Identifying Susceptibility Genes for Prostate Cancer—A Family-Based Association Study of Polymorphisms in CYP17, CYP19, CYP11A1, and LH-β


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Abstract

Polymorphisms in genes that code for enzymes or hormones involved in the synthesis and metabolism of androgens are compelling biological candidates for prostate cancer. Four such genes, CYP17, CYP19, CYP11A1, and LH-β, are involved in the synthesis and conversion of testosterone to dihydrotestosterone and estradiol. In a study of 715 men with and without prostate cancer from 266 familial and early-onset prostate cancer families, we examined the association between prostate cancer susceptibility and common single-nucleotide polymorphisms in each of these four candidate genes. Family-based association tests revealed a significant association between prostate cancer and a common single-nucleotide polymorphism in CYP17 (P = 0.004), with preferential transmission of the minor allele to unaffected men. Conditional logistic regression analysis of 461 discordant sibling pairs from these same families reaffirmed the association between the presence of the minor allele in CYP17 and prostate cancer risk (odds ratio, 0.51; 95% confidence interval, 0.28-0.92). These findings suggest that variation in or around CYP17 predicts susceptibility to prostate cancer. Family-based association tests may be especially valuable in studies of genetic variation and prostate cancer risk because this approach minimizes confounding due to population substructure, which is of particular concern for prostate cancer given the tremendous variation in the worldwide incidence of this disease. (Cancer Epidemiol Biomarkers Prev 2005;14(8):2035–9)

Introduction

Prostate cancer is now the most commonly diagnosed malignancy among men in the United States, with over 232,090 new cases and 30,350 deaths expected in 2005 according to the American Cancer Society. Besides age and race, a positive family history is recognized as one of the strongest epidemiologic risk factors for prostate cancer (1). The latter observation has motivated the search for prostate cancer susceptibility genes by many research groups around the world for the past decade. Indeed, a large number of genome-wide linkage scans have been applied in studies of several different populations to locate susceptibility genes for prostate cancer. To date, a number of candidate genes for prostate cancer susceptibility have been studied, including ELAC2/HPC2 (10), RNASEL (11), MSR1 (12), and BRCA2 (13). Germ line mutations in these genes, however, seem to account for only a small proportion of the observed genetic predisposition to prostate cancer.

In an effort to identify other unknown prostate cancer susceptibility genes, we and others are searching for candidate genes and pathways to evaluate for association with the disease. Epidemiologic and pathologic evidence indicates that androgens play a fundamental role in the pathogenesis of prostate cancer, and thus genes coding for enzymes or hormones that are involved in the synthesis and metabolism of testosterone and other androgens are compelling biological candidates for prostate cancer (14, 15). The goal of the current study was to investigate the association between prostate cancer and common single-nucleotide polymorphisms (SNPs) in the LH-β (19q13.32), CYP11A1 (15q23-24), CYP17 (10q24.3), and CYP19 (15q21.1) genes. All four genes are involved in the synthesis and conversion of testosterone to dihydrotestosterone and estradiol (see Fig. 1). LH-β mediates the activity of CYP11A1, which converts cholesterol to pregnenolone as the first step in the biosynthesis of testosterone (16). CYP17 functions in the biosynthesis of testosterone through the regulation of both 17-hydroxylase and 17,20-lyase (17), whereas CYP19 is an aromatase enzyme that catalyzes the conversion of androgens to estrogens (18). Some studies have found an association between prostate cancer and a promoter variant in CYP17 (19-26). CYP19 and CYP11A1 have been less well studied, although a tetranucleotide repeat polymorphism in intron 4 of CYP19 has been associated with prostate cancer in at least two studies (27, 28) and a microsatellite upstream of CYP11A1 has been associated with clinically advanced prostate cancer (29). In the only study to date that assessed germ line variation in LH-β with regard to prostate cancer risk, a weak positive association between a variant LH-β genotype and prostate cancer risk was reported (30).

We present results from family-based association analyses of 266 prostate cancer families from the University of Michigan Prostate Cancer Genetics Project. Specifically, we illustrate our family-based approach, which studies men with early onset and/or hereditary prostate cancer and their unaffected brothers, to assess the potential contribution of polymorphisms...
in the aforementioned genes to prostate cancer susceptibility. Using unaffected brothers is a natural extension of our existing family- and clinic-based patient resource and provides information that is complementary to our ongoing linkage analyses, including the ability to jointly test for linkage and association. In addition, and in contrast to most association studies of prostate cancer, our family-based design uses “controls” ascertained from the same genetic source population as the “cases,” thereby excluding the possibility of confounding due to population substructure. By utilizing unaffected brothers of affected men, we also exploit the inherent matching on potentially nongenetic but shared risk factors for prostate cancer.

Materials and Methods

Study Subjects. The Prostate Cancer Genetics Project is a large family-based study designed to map and clone genes predisposing to inherited forms of prostate cancer. Enrollment into the Prostate Cancer Genetics Project is restricted to (a) families with two or more living members with prostate cancer in a first- or second-degree relationship or (b) men diagnosed with prostate cancer at ≤55 years of age without a known family history of the disease. All participants are asked to provide a blood sample, extended family history information, and access to medical records. For the present investigation, we identified 266 families in which we had DNA from at least one pair of brothers discordant for prostate cancer. These discordant sibling pairs (DSPs) were selected from a single generation to mitigate potential cohort effects. We also preferentially enrolled the oldest available unaffected brother from each family to maximize the probability that unaffected men were truly unaffected and not simply unaffected by virtue of being younger than their affected brother(s). Additional male siblings as well as multiple sibships from the same family were included if DNA was available. The majority of the Prostate Cancer Genetics Project families were recruited directly from the University of Michigan Comprehensive Cancer Center; other sources included direct patient or physician referrals. Diagnosis of prostate cancer was confirmed by review of pathology reports or medical records, and age at diagnosis was calculated from the date of the first biopsy positive for prostate cancer. Cases were classified as clinically aggressive if they met at least one of the following criteria: (a) pathologic Gleason sum > 7; (b) pathologic stage T3b (pT3b) tumor (indicating seminal involvement) or pT4 or N1 (positive regional lymph nodes); (c) pathologic Gleason sum of 7 and a positive margin; or (d) preoperative serum prostate-specific antigen value > 15 ng/mL, or a biopsy Gleason score > 7, or a serum prostate-specific antigen level > 10 ng/mL and a biopsy Gleason score > 6. Based on data from D’Amico et al. (31), these criteria were developed by the Southwest Oncology Group (protocol 9921) to identify men at intermediate to high risk of clinical recurrence after primary therapy. Disease status of the unaffected brothers was confirmed through serum prostate-specific antigen testing whenever possible. The majority of the families were non-Hispanic white, although 12 African American and 2 Asian families were also included. The Institutional Review Board at the University of Michigan Medical School approved all aspects of the protocol, and all participants gave written informed consent, including permission to release their medical records.

Genotyping Assays. Genomic DNA was isolated from whole blood using the Puregene kit (Gentra Systems Inc., Minneapolis, MN). Four common SNPs were selected and genotyped from the Assays on Demand SNP catalogue (Applied Biosystems, Foster City, CA): pos −15,891 C>A from the transcription start site of the CYP17 gene (rs619824), pos −67,703 T>G from the transcription start site (intron 1) of CYP19 gene (rs11636639), pos −37,511 C>A from the transcription start site of the CYP11A gene (rs2277602), and pos −1,864 C>T from the transcription start site of the LHβ gene (rs753307; Table 1). Assay details are available from the authors on request. Briefly, Assays on Demand consist of a 20× mix of PCR primers and dye-labeled TaqMan MGB probes that are designed to interrogate a specific SNP within a given sequence. PCR reactions were conducted in a 384-well plate format with 2.25 μL genomic DNA (5 ng/μL), 0.25 μL 20× SNP Genotyping Assay Mix, 1 μL 5× Real-Time Ready Mastermix (Qbiogene, Montreal, Canada), and 1.5 μL dH2O for a 5 μL total volume reaction. All assays were optimized to use a universal thermal cycling protocol with an initial hold at 95°C for 10 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds, and a combined annealing extension step at 60°C.

Table 1. Allele frequencies by clinical subgroup for SNPs in candidate genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>SNP</th>
<th>Position*</th>
<th>Major&gt;minor allele</th>
<th>Minor allele frequency in</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Affected men</td>
<td>Unaffected men</td>
</tr>
<tr>
<td>CYP17</td>
<td>10q24</td>
<td>rs619824</td>
<td>−15,891</td>
<td>C&gt;A</td>
<td>0.41</td>
<td>0.46</td>
</tr>
<tr>
<td>CYP19</td>
<td>15q21</td>
<td>rs11636639</td>
<td>−67,703</td>
<td>T&gt;G</td>
<td>0.42</td>
<td>0.43</td>
</tr>
<tr>
<td>CYP11A</td>
<td>15q25</td>
<td>rs2277602</td>
<td>−37,511</td>
<td>C&gt;A</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>LHβ</td>
<td>19q13</td>
<td>rs753307</td>
<td>−1,864</td>
<td>C&gt;T</td>
<td>0.47</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Base pair position from the transcription start site of each gene according to the human reference sequence (UCSC Genome Browser, Build 35; May 2004).
*Calculated by treating all men as unrelated subjects (i.e., unadjusted for the within-family correlation).

Cancer Epidemiol Biomarkers Prev 2005;14(8). August 2005
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for 1 minute. Allelic discrimination was carried out using the ABI PRISM 7900HT Sequence Detection System and the SDS version 2.1 software (Applied Biosystems). Approximately 5% of the samples were duplicated and verified on this platform. Genotypes were also verified by direct sequencing of 2% of the samples for each of the SNPs in CYP17, CYP11A1, and LH-β and by RFLP analysis of 16% of the samples for the SNP in CYP19 with an estimated genotyping error rate of 0.6%.

**Statistical Methods.** We used the family-based association test package (version 1.51) to test for association between genotypes and prostate cancer. Family-based association tests are a class of generalized score statistics that use within- and between-family marker-inheritance patterns to test for association (32, 33) and, as such, eliminate any potential bias arising from population stratification. To maximize power, we analyzed the combined sample of affected and unaffected men using the offset option, which optimally weights the contribution of affected and unaffected subjects by minimizing the variance of the family-based association test statistic under the null hypothesis of no association and no linkage. In principle, the offset should be equal to the population prevalence, although this is an inappropriate choice for our highly selected sample. We also carried out “affecteds-only” analyses to allow for the possibility of misclassification of unaffected men (e.g., via reduced penetrance) and the resulting reduction in power. In the absence of knowledge of definitive linkage of prostate cancer to each of the gene regions, we carried out the affecteds-only analyses with the empirical variance function in family-based association test, which is a valid test of the null hypothesis of no association in the presence of linkage. We note, however, that the results did not materially differ from those produced without employing the empirical variance function. In parallel, we used conditional logistic regression with family as the stratification variable and a robust variance estimate that incorporates familial correlations. Before conducting the conditional logistic regression analyses, we carried out assuming additive, dominant, recessive, and general (2 degrees of freedom) genetic models. Stratified analyses were also done to explore the relationship between genotypes and prostate cancer, stratifying on clinically advanced prostate cancer, age at diagnosis (<50 years), or number of confirmed cases of prostate cancer within a family (≥4). All statistical tests were two sided and *P < 0.05 was considered statistically significant. The observed genotype distributions were tested for departures from Hardy-Weinberg equilibrium in a subset of unaffected, unrelated men (i.e., by selecting the oldest unaffected man from each family). All data analyses (except the family-based association tests) were conducted using version 8.2 of the SAS programming language (SAS Institute, Cary, NC).

**Results**

**Characteristics of Families and Men.** For this investigation, we identified 266 families with at least one DSP, resulting in a total of 474 DSPs (Table 2). Of the 266 families, 256 included only the index case and one or more of his brothers. The remaining 10 families included additional DSPs unrelated to the index case as a brother (e.g., a pair of DSPs related as first cousins). Of the 266 families, 18%, 32%, 26%, and 24% included one, two, three, and four or more confirmed affected men, respectively. In total, 715 men were included in the analyses (376 cases and 339 controls). The clinical characteristics of the men with prostate cancer are shown in Table 3. The median age at diagnosis was 55 years (interquartile range of 50-64 years). The median age of the unaffected men at the time of consent was also 55 years (interquartile range of 50-63 years). Nearly 70% of unaffected men reported their most recent prostate-specific antigen testing results and >90% of them reported a prostate-specific antigen level <4.0 mg/dL or normal. Per our design, unaffected men were significantly older than their affected brothers (*P < 0.0005 for paired t test of within-family means), with a median age difference of 2 years (interquartile range of ~3 to 5 years). In addition, at the time of consent, unaffected men were significantly older than their affected brothers were at their time of diagnosis (*P < 0.0001 for paired t test of within-family means), with a median age difference of 2 years (interquartile range of ~2.5 to 6.7 years). Within all families, the median difference between the maximum age at diagnosis of affected men and the minimum age at consent of unaffected men was 0 years (interquartile range of ~6 to 4; *P = 0.630 for paired t test).

**Family-Based Association Tests and Conditional Logistic Regression.** Minor allele frequencies for the SNPs in CYP17, CYP19, CYP11A1, and LH-β are given in Table 1. There were no significant differences in the distribution of alleles (Table 1) or genotypes (data not shown) between affected and unaffected men when ignoring family structure and treating all men as unrelated subjects, although the minor allele of CYP17 was overrepresented among unaffected men (46% versus 41% in affected men; *P = 0.068). The observed genotype data were consistent with Hardy-Weinberg equilibrium in a subset of unrelated, unaffected men. Table 4 summarizes results for all four genes using both conditional logistic regression and family-based association tests, both of which incorporate familial correlations. Before conducting the conditional logistic regression analysis, we excluded from 10 families the 23 men who were not brothers of the index case; the resulting data set consisted of 692 men and 461 DSPs. Under a dominant model for disease (i.e., presence of one or both copies of the minor allele versus no copies of the minor allele, where the latter is the referent group), we estimated an odds ratio of 0.51 (95% confidence interval, 0.28-0.92; *P = 0.027) for the SNP in CYP17. We found no evidence of an association between the presence of the minor allele in CYP19, CYP11A1, or LH-β and prostate cancer (data not shown). In addition, we found no evidence of a gene-dosage effect for any of the SNPs.

Table 2. Sibship pairs discordant for prostate cancer

<table>
<thead>
<tr>
<th>Sibship structure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>a</em></td>
<td>171</td>
</tr>
<tr>
<td><em>b</em></td>
<td>45</td>
</tr>
<tr>
<td><em>c</em></td>
<td>13</td>
</tr>
<tr>
<td><em>d</em></td>
<td>8</td>
</tr>
<tr>
<td><em>e</em></td>
<td>22</td>
</tr>
<tr>
<td><em>f</em></td>
<td>6</td>
</tr>
<tr>
<td><em>g</em></td>
<td>1</td>
</tr>
<tr>
<td><em>h</em></td>
<td>10</td>
</tr>
<tr>
<td>total</td>
<td>474</td>
</tr>
</tbody>
</table>

*Note:* 266 independent families were ascertained with at least one discordant sibling pair. 

*As: affected; ○, unaffected. 

*Total number of discordant sibling pairs.*
In summary, we found a common polymorphism in the CYP17 gene region associated with reduced prostate cancer risk among men and families with a history of the disease. We estimate that men carrying at least one copy of the CYP17 minor allele are ~2 times less likely to develop prostate cancer. Although linkage to the CYP17 gene region, which is located at 10q24.3, has not been previously reported in hereditary prostate cancer families (35), a number of studies have shown an association between a CYP17 promoter variant and prostate cancer risk (19-26).

To explore the potential functional significance of the associated SNP in CYP17 (rs619824), we used the bioinformatic TFSEARCH program (http://www.rwcp.or.jp/papia/) to identify transcription factors that could potentially bind to this site. TFSEARCH uses the TRANSFAC (36) catalogue of eukaryotic cis-acting regulatory DNA elements and trans-acting factors. SNP rs619824 is located at base pair position 104,571,278 on chromosome 10, ~16 kb downstream from the transcription start site of CYP17, and falls within a region showing sequence homology to a CCAAT/enhancer-binding protein, which is known to be a strong regulator of transcription. Thus, it is possible that the associated SNP in CYP17 may have direct functional relevance to prostate cancer risk.

Because we tested only one SNP in CYP17, we cannot exclude the role of other polymorphisms in this gene or in other functionally relevant sequences in linkage disequilibrium with this SNP. Little is known about the pattern of linkage disequilibrium in and around the CYP17 gene, although a recent study reported reduced haplotype diversity in the CYP17 gene region (37). Results from the latter study suggest the possibility of rs619824 being in linkage disequilibrium with a susceptibility locus, but more remains to be explored with regard to the structure of linkage disequilibrium surrounding CYP17 to place our result in the context of other findings of association between variation in CYP17 and prostate cancer.

Interestingly, we also found evidence of linkage and association between prostate cancer risk and a SNP in the CYP19 gene, but only in the subset of families in which men were diagnosed at an early age (<50 years). Although tentative, this finding suggests that particular subsets of families contribute disproportionately to our results. Indeed, even after removing over half of informative or contributing families, family-based association test results remained or became significant. These findings imply the presence of genetic heterogeneity and reinforce the notion that analysis approaches which acknowledge the etiologic and genetic heterogeneity of prostate cancer are likely to have greater power to identify more modest but restricted genetic effects. In general, the families included in our study are likely to be enriched for a heritable form of prostate cancer, given our selective recruitment of men with early-onset prostate cancer and/or a family history of the disease. Further restricting our analyses to more heritable forms of prostate cancer (i.e., by including families with a strong history of the disease) may have further increased our power to detect inherited risk.

Our work to date shows the feasibility of collecting a large number of DSP families and illustrates the power of jointly analyzing linkage and association (or association in the presence of linkage) with a family-based study design. In addition, both of our statistical approaches, conditional logistic regression and family-based association test, permit the combined analysis of subjects from different racial backgrounds without introducing complications related to population substructure. One of the disadvantages of our study design, however, is the possible misclassification of men with prostate cancer as unaffected subjects, which we tried to minimize by our age selection strategy. It is also possible that men with undetected prostate cancer were misclassified as unaffected because they had not undergone prostate cancer screening. Still, nearly 70% of unaffected men in the current study reported recent screening results and over 90% of them reported prostate-specific antigen values within the reference range (<4 mg/dL). Further, an independent set of Prostate Cancer Genetics Project families suggests that over 95% of unaffected men with undetected prostate cancer were misclassified as prostate cancer (38). In any case, the nondifferential misclassification of unaffected men (with respect to genotype) is only expected to bias our results toward the null hypothesis of no

### Table 3. Characteristics of men with prostate cancer (n = 376)

<table>
<thead>
<tr>
<th>Trait</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55 [50-64]</td>
</tr>
<tr>
<td>Pre-diagnosis prostate-specific antigen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.0 [4.3-10.3]</td>
</tr>
<tr>
<td><strong>Surgery</strong> (% yes)</td>
<td>286 (76.7)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>316 (89.0)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>22 (6.2)</td>
</tr>
<tr>
<td>Metastasized</td>
<td>17 (4.8)</td>
</tr>
<tr>
<td><strong>Gleason</strong></td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>179 (49.9)</td>
</tr>
<tr>
<td>≥7</td>
<td>144 (40.1)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>36 (10.0)</td>
</tr>
<tr>
<td><strong>Clinically aggressive prostate cancer (%)</strong></td>
<td>112 (30.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Note that column subtotals do not sum to 376 due to missing data.

### Table 4. Results from conditional logistic regression and family-based association tests

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>DSPs</th>
<th>Odds ratio (95% confidence interval)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P</th>
<th>No. families&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Z score</th>
<th>P</th>
<th>No. families&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Z score</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17</td>
<td>CC vs AC or AA</td>
<td>0.51 (0.28-0.92)</td>
<td>0.022</td>
<td>77</td>
<td>−2.49</td>
<td>0.013</td>
<td>78</td>
<td>−2.92</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>CYP19</td>
<td>TT vs TG or GG</td>
<td>0.95 (0.62-1.44)</td>
<td>0.793</td>
<td>86</td>
<td>0.079</td>
<td>0.937</td>
<td>87</td>
<td>−0.36</td>
<td>0.717</td>
<td></td>
</tr>
<tr>
<td>CYP11A</td>
<td>CC vs CA or AA</td>
<td>0.95 (0.59-1.52)</td>
<td>0.831</td>
<td>76</td>
<td>−0.59</td>
<td>0.553</td>
<td>77</td>
<td>−0.35</td>
<td>0.726</td>
<td></td>
</tr>
<tr>
<td>LHB</td>
<td>CC vs CT or TT</td>
<td>1.09 (0.70-1.69)</td>
<td>0.708</td>
<td>79</td>
<td>0.15</td>
<td>0.879</td>
<td>79</td>
<td>0.26</td>
<td>0.798</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>First genotype is the referent.
<sup>b</sup>Number of informative families.

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association or linkage. In other words, the inclusion of unaffected men should not lead to a spurious result.

In testing for the association between prostate cancer and SNPs in CYP17, CYP19, CYP11A1, and LH-β, it is difficult to address whether we found more significant associations than would be expected by chance given the number of correlated tests that we did. A thorough assessment of the multiple testing issue would require considerable computational investigation, and seems unjustified given the small number of SNPs tested and the previous evidence in the literature for an association between variation in CYP17 and prostate cancer. However, because of our (a) concern about multiple testing, (b) initial consideration of only a single SNP in each gene, and (c) modestly powered sample, we deliberately chose to evaluate only marginal (not interaction) effects for each of the SNPs in CYP17, CYP19, CYP11A1, and LH-β, although these genes share a common pathway. Analysis of all pairwise or higher-order SNP combinations would only exacerbate the issue of multiple testing in our relatively modest sample of 266 families. More importantly, appropriate analysis of gene-by-gene interactions would require the development of statistical transmission models that can take into account multiple susceptibility genes and models of gene action in a family-based study design.

In summary, using a family-based study design, we found a SNP in the CYP17 gene region that seems to be associated with an ~2-fold increased risk of prostate cancer. Because we only tested this particular variant, we cannot exclude the role of other CYP17 variants or variants in nearby genes, possibly in linkage disequilibrium with the associated SNP. Further studies, including functional analyses, will be required to fully understand the role of this gene and related pathways in prostate cancer. Because the incidence of prostate cancer varies widely by race and country of origin, unrecognized, genetic differences between cases and controls may well contribute to spurious results in association studies. By design, family-based association studies, however, exclude the possibility of confounding due to population substructure, but in exchange, require larger sample sizes to detect associations (owing to the inherent genetic overmatching of cases and controls). Despite the latter, we were able to detect a statistically significant association between prostate cancer and a CYP17 variant in only 474 DSPs from 266 families. We cannot, however, exclude an association between prostate cancer and our tested SNPs or other unmeasured variants in CYP19, CYP11A1, and LH-β without further follow-up work, including the accrual of additional families and the examination of additional variants and patterns of linkage disequilibrium within these candidate gene regions.

Acknowledgments

We thank all of the Prostate Cancer Genetics Project men and their families who generously volunteered their time to participate in our study.

References

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