on chromosome 10q11 [odds ratio (OR), 1.42; 95% confidence interval (95% CI), 1.05-1.90; *P* = 0.022] and rs5945619 on chromosome Xp11 (OR, 1.54; 95% CI, 1.03-2.31; *P* = 0.035). Restricting analysis to familial prostate cancer cases with aggressive disease yielded very similar risk estimates at both SNPs. However, subset analysis for familial, early-onset disease indicated highly significant association evidence and substantially higher risk estimates for rs10993994 (OR, 2.20; 95% CI, 1.48-3.27; *P* < 0.0001). This result suggests that the higher risk estimates from the stage 1 cohort in the original study for rs10993994 may have been due to the early-onset and familial nature of the prostate cancer cases in that cohort. In conclusion, in a small case-control study of prostate cancer cases from Utah high-risk pedigrees, we have significantly replicated association of prostate cancer with rs10993994 (10q11) upon study-wide correction for multiple comparisons. We also nominally replicated the association of prostate cancer with rs5945619 (Xp11). In particular, it seems that the susceptibility locus at 10q11 maybe involved in familial, early-onset disease. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1290–4)

Introduction

Prostate cancer is the most common noncutaneous cancer in men in the United States, with an estimated 234,460 new cases and 27,350 deaths in the United States in 2006 (1). There is strong evidence for a genetic component to prostate cancer (2, 3), although identifying susceptibility variants has proven difficult (4). In search of lower penetrance susceptibility variants, genome-wide association (GWA) studies for prostate cancer are being pursued, and already some highly robust and replicated association results have been reported (5, 6). Beyond these first few initial successes, further susceptibility variants are believed to exist. A recent prostate cancer GWA study has implicated seven new loci (7). To increase power, stage 1 of this GWA study focused on clinically diagnosed disease in addition to early onset (diagnosis ≤60 years) or a positive family history, and compared with population-screened controls (prostate-specific antigen levels <0.5 ng/mL) ages ≥50 years. A second-stage replication was also done. The design for the second stage was less stringent, including a mixture of early-onset, familial and population-based cases, and a mixture of cancer-free, prostate-specific antigen <10 ng/mL, and population-based controls. Seven single nucleotide polymorphisms (SNP) were found to replicate and to be independently significant on chromosomes 3p12, 6q25, 7q21, 10q11, 11q13, 19q13, and Xp11 (combined two-stage *P* values ranged from 2.7×10^{-8} to 8.7×10^{-29}).

We studied two sets of cases and controls, including prostate cancer cases selected from Utah high-risk prostate cancer pedigrees, to examine the association between each of the identified seven SNPs and prostate cancer. Both sets of cases and controls included cases selected from high-risk prostate cancer pedigrees (those with significant excess disease). In set 1, one prostate cancer case was selected from each of 142 high-risk pedigrees and controls were independent individuals that were cancer-free and matched to the cases based on

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sex and birth cohort. Set 1 is most similar to the stage 2 design of Eeles (7), which can be important for replication studies. Set 2 included related prostate cancer cases belonging to two very large pedigrees and a set of ''general'' controls that were genotyped on the same platform. This second design not only supplements the power of set 1, but also can be used to assess segregation of alleles through the pedigrees. Early prostate cancer diagnosis and aggressive prostate cancer analyses were also considered.

Materials and Methods

Study Population. The Utah prostate cancer resource consists of a set of high-risk pedigrees. Each high-risk pedigree is a cluster of prostate cancer cases identified in the Utah Population Database (8) that was selected for study due to a statistical excess of prostate cancer. The Utah Population Database combines an extensive genealogy consisting of Utah pioneers and up to 10 generations of their descendants (~2.2 million individuals), with cancer diagnosis data from the Utah Cancer Registry. The Utah Cancer Registry is a Surveillance, Epidemiology and End Results registry that contains all independent primary cancers diagnosed or treated in the state of Utah, with a malignant or *in situ* behavior code, since 1966.

Two sets of cases and controls were used. The first set consisted of 142 prostate cancer cases, one selected from each of 142 previously ascertained high-risk prostate cancer pedigrees, and 147 frequency matched controls. The controls were cancer-free according to the Utah Cancer Registry and self-report, and matched for sex (male) and 5-year birth cohort. Controls were selected to be marry-in individuals in nonprostate cancer high-risk pedigrees; that is, not an ancestral founder or part of the related cluster of individuals. The second set consisted of 27 prostate cancer cases contained in two very large extended pedigrees previously genotyped for shared genomic segment analysis (9) using the Illumina HumanHap550 chip that includes all seven variants of interest; both pedigrees were six generations deep, the first contained 6 prostate cancer cases separated by 23 meioses; the second pedigree contained 21 prostate cancer cases separated by 68 meioses; the average relatedness between pairs in pedigrees was approximately that of second cousins (average coefficient of kinship of 0.019 and 0.014). Controls for set 2 were 658 males selected from the iControlDB (a database of controls provided by Illumina). These controls are unknown for cancer status. All individuals studied were Caucasian.

Our study is small, although enriched for familial disease, and power must be considered when interpreting our findings. Based on the combined sample size (n = 169), average control allele frequencies, and risk sizes from stage 1 of Eeles et al. (7), power to detect nominally significant evidence ($P \leq 0.05$) was estimated to be good for rs10993994, rs5945619, and rs2735839 (98%, 90%, and 78%, respectively), moderate for rs646567 and rs7931342 (both 61%) and low for rs9364554 and rs2660753 (49% and 40%, respectively).

This study was approved by the appropriate University of Utah institutional review board and informed consent was obtained from all human subjects ascertained at the University of Utah. For individuals in the iControlDB, all necessary approvals, consents, and authorizations were obtained by the submitting institutions.

Genotyping. Genomic DNA was extracted from blood buffy coats using PUREGENE DNA isolation kits (Gentra Systems). Five prostate cancer cases from set 1 were dropped due to poor-quality DNA. Genotyping for set 1 was carried out using fluorescent-based TaqMan SNP Genotyping Assays (Applied Biosystems). Reaction volumes of 5 mL were used, including 20 ng of DNA, TaqMan Universal Mastermix, and the SNP assay mix. SNPs genotyped were rs2660753, rs9364554, rs6465657, rs10993994, rs7931342, rs2735839, and rs5945619. The PCR reactions were done on a GeneAmp 9700 (Applied Biosystems) with the following protocol: 10 min at 95°C and then 40 cycles of 15 s at 92°C and 1 min at 60°C. The SNP assays were analyzed on a 7900HT and alleles were called using Sequence Detection System version 2.3. For set 2, genotyping was done as a service by deCode Genetics using the Illumina Sentrix HumanHap550 BeadChip technology.

Statistical Analysis. All subjects in set 1 (both cases and controls) were selected to avoid relatedness. However, because all high-risk pedigrees are small subsets from the Utah Population Database, we used the Utah Population Database to identify any relationships between studied individuals (back 10 generations). Due to the existence of familial relationships between some study subjects, all analyses were carried out using Genie (10, 11), a software that provides valid statistical tests for related individuals using Monte Carlo testing. Briefly, an empirical null distribution is generated from a large number of null simulations and used to determine an empirical significance level for the statistical test. Here, we used 10,000 simulations for the null distribution. We performed tests for deviation from Hardy-Weinberg equilibrium for each SNP, single-study Cochran-Armitage trend tests, and meta-analysis Cochran-Mantel-Haenszel χ^2 trend tests, and single-study per allele odds ratios (OR) and meta-analysis Mantel-Haenszel per allele ORs with 95% confidence intervals (95% CI). Cochran's Q statistic was used to test for homogeneity of the per allele ORs across the two case-control sets. For rs5945619 at Xp11, an allele test was done in place of the trend test, because for male-only analyses on the X chromosome there are only two genetic groups based on the two SNP alleles. We repeated analyses for subsets of aggressive disease and early-onset prostate cancer. As in Christensen et al. (12), cases were required to meet at least one of the following criteria to be classified as aggressive: (a) regional lymph nodes or distant metastasis, (b) poorly differentiated or undifferentiated grade (Gleason sum 8-10), or (c) death due to metastatic prostate cancer, confirmed by death certificate. Early onset was defined to be diagnosis of disease at ≤65 years of age. In the combined sets, 60% of prostate cancer cases had regional or distant disease, 15% of tumors were poorly differentiated or undifferentiated, and the mean age at diagnosis was 68.4 years.

We considered a nominal significance threshold of 0.05 and a study-wide significance threshold of 0.001 to represent seven SNPs, two case-control sets, and three prostate cancer phenotype definitions.

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Table 1. Association results for familial prostate cancer

SNP	Position*	Results from prior GWA† (7)	Case-control set	MAF		Per allele OR (95% CI)	P trend‡	Homogeneity P§
				Controls	Cases			
rs2660753	3p12	1.52 (1.30-1.77)	Set 1	0.112	0.130	1.18 (0.71-1.98)	0.5196	
	87,193,364	1.18 (1.06-1.31)	Set 2	0.133	0.148	1.33 (0.55-2.35)	0.7729	
		2.7×10^{-8}	Combined‖			1.17 (0.76-1.80)	0.4768	0.9268
rs9364554	6q25	1.28 (1.16-1.41)	Set 1	0.354	0.327	0.89 (0.62-1.27)	0.5227	
	160,753,654	1.17 (1.08-1.26)	Set 2	0.262	0.352	1.50 (0.81-2.81)	0.2019	
		5.5×10^{-10}	Combined			1.02 (0.74-1.39)	0.9214	0.1484
rs6465657	7q21	1.30 (1.19-1.43)	Set 1	0.401	0.430	1.12 (0.81-1.57)	0.4769	
	97,654,263	1.12 (1.19-1.20)	Set 2	0.441	0.556	1.59 (0.87-2.88)	0.1281	
		1.1×10^{-9}	Combined			1.23 (0.92-1.65)	0.1515	0.3184
rs10993994	10q11	1.62 (1.47-1.78)	Set 1	0.347	0.457	1.59 (1.14-2.22)	0.0074	
	51,219,502	1.25 (1.17-1.34)	Set 2	0.434	0.444	1.04 (0.58-1.88)	0.8935	
		8.7×10^{-29}	Combined			1.42 (1.05-1.90)	0.0222	0.2357
rs7931342	11q13	0.79 (0.72-0.86)	Set 1	0.459	0.458	0.99 (0.71-1.40)	0.9785	
	68,751,073	0.84 (0.79-0.90)	Set 2	0.466	0.389	0.73 (0.40-1.35)	0.3078	
		1.7×10^{-12}	Combined			0.92 (0.68-1.23)	0.5709	0.3858
rs2735839	19q13	0.56 (0.50-0.64)	Set 1	0.136	0.141	1.05 (0.65-1.68)	0.8916	
	56,056,435	0.83 (0.75-0.91)	Set 2	0.157	0.241	1.70 (0.83-3.46)	0.1367	
		1.5×10^{-18}	Combined			1.22 (0.81-1.82)	0.3374	0.2634
rs5945619	Xp11	1.46 (1.28-1.66)	Set 1	0.370	0.453	1.41 (0.88-2.27)	0.1549	
	51,258,412	1.19 (1.07-1.31)	Set 2	0.353	0.519	1.98 (0.86-4.57)	0.1023	
		1.5×10^{-9}	Combined			1.54 (1.03-2.31)	0.0352	0.5016

Abbreviation: MAF, minor allele frequency.
*Chromosome and bp position (build 36).
†OR (95% CI) for the first and second stage, and the combined P value as shown in Table 1 of Eeles et al. (7).
‡Cochran-Armitage trend test and the Cochran-Mantel-Haenszel meta trend test (except for the X chromosome SNP where an allele test has been done).
§Cochran Q test for homogeneity of the per allele ORs across the two Utah case-control sets.
‖Combined total of 169 familial prostate cancer cases.

Results

Genetic relationships were found between 59 cases and 14 controls in set 1; however, these were all quite distant, as expected. The average pair-wise relationship was approximately third cousins (~8 meioses between any pair), compared with the average relatedness in set 2 of approximately second cousins (~6 meioses between any pair). No relationships were found for the remaining 216 individuals in set 1, and the 658 controls in set 2 are also unrelated. For the subset analyses, 105 prostate cancer cases could be defined as aggressive and 73 as early onset.

The overall genotyping success rate was 99.75% and 99.98% for sets 1 and 2, respectively, with at most three individuals missing from any one analysis. No significant departures from Hardy-Weinberg equilibrium were observed (all $P > 0.1$). With one exception, the minor allele frequencies for all SNPs were within 0.05 of that previously reported (7). One SNP, rs9364554, in set 1 was slightly more discrepant (0.354 compared with 0.291), but given the small sample sizes and the limited power for this SNP (see Materials and Methods), none were significantly different.

Table 1 shows the Cochran-Armitage trend test results for our primary familial prostate cancer phenotype (all cases in our study are highly familial, but the primary prostate cancer phenotype is unselected for age at diagnosis or tumor aggression). As can be seen from Table 1, two of the seven SNPs attained nominal

Table 2. Results for aggressive and early onset prostate cancer subset analyses

SNP	Aggressive PRCA*		Early-onset PRCA†	
	Per allele OR (95% CI)‡	Trend P§	Per allele OR (95% CI)	Trend P
rs2660753	1.17 (0.76-1.80)	0.8288	1.33 (0.78-2.28)	0.3138
rs9364554	1.02 (0.74-1.39)	0.7546	0.96 (0.63-1.46)	0.8349
rs6465657	1.23 (0.92-1.65)	0.5661	1.24 (0.84-1.81)	0.2639
rs10993994	1.42 (1.05-1.90)	0.0064	2.20 (1.48-3.27)	<0.0001
rs7931342	0.92 (0.68-1.23)	0.4594	0.89 (0.60-1.32)	0.5792
rs2735839	1.22 (0.81-1.82)	0.5033	1.04 (0.62-1.74)	0.8976
rs5945619	1.55 (0.97-2.49)	0.0697	1.46 (0.85-2.49)	0.1779

Abbreviation: PRCA, prostate cancer.
*Aggressive prostate cancer was defined as: (1) regional lymph nodes or distant metastasis; (2) poorly differentiated or undifferentiated grade (Gleason sum 8-10); or (3) death due to metastatic prostate cancer, confirmed by death certificate. Combined total for familial, aggressive prostate cancer was 105.
†Early onset was defined as diagnosis of disease at ≤65 y of age. Combined total for familial, early-onset prostate cancer was 73.
‡Cochran-Mantel-Haenszel meta OR across both case-control sets.
§Cochran-Mantel-Haenszel meta trend test (except for the X chromosome SNP where an allele test has been done).

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evidence for association with prostate cancer, rs10993994 on chromosome 10 (P = 0.0222) and rs5945619 on chromosome X (P = 0.0352). For both these SNPs, the effect sizes estimated were in the same direction and of similar magnitude to that observed in stage 1 of the previous GWA, which included familial and/or early-onset prostate cancer cases (7). For example, an OR of 1.62 was previously estimated for rs10993994, compared with 1.59 observed here for set 1, and an OR of 1.46 previously for rs5945619 compared with 1.41 for set 1. All other SNPs were nonsignificant (all meta $P > 0.15$); however, it is of note that for rs2660753, rs6465657, and rs7931342, the control minor allele frequencies and ORs were of similar magnitude in the same direction to that observed previously (7). Results for two SNPs, rs9364554 and rs2735839, showed no similarity to that previously reported. To match that presented by Eeles et al. (7), for each autosomal SNP, we additionally performed the general 2 × 3 contingency table test for independence (2 *df*). All results were nonsignificant (data not shown). There was no evidence for heterogeneity across the two case-control sets (all $P \geq 0.15$ for test of homogeneity).

Table 2 shows the meta results for the subset analyses for prostate cancer cases selected for aggression or early age at diagnosis among both set 1 and set 2 subjects. Similar to the analyses for familial prostate cancer, the results for two SNPs (rs10993994 and rs5945619) were of interest. For the familial, aggressive subset analysis, the results for rs10993994 and rs5945619 remained very consistent with that observed for familial prostate cancer, despite the decrease in number of cases considered in the analysis. For rs10993994, OR 1.42 (95% CI, 1.05-1.90; P = 0.022) changed to OR 1.42 (95% CI, 1.05-1.90; P = 0.0064), and for rs5945619, OR 1.54 (95% CI, 1.03-2.31; P = 0.035) changed to OR 1.55 (95% CI, 0.97-2.49; P = 0.070). For the familial, early-onset subset analysis, however, a substantial increase in OR to 2.20 (95% CI, 1.48-3.27) was observed for rs10993994, and the meta P value reached the minimum for the number of Monte Carlo simulations used in the analysis ($P < 0.0001$).

To follow up the study-wide significant result for rs10993994 for early-onset prostate cancer, we investigated evidence for a shared genomic segment (9) that may have segregated from a common ancestral founder to the early-onset prostate cancer cases in the two extended pedigrees in set 2. The early-onset prostate cancer results for rs10993994 in sets 1 and 2 were both consistent with increased risk (per allele ORs 2.34 and 1.63 for sets 1 and 2, respectively). Evidence for such a shared segment identical by descent could be used to delimit the locus. Surrounding rs10993994, only six consecutive SNPs were shared by all three early-onset prostate cancer cases in one pedigree (separated by 14 meioses), and nine flanking SNPs shared by five early-onset prostate cancer cases in the second pedigree (separated by 19 meioses). These lengths of sharing are no more than would be expected by chance and does not suggest a segment of chromosome shared identical by descent.

Discussion

We have performed a small replication study focusing on prostate cancer cases from high-risk prostate cancer pedigrees in Utah. At a nominal significance level, our study confirms the associations previously found for rs10993994 and rs5945619 at chromosomes 10q11 and Xp11 (P = 0.022 and P = 0.035, respectively; ref. 7). For three other SNPs, rs2660753, rs6465657, and rs7931342, our minor allele frequency and risk estimates, although not significant, were also consistent with that previously suggested. Risk estimates for rs10993994 and rs5945619 remained similar when prostate cancer cases were restricted to only those with aggressive disease. For familial, early-onset disease, a study-wide significant association was identified for rs10993994 ($P < 0.0001$).

Due to our ability to analyze pedigree-based samples using Genie (10, 11), we were able to incorporate into our association study existing genotype data from two very large pedigrees. A benefit of this is the ability to follow the segregation of associated variants through the pedigrees. For rs10993994, we investigated the existence of a shared genomic segment identical by descent in the early-onset prostate cancer cases of two large pedigrees, but found no evidence of such. This is, perhaps, the expected outcome for common, moderate-risk variants.

It is of note that of the seven variants identified by Eeles et al. (7), each of the two that we are able to replicate here (rs10993994 and rs5945619), were independently identified as best findings in other recent genome-wide studies (13, 14). Variant rs5945572, ~12 kb p-ter and in strong linkage disequilibrium with rs5945619 (r^2 of 0.91), was the most significant finding on the X chromosome in a GWA analysis of Icelanders (14). Variant rs10993994 was the most significant finding in both the Eeles et al. (7) and the Thomas et al. (13) GWA studies, with an estimated effect size second in magnitude only to those found at 8q24 in both.

Lines of evidence, including from our study, are beginning to seem to suggest that enriching for familial disease and early age at diagnosis may increase power to detect the association for rs10993994. Our result was highly significant ($P < 0.0001$) for familial, early-onset disease (diagnosis ≤65 years), with a per allele OR of 2.20 (95% CI, 1.48-3.27), compared with OR 1.42 (95% CI, 1.05-1.90) for familial prostate cancer only. This is consistent with what has previously been observed. The GWA phase of the Eeles et al. (7) study (stage 1) focused on prostate cancer cases with either a family history or early onset. The risk estimate for stage 1 was a per allele OR of 1.62 (95% CI, 1.47-1.78). The stage 2 population-based sample estimated the same risk to be OR 1.25 (95% CI, 1.17-1.34). Supplemental material from Eeles et al. (7) showed that when stage 2 was stratified by age at diagnosis, a linear trend was observed with the highest risk for rs10993994 exhibited in the earliest cohort 1.36 (95% CI, 1.18-1.57 for diagnosis <55 years) and lowest in the oldest cohort 1.17 (95% CI, 1.04-1.31, for diagnosis ≥70 years), although the trend was not statistically significant. In the GWA study of Thomas et al. (13), prostate cancer cases were not selected for family history and the risk estimate was a heterozygous OR 1.24 (95% CI, 1.10-1.39). Our higher risk estimates for familial and early-onset prostate cancer suggest that the higher risk estimates also observed for the phase 1 Eeles et al. (7) study are due to the prostate cancer characteristics that were enriched for (family history and early onset) rather than an initial overestimate of the risk size.

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Whereas the value of this study is the strong familial nature of the cases, the clear limitation is the limited sample size and low power for several of the SNPs studied. It is of note that the two SNPs replicated with nominal evidence were those with the most power (both ≥90%). The negative results for other SNPs should be considered in light of the more limited power for analyses at those loci.

In conclusion, in a small case-control sample containing prostate cancer cases from Utah high-risk pedigrees, we have significantly replicated variants rs10993994 (10q11) and rs5945619 (Xp11). In particular, it seems that the susceptibility locus at 10q11 maybe involved in familial, early-onset disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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