HPC2 Variants and Screen-Detected Prostate Cancer

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Two studies have reported significant associations between susceptibility to prostate cancer and two common missense variants of the HPC2/ELAC2 gene, with estimated relative risks in the range of two- to threefold. We investigated whether these polymorphisms could be informative in the prediction of the presence of prostate cancer in men undergoing prostatic biopsy for the evaluation of an elevated serum-PSA level (≥4.0 ng/ml). We genotyped 944 men who underwent a prostate biopsy at our institution, as well as a control population of 922 healthy, unselected women from the same population. The prevalence of the HPC2 Ala541Thr allele was similar in men with prostate cancer (6.3%), men with other prostatic conditions (6.8%), and healthy women (6.3%) ($P = .83$). We conclude that HPC2 genotyping is unlikely to be a useful adjunct to PSA in the prediction of the presence of biopsy-detected prostate cancer in asymptomatic men.

Introduction

Both epidemiological and molecular studies support the hypothesis that there is a significant hereditary component to prostate cancer (MIM 176806) susceptibility (reviewed by Narod [1998]). Linkage studies of multiplex families with prostate cancer have led to the assignment of several putative highly penetrant dominant genes for prostate cancer (Smith et al. 1996; Berthon et al. 1998; Xu et al. 1998; Gibbs et al. 1999; Berry et al. 2000). In addition, evidence for the contribution of low-penetrance genes to prostate cancer susceptibility comes from association studies; many of the candidate genes are involved in androgen metabolism and include the gene for the androgen receptor (Giovannucci et al. 1997; Stanford and Just 1997), SRD5A2 (Makridakis et al. 1999; Jaffe et al. 2000; Nam et al. 2001), and CYP3A4 (MIM 124010) (Rebbeck et al. 1998). The vitamin D receptor has also been proposed to be a prostate cancer–risk modifier (Ingles et al. 1997).

Recently, a gene on chromosome 17p, HPC2/ELAC, has been mapped and characterized (Tavtigian et al. 2001). HPC2 (MIM 605367) was originally linked to prostate cancer susceptibility in a large Utah kindred. The authors of that study proposed that missense variant alleles of HPC2 may function as low-penetrance modifiers of prostate cancer risk (Tavtigian et al. 2001). The first variant, Ser217Leu, is located in a hydrophilic segment of the protein sequence, and the substitution of the hydrophobic leucine residue may alter the protein structure (Tavtigian et al. 2001). A second variant, Ala541Thr, is adjacent to a histidine motif and may impair protein function. The two variants are in linkage disequilibrium, and, to date, all individuals who carry the Ala541Thr variant have also been found to carry the Ser217Leu variant. The authors of the study estimated that the Ala541Thr variant was associated with an odds ratio of 2.4 for prostate cancer ($P = .02$). A second, independent study, of 359 cases and 266 controls, confirmed the original association (Rebbeck et al. 2000).

Men with prostate cancer may present with clinical manifestations of local or metastatic disease or may be asymptomatic and come to the attention of physicians through serum-PSA screening. The incidence of prostate cancer in North America rose significantly after the introduction of PSA testing. The present study was designed to determine whether the two missense HPC2 variants are associated with an increased risk of screen-detected prostate cancer among men with an elevated serum-PSA level. We have genotyped 944 men who had an elevated serum-PSA level (>4.0 ng/ml) and who underwent a prostate biopsy, to establish whether the HPC2 genotype was predictive of the presence of screen-detected cancer.

Subjects and Methods

Subjects

Subjects were selected from among all men who had been consecutively referred, for the evaluation of an elevated PSA or abnormal digital rectal examination

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(DRE), to the Prostate Center of the University Health Network; the men had been referred to the Prostate Center by 92 urologists and other physicians in the Toronto region. In Ontario, there are no formal criteria for PSA screening, but the practice is widespread. In general, screening is not recommended to men aged <50 years, except in the presence of a positive family history. The study population was not part of a formal screening program, but it is representative of all clinical referrals. At the Prostate Center, a transrectal ultrasound–guided prostate biopsy is recommended if the DRE is abnormal or if the serum-PSA level is ⩾4.0 ng/ml. Between June 1998 and June 2000, a total of 1,105 men with a PSA ⩾4.0 were asked to participate in the study, of whom 944 (85%) consented. Sextant ultrasound-guided needle biopsy samples were obtained with an 18-gauge needle with a spring-loaded biopsy device (Bard Magnum). Additional samples were taken from ultrasonically suspect areas if these areas were outside the sextant distribution. Of the 944 men who underwent a prostate biopsy, 431 were found to have adenocarcinoma. These men with invasive cancer served as the cases for the study.

The 513 men who did not show invasive cancer on the biopsy served as the male controls. These men may have had prostatic intraepithelial neoplasia (PIN) or benign prostate disease. A second control population consisted of 992 unselected, healthy women who participated in a study that was designed to identify genetic determinants of serum-hormone levels. The female control group was added because women are not at risk for prostate cancer or related conditions, and the distribution of HPC2 alleles in women therefore should be representative of the underlying population. These women were aged 17–90 years and were recruited from the University of Toronto, the Bay Centre for Birth Control, the Health Watch Clinic at Women's College Hospital in Toronto, and elsewhere in the Toronto community. None had had a previous diagnosis of cancer. All women completed a self-administered questionnaire detailing information on age, ethnic group, and medical history. In total, there were 431 cases and 1,505 controls available for study.

Laboratory Analysis

Genomic DNA was extracted from peripheral blood through use of Puregene DNA extraction kits. PCRs were performed using, for each reaction, 25 ng of template DNA, 0.4 mM of each primer, 200 mM of each deoxynucleotide triphosphate, 1.0 mM $MgCl_2$, 2% dimethyl sulfoxide, 1.25 U of *Taq* polymerase (Gibco), and the manufacturer's standard buffers in a final reaction volume of 12.5 μl. PCR amplification consisted of 30 cycles (94°C for 1 min, 55°C for 1 min, and 72°C for 1 min).

Both of the variants in HPC2 were detected through use of a procedure modified from that of Tavtigian et al. (2001). The Ser217Leu variant was detected by *Taq*I (New England Biolabs) digestion of a 276-bp PCR fragment amplified by the upstream primer 5′-GTTTTCCCAGTCACGACGCATTCCCATGTATGAACGTCT-3′ and downstream primer 3′-GAAACAGCTATGACCATCTACAAGCATTACAAGGCAGAG-5′. The Ala541Thr variant was identified by *Fnu*4HI (NEB) digestion of the 419-bp PCR fragment amplified by the upstream primer 5′-CCAGCCTTTGTGTAAGTCTAC-3′ and the downstream primer 3′-AATTCTTGATAGGAAACAGCTATGACCATCAGCTTTGTGGTCCAGCCCAAC-5′. After digestion, the PCR products were separated on 3% agarose gels and were visualized by UV light after ethidium bromide staining. For each genotype assay, 25% of the samples were randomly repeated to ensure consistency in allele designation.

Data Analysis

We compared the frequencies of the two candidate polymorphic variants, between the prostate cancer cases and the controls. The frequencies also were compared between subgroups defined by age at onset, ethnic group, family history, and clinical and pathologic findings. Because serum-PSA levels are not distributed normally, a log transformation was used when the mean serum-PSA levels were compared between men with different genotypes. DRE results were categorized as either "normal" or "abnormal" (asymmetric firmness or a palpable nodule). Ethnicity was categorized as "white," "black," "Asian," or "other;" the majority of cases (94%) and controls (84%) were white. To control for minor differences, in ethnic makeup, between cases and controls, ethnic-subgroup analyses were performed. A family history of prostate cancer was considered to be positive if one or more first- or second-degree relatives were reported to have prostate cancer.

Results

A total of 944 men with elevated serum-PSA levels underwent a prostate biopsy. The majority (84.1%) of the men were white; 9.1% were black, 5.5% were Asian and 1.3% were of other ethnic backgrounds. The mean serum-PSA level was 12.8 ng/ml (range 4.0–499 ng/ml). The mean age at biopsy was 65.6 years (range 42–91 years). Fifteen percent of the cases had a positive family history of prostate cancer (mean age 64.2 years). Twenty-seven percent of the subjects had a previous biopsy that did not show evidence of cancer.

Of the 944 men examined, 431 (45.7%) were found to have adenocarcinoma of the prostate (the case group). The remainder of the men (513 [54.3%]) had no evidence of invasive cancer (the control group); of these, 33 had normal prostate tissue, 356 had benign

Table 1

Comparison of Patients with Prostate Cancer and Male Controls

Subgroup	No. (Proportion of Total Sample) in		*P* Value[a]
	Cases	Controls	
Age (years):[b]			
<51	8 (1.9%)	18 (3.5%)	
51-60	96 (22.3%)	130 (25.3%)	
61-70	174 (40.3%)	243 (47.4%)	
>70	153 (35.5%)	122 (23.8%)	.0007
Ethnic group:			
White	379 (87.9%)	415 (80.9%)	
Black	37 (8.6%)	49 (9.6%)	
Asian	10 (2.3%)	2 (8.2%)	
Other	5 (1.2%)	7 (1.4%)	.001
Serum-PSA level[c] (ng/ml):			
4 – 9.9	248 (57.5%)	337 (65.7%)	
10 – 19.9	126 (29.2%)	144 (28.1%)	
20+	57 (13.2%)	32 (6.2%)	.0006
DRE:			
Normal	206 (48.5%)	367 (72.5%)	
Abnormal	219 (51.5%)	139 (27.5%)	<.0001
Family history:			
Positive	57 (16.5%)	59 (13.6%)	
Negative	286 (83.4%)	375 (86.4%)	.24

[a] Calculated, for the comparison of proportions, by the χ^2 statistic.

[b] Mean age of cases = 66.0 years; mean age of controls = 63.9 years (*P* value [Student's *t*-test] = .0001).

[c] Mean in cases = 16.0 ng/ml; mean in controls = 10.1 ng/ml (*P* value [Student's *t*-test] = .0007). Median in cases = 8.8 ng/ml; median in controls = 8.2 ng/ml.

findings (inflammation, benign prostatic hyperplasia, or cellular atypia), and 124 had PIN. Cases and controls are compared in table 1. The cases were, on average, 2 years older than the controls, were more likely to have had an abnormal DRE, and had a higher mean serum-PSA level. These are established risk factors for prostate cancer. With the exception of Asians, the distributions of ethnic subgroups within the case and control groups were similar.

The Ser217Leu missense variant was present in 49.0% of the cases, in 49.5% of the male controls, and in 47.4% of the female controls ($P = .86$) (table 2). There was no significant difference, in the prevalence of this variant, between the two control groups. The probabilities of prostate cancer detection were 45.9% for men with no variant allele, 44.2% for men with one variant allele, and 50.6% for men with two variant alleles ($P = .57$).

The Ala541Thr variant was present in 6.3% of the cases, 6.8% of the male controls, and 6.3% of the female controls ($P = .83$) (table 2). The probabilities of prostate cancer detection were 45.8% in men with no variant allele, 43.3% in men with one variant allele, and 50.0% in men with two variant alleles ($P = .93$). The two variants were in Hardy-Weinberg equilibrium in the case group and in both control groups. The two missense variants are in linkage disequilibrium, and all carriers of the Ala541Thr variant also carried the Ser217Leu variant. Only 12 cases (2.8%) were homozygous for both the Ala541Thr variant and the Ser217Leu variant. This frequency was slightly greater than the frequency of double homozygotes in the male controls (1.9%) and in the female controls (1.9%), but the difference was not statistically significant ($P = .18$).

Asians constituted a smaller proportion of the case group than of the control group (2.5% and 8.2%, respectively; $P < .001$); this difference reflects the relatively low prevalence of prostate cancer among Asians in Ontario. To control for possible confounding due to ethnic group, the data were analyzed in terms of ethnic subgroup (table 3). Among whites, the Ser217Leu variant was present in 52.0% of the cases and in 52.4% of the controls. Ser217 homozygotes constituted 10.3% of the cases and 9.9% of the controls. There were no significant associations among the subgroups of black and Asian men. The Ala541Thr variant was not observed in black or Asian men (table 3); therefore, it was only possible to evaluate the association in the white subgroup of cases and controls. Among whites, the Ala541Thr variant was present in 7.1% of cases and in 7.2% of controls ($P = .90$).

It has been reported elsewhere that the association between prostate cancer and the Ala541Thr variant is modified by age at diagnosis (Tavtigian et al. 2001). In the present study, no effect was seen in any subgroup defined by year of birth (table 4).

There was no significant association between the presence of the HPC2 Ala541Thr variant and the results of the DRE. Among cases, 5.8% of men with a normal DRE carried the variant, compared with 6.8% of men with an abnormal DRE ($P = .67$); among controls, 7.9% of men with a normal DRE carried the variant,

Table 2

Genotypes of HPC2 Polymorphisms in Cases and Controls

Polymorphism	No. (Proportion of Total Sample) in		
		Controls	
	Cases	Male Controls	Female Controls
Ser217Leu:			
Ser/Ser	220 (51.0%)	259 (50.5%)	522 (52.6%)
Ser/Leu	169 (39.2%)	213 (41.5%)	374 (37.7%)
Leu/Leu	42 (9.8%)	41 (8.0%)	96 (9.7%)
Ala541Thr:			
Ala/Ala	404 (93.8%)	478 (93.2%)	930 (93.8%)
Ala/Thr	26 (6.0%)	34 (6.6%)	61 (6.1%)
Thr/Thr	1 (.2%)	1 (.2%)	1 (.1%)

Table 3

Prevalence of HPC2 Variant Alleles, by Ethnic Group in Cases and Controls

Polymorphism and Ethnic Group	No. (Proportion of Total Sample) in			
		Controls		
	Cases	Males	Females	Combined
Ser217Leu:				
White	197 (52.0%)	227 (54.7%)	380 (51.1%)	607 (52.4%)
Black	11 (29.7%)	18 (36.7%)	32 (38.6%)	50 (37.9%)
Asian	2 (20.0%)	5 (11.9%)	11 (13.1%)	16 (12.1%)
Other	1 (20.0%)	4 (57.1%)	47 (57.3%)	51 (57.3%)
Ala541Thr:				
White	27 (7.1%)	34 (8.2%)	49 (6.6%)	83 (7.2%)
Black	0	0	0	0
Asian	0	0	4 (4.8%)	4 (3.2%)
Other	0	1 (14.3%)	9 (11.0%)	10 (11.2%)

compared with 4.3% of men with an abnormal DRE ($P = .16$).

Because the male subjects were selected for a serum-PSA level >4.0 ng/ml, the prevalence of benign and preneoplastic prostate disease in this population was high. However, the frequency of the Ala541Thr variant was similar for all subgroups with pathologies (table 5). There was a nonsignificant association between the presence of the Ala541Thr variant allele and tumor grade. The variant was present in 9.8% of 122 men with low-grade tumors (Gleason grades 2–6), in 5.0% of 221 men with intermediate-grade tumors (Gleason 7), and in 4.9% of 82 men with high-grade tumors (Gleason 8–10) ($P = .18$).

The HPC2 gene was initially identified through the study of familial cases of prostate cancer (Tavtigian et al. 2001). In the present study, there was a modest association between the presence of the Ala541Thr variant and a family history of prostate cancer. Among cases, the variant was present in 2 (3.5%) of 57 familial cases and in 20 (7.0%) of 286 non-familial cases ($P = .33$); among controls, the variant was present in 8 (13.6%) of 59 men with a family history of prostate cancer, compared with 20 (5.3%) of 375 men without a family history ($P = .04$).

A borderline-significant association was present between the mean serum-PSA level at diagnosis and the HPC2 genotype. Among cases, the (geometric) mean serum-PSA level was 8.3 ng/ml for carriers of one or two Ala541Thr alleles and was 10.7 ng/ml for noncarriers (*t*-test on log-transformed serum-PSA level; $P = .07$). The frequency of the Ala541Thr allele was 7.7% among cases with a serum-PSA level of 4.0–9.9 ng/ml, 4.8% among cases with a serum-PSA level of 10.0–19.9 ng/ml, and 3.5% among cases with a serum-PSA level of ≥20.0 ng/ml ($P = .36$). Among controls, the mean serum-PSA level was 10.1 ng/ml for carriers of the Ala541Thr allele and was 10.0 ng/ml for noncarriers ($P = .54$).

Discussion

Our data do not support the hypothesis that common missense variants of the HPC2 gene predict prostate cancer risk among men with an elevated serum-PSA level. We observed the same frequencies of the Ser217Leu variant and of the Ala541Thr variant in 431 men with screen-detected cancer and in 513 men with negative prostate biopsies. Furthermore, the frequency (6.6%) of the Ala541Thr variant in our population of 944 men who were referred for prostate biopsy because of a high serum-PSA level was not substantially different from the frequency (6.3%) in a group of 992 control women unaffected with cancer.

There are several possible reasons why we did not see an association between the Ala541Thr variant and the risk of screen-detected prostate cancer. Our CI for the odds ratio was relatively wide (odds ratio .97; 95% CI 0.58–1.63), and our data are consistent with the pos-

Table 4

Prevalence of HPC2 Variant Alleles, by Year of Birth (Cases Only)

Polymorphism and Year of Birth	No. (Proportion of Total Sample)
Ser217Leu:	
1900–1920 ($n = 26$)	14 (53.9%)
1920–1930 ($n = 127$)	58 (45.7%)
1930–1940 ($n = 174$)	86 (49.4%)
1940– ($n = 104$)	53 (51.0%)
Ala541Thr:	
1900–1920 ($n = 26$)	2 (7.8%)
1920–1930 ($n = 127$)	8 (6.3%)
1930–1940 ($n = 174$)	10 (5.8%)
1940– ($n = 104$)	7 (6.7%)

Table 5

Prevalence of HPC2 Variant Alleles, by Prostate Pathology

Polymorphism and Prostate Pathology	No. (Proportion of Total Sample)
Ser217Leu:	
Cancer (n = 431)	211 (49.0%)
Hyperplasia or inflammation (n = 356)	180 (50.6%)
PIN (n = 124)	60 (48.4%)
Normal (n = 33)	14 (42.4%)
Ala541Thr:	
Cancer (n = 431)	27 (6.3%)
Hyperplasia or inflammation (n = 356)	24 (6.7%)
PIN (n = 124)	9 (7.3%)
Normal (n = 33)	2 (6.1%)

sibility that a modest relative risk is associated with the missense allele. There were important differences in the selection of cases for the present study and for the two studies by other researchers (discussed below), but it appears that the principal reason for the different results is variation in the control frequencies. We observed the Ala541Thr variant in 6.3% of cases and in 6.4% of controls, compared with 9.8% of cases and 3.4% of controls in the study by Tavtigian et al. (2001) and 7.5% of cases and 3.5% of controls in the study by Rebbeck et al. (2000). The size of the control group (1,505 individuals) in the present study was much larger than the total (406 individuals) in the two previous studies combined. The extent to which ethnic variation between the study populations accounts for the differences in the allele frequencies reported is not clear. Future studies will help to establish whether the frequency of the variant genotypes in the previous two studies has been underestimated.

It is possible that differences in the ethnic makeup of the cases and controls will lead to a spurious effect in an association study. We did not observe the Ala541Thr variant in the nonwhite cases or in nonwhite male controls. However, when the analysis was restricted to white subjects, no association was present (odds ratio 1.1; 95% CI 0.48–2.5; P = .84).

A second limitation of our study is that a single prostate biopsy was performed. Among patients with elevated serum-PSA levels, false-negative biopsies are common (Fleshner et al. 1997). On rebiopsy, up to 30% of these patients are found to have cancer, and, therefore, we may have considerable misclassification in our study. However, because we found no significant difference, in the frequencies of the two candidate alleles, between the men with screen-detected cancer and healthy female controls, misclassification cannot account entirely for our negative findings.

Rebbeck et al. (2000) studied incident cases of prostate cancer, including men who presented with clinical disease. Our study population was restricted to incident cases of screen-detected prostate cancer, and all of our (male) controls had elevated serum-PSA levels. It is possible that genetic predisposing factors for the two clinical subgroups are different. It is also possible that the Ala541Thr variant may be associated with a serum PSA–level increase that is independent of the presence of prostate cancer—and that this increase in the serum-PSA level may prompt a diagnostic evaluation. In asymptomatic men, an increasing proportion of prostate cancer cases are diagnosed as a result of the PSA-screening test, and the prevalence of prostate cancer among screened men in the general population is ~4% (Narod et al. 1995). Therefore, any gene that leads to an increase in serum-PSA level may appear to be a prostate cancer–susceptibility gene if nonscreened controls are used in an association study. Because mean PSA values increase with age, this may also explain the observation, in the study by Tavtigian et al. (2001), that the frequency of the Ala541Thr allele increases with age. However, we observed a modestly lower mean serum-PSA level among cases with the Ala541Thr variant, compared with the level among cases without this allele. No difference was seen in the control group. Furthermore, no overall excess of the Ala541Thr genotype was seen in the male control group (selected for elevated PSA) compared with the female control group. We saw a marginally significant association between the presence of the Ala54Thr variant and a family history of prostate cancer in the controls, but this was not seen among the cases. In conclusion, our data do not support the hypothesis that variant missense alleles of the HPC2 gene influence prostate cancer susceptibility.

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Electronic-Database Information

Accession numbers and the URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for HPC2 [MIM 605367], prostate cancer [MIM 176806], and CYP3A4 [MIM 124010])

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