Analysis of Chromosome 1q42.2-43 in 152 Families with High Risk of Prostate Cancer

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Summary

One hundred fifty-two families with prostate cancer were analyzed for linkage to markers spanning a 20-cM region of 1q42.2-43, the location of a putative prostate cancer–susceptibility locus (*PCAP*). No significant evidence for linkage was found, by use of both parametric and nonparametric tests, in our total data set, which included 522 genotyped affected men. Rejection of linkage may reflect locus heterogeneity or the confounding effects of sporadic disease in older-onset cases; therefore, pedigrees were stratified into homogeneous subsets based on mean age at diagnosis of prostate cancer and number of affected men. Analyses of these subsets also detected no significant evidence for linkage, although LOD scores were positive at higher recombination fractions, which is consistent with the presence of a small proportion of families with linkage. The most suggestive evidence of linkage was in families with at least five affected men (nonparametric linkage score of 1.2; $P = .1$). If heterogeneity is assumed, an estimated 4%–9% of these 152 families may show linkage in this region. We conclude that the putative *PCAP* locus does not account for a large proportion of these families with prostate cancer, although the linkage of a small subset is compatible with these data.

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Introduction

A variety of studies—including case-control, family, and twin studies (Ross et al. 1987; Steinberg et al. 1990; Grönberg et al. 1994; Whittemore et al. 1995)—and segregation analyses have suggested strong evidence for an inherited component to prostate cancer susceptibility. Whereas data from one population-based cohort study are most consistent with an X-linked or recessive model of inheritance of susceptibility genes (Monroe et al. 1995), three independent segregation analyses (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998) supported an autosomal dominant model of prostate cancer inheritance. Dominant alleles are estimated to have a low population frequency (0.3%–1.67%) and to account for ~9% of all cases of prostate cancer by 85.0 years of age and for as much as 43% of cases of disease among men affected at <55.0 years of age (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998). Importantly, there is strong evidence from these studies that such genes are likely to have high lifetime penetrances of 63%–89%.

Analyses of candidate genes that may be involved in prostate cancer initiation or progression have included genes involved in the normal regulation of prostatic cells, such as the androgen-receptor gene, and other known tumor-suppressor genes, including *P53, PTEN,* and *BRCA1*. There is evidence that polymorphisms within the coding regions of some genes, including the vitamin D and androgen-receptor genes, may modify risk (Irvine et al. 1995; Taylor et al. 1996; Giovannucci et al. 1997; Ingles et al. 1997; Stanford et al. 1997), and loss-of-heterozygosity and mutation-detection studies have suggested a role for known tumor suppressors in the progression of sporadic tumors (Cairns et al. 1997; Feilotter et al. 1998). To date, however, no obvious candidate gene has emerged as a major component of inherited risk, suggesting that other, unidentified loci determine prostate cancer susceptibility.

One strategy for the identification of susceptibility loci of unknown function uses genomewide screens of high-

risk families, with polymorphic markers analyzed by LOD linkage methods. However, the etiology of prostate cancer is such that the disease does not readily lend itself to these types of analyses, for two reasons. First, prostate cancer is a late onset, often undiagnosed disease; <5% of diagnoses are in men <55.0 years of age (Stanford et al., in press). This reduces the availability of genotypic information from multiple generations of affected men and necessitates analysis of large numbers of families, to achieve sufficient power to detect linkage. Second, prostate cancer is a very common disease (~184,500 new diagnoses in the United States in 1997 [Landis et al. 1998]) with complex inheritance and is expected to exhibit both locus heterogeneity and sporadic disease. In the absence of refined clinical or epidemiological criteria to stratify cases on the basis of different kinds of prostate tumors or, alternatively, the identification of subsets of families that likely share a single founder effect, the etiologic heterogeneity may confound linkage analysis and may cause the identification of any single locus to be problematic. To date, no prostate cancer–susceptibility gene has been isolated by positional cloning. Nevertheless, some promising regions have been identified by means of genomewide screens, suggesting that the approach is valid.

The first prostate cancer–susceptibility locus localized by linkage analysis was *HPC1* on chromosome 1q24-25 (Smith et al. 1996). Heterogeneity analysis suggested that this locus accounted for disease segregation in 34% of families with high risk of prostate cancer, in the original data set of 91 North American and Swedish families. Further analysis of an expanded data set suggested that the majority of families with linkage were those with an early age at diagnosis, with the proportion of families with linkage rising to 66% among 14 families with a mean age at diagnosis of <60.0 years (Grönberg et al. 1997*b*).

Efforts to confirm this result in other data sets have produced mixed results, with some studies supporting linkage (Cooney et al. 1997; Hsieh et al. 1997) and others finding no evidence for linkage (McIndoe et al. 1997; Berthon et al. 1998; Eeles et al. 1998; authors' unpublished data). In aggregate, these results suggest that issues related to locus heterogeneity and *HPC1* are not well understood. Multiple analyses have estimated that the proportion of families with linkage to *HPC1* is <10%, rather than the original estimate of 34%, supporting the hypothesis that multiple susceptibility loci affect prostate cancer risk (McIndoe et al. 1997; Berthon et al. 1998; Eeles et al. 1998; authors' unpublished data).

The second reported prostate cancer–susceptibility gene, *PCAP,* was localized to 1q42.2-43, by Berthon et al. (1998). An analysis of 47 families of French and German origin, with a mean of 3.3 affected men per family, suggested linkage to this region, with a maximum two-point LOD score of 2.7 with marker *D1S2785* and a nonparametric linkage (NPL) score of 3.1 ($P = .001$). Heterogeneity analysis suggested that the proportion of families with linkage to the locus was as much as 50%. A stratified analysis of nine families with age at diagnosis <60.0 years in the final generation gave significant multipoint LOD and NPL scores of 3.3 ($P = .001$; Berthon et al. 1998).

Confirmation and calculation of the overall contribution of this second locus to hereditary prostate cancer will be determined by analysis of additional data sets. We report here the analysis of 152 families with high risk of prostate cancer, including 522 genotyped men with prostate cancer, for linkage to this region.

Methods

Family Ascertainment and Confirmation of Diagnosis

Families with high risk of prostate cancer were recruited nationally as part of the ongoing Prostate Cancer Genetic Research Study (PROGRESS) initiated in 1995. All families met at least one of three criteria: three or more first-degree affected relatives, prostate cancer in three generations, or two affected siblings with prostate cancer diagnosed at ≤60.0 years of age. Blood samples and medical and demographic information, including family history of cancer, were provided by affected men and selected unaffected male and female family members. In addition, consent to access medical records related to the diagnosis and treatment of cancer was requested. All study procedures and forms were approved by the institutional review board of the Fred Hutchinson Cancer Research Center. Detailed procedures for the contacting of families, the selection of individuals for collection, and the isolation of DNA have been summarized elsewhere (McIndoe et al. 1997).

Diagnoses of prostate cancer in sampled affected men were made during 1974–97. Medical records were received for 494 (94.6%) of 522 genotyped affected men. The medical records for all but 1 man confirmed the prostate cancer diagnosis.

Markers and Genotyping

The 1q42-43 markers used were *D1S235*–11.63 cM–*D1S2785*–1.24 cM–*D1S547*–8.26 cM–*D1S1609*. Sex-averaged distances are from genetic maps from the Marshfield Medical Research Foundation. PCR amplifications incorporated an infrared dye (IRD40-dATP [Boehringer Mannheim] or IRD700-dATP [Enzo/LI-COR]) and were analyzed on LICOR 4200 automated sequencing machines, as described elsewhere (McIndoe et al. 1997). Because many pedigrees contained ungenotyped founders, allele frequencies were estimated from all genotyped individuals. We expected, given 152 fam-

Table 1

Characteristics of 152 PROGRESS Families

		No. of Sampled Men, by Family Mean Age at Diagnosis			
		<66.0 Years		<61.0 Years	
Group	Total	White	Nonwhite	White	Nonwhite
Families	152	67	4	20	1
Affected men (range, per family)	648 (3–9)	281 (3–9)	26 (4–9)	79 (3–6)	4
Genotyped affected men (range, per family)	522 (2–7)	231 (2–5)	20 (3–7)	64 (2–5)	3

ilies, that these frequencies would approximate the true population frequencies (Terwilliger and Ott 1994), not accounting for any racial differences. The derived frequencies closely corresponded to allele frequencies in the Genome Database.

Linkage Analysis

Two-point parametric analyses were performed with the ANALYZE software package (Terwilliger 1996) and LINKAGE, version 5.1 (Lathrop et al. 1984). Multipoint parametric and nonparametric analyses used GENEHUNTER, version 1.2 (Kruglyak et al. 1996). Three autosomal dominant parametric models were used. The first, referred to as "S1," was based on the segregation-analysis data of Carter et al. (1992) and has been described elsewhere (McIndoe et al. 1997). Models B1 and B2 are identical to models 1 and 2 used by Berthon et al. (1998) to identify the original linkage to the 1q42.2-43 region. For purposes of the analyses, affected status was coded as unknown for men ⩾45.0 years of age who reported being unaffected but who indicated that they had not had a prostate specific antigen (PSA) test in the previous 5 years, did not know if they had ever had a PSA test, or had an elevated or abnormal PSA level but did not have physician-diagnosed benign prostatic hyperplasia.

Results

Analysis of 152 Families with High Risk of Prostate Cancer

To ensure maximum reliability of information, the pedigrees analyzed included only information from sampled questionnaire respondents or from unsampled family members who are first-degree relatives of a questionnaire respondent. The 152 families included a total of 648 affected men (range, 3–9 per family; mean, 4.3 per family). The number of genotyped individuals was 1,189, including 522 affected men (range, 2–7 per family; mean, 3.4 per family). The mean age at diagnosis of prostate cancer in the sampled affected men in each family was within the range 52.8–78.0 years (mean, 66.7 years; table 1).

Four polymorphic microsatellite markers spanning a 20-cM region of 1q42.2-43 were analyzed, including *D1S2785,* which gave the maximum two-point LOD score in the study by Berthon et al. (1998). Two-point LOD scores summed across 152 families (table 2) did not show evidence for linkage, under any model, and ranged from −8.5 to −52.4 at recombination fraction (θ) = .0. In all cases, the maximum LOD score at any θ was <0.1. Analysis of all 152 families, by means of multipoint nonparametric methods, resulted in a maximum NPL score of 0.23 (P = .40; table 2). The parametric multipoint LOD scores were highly negative across the entire region (range, −29.7 to −42.0 for model S1). A maximum LOD score under the assumption of heterogeneity (HLOD) of 0.054 was found when α (proportion of families with linkage) was assumed to be .029.

The six nonwhite families were Native American, African American, Latino, or Japanese. No ethnic/racial group accounted for more than two families; thus, these groups were not analyzed independently (the total LOD score for nonwhite families was −1.3 at *D1S2785;* LOD scores for individual families ranged from 0.30 to −1.18). Exclusion of these families from the total data set did not significantly alter the results.

Analysis of Age-Stratified Subsets

Families with a large number of affected individuals or with individuals affected at an early age may be expected to be the most likely to have an inherited predisposition to prostate cancer. Stratifications based on age have proved useful for enriching for families with linkage to prostate cancer–susceptibility loci (Grönberg et al. 1997*b;* Berthon et al. 1998; Gibbs et al. 1999). The 152 families included in this study can be divided into subsets of 71 and 81 families, with a mean age for sampled affected men of <66.0 years and ⩾66.0 years, respectively (table 1).

Analysis of 67 white families with a mean age at di-

Table 2

Two-Point and Multipoint Analyses with 1q42.2-43 Markers, for 152 Families

		Two-Point Analysis				Multipoint Analysis				
Marker	Distance (cM)	LOD Score at $\theta = .0$	Maximum LOD Score (θ)	Maximum HLOD Score (θ)	α	LOD Score	HLOD Score	α	NPL Score	*P* Value
D1S235	...	−27.706	.000 (.50)	.000 (.50)	1.00	−36.957	−.001	.000	−1.347	.914
D1S2785	11.63	−30.638	.070 (.40)	.168 (.00)	.05	−42.387	.003	.010	.028	.483
D1S547	1.24	−23.518	.078 (.38)	.078 (.38)	1.00	−42.016	.011	.014	.175	.425
D1S1609	8.26	−24.617	.000 (.50)	.087 (.00)	.05	−34.802	.054	.029	.230	.403

Note.—Distance is from the preceding marker. LOD scores shown were calculated by use of model S1; other models gave similar results. Multipoint scores are shown only for positions corresponding to markers.

agnosis among sampled affected men of <66.0 years did not suggest linkage, for any model, with negative LOD scores at low θ values (data not shown). At $\theta = .0$, all LOD scores, except those with *D1S547* and model B2, were <−2.0, which in general is considered to be significant evidence against linkage (data not shown). Positive LOD scores were found at higher θ values; the maximum LOD score for any marker in the region was 0.32 at $\theta = .28$, with *D1S547* and model S1. Multipoint analyses also did not support linkage in this subset of families; multipoint LOD scores and model-independent NPL scores were negative across the entire region, with a maximum NPL score of −0.286 ($P = .60$; data not shown).

The most provocative evidence for linkage was found, by Berthon et al. (1998), in nine families with very early onset of prostate cancer; therefore, we further restricted the younger age group to 20 white families with a mean age at diagnosis of <61.0 years. Analysis of these families, by use of models S1 and B1, gave negative LOD scores at $\theta = .0$ but gave positive maximum LOD scores at θ values of .0–.362 for markers *D1S2685, D1S547,* and *D1S1609,* by use of all three models (table 3). When model B2 was used, a nonsignificant positive LOD score was seen with *D1S1609* (1.176 at $\theta = .0$). Multipoint analysis, however, gave no evidence for linkage (table 4).

Stratification by Number of Affected Men per Family

The 152 families also were stratified by the number of affected men in each pedigree. The data for 46 white families with at least five affected men were analyzed. Although LOD scores were significantly negative at small θ values, LOD scores were positive at *D1S2785, D1S547,* and *D1S1609* at $\theta = \sim .3$, for all three models (table 5). Under the assumption of heterogeneity, LOD scores at *D1S2785* were within the range 0.44–0.47 at $\theta = .0$ and $\alpha = .12$–.17 with all three models. LOD scores at *D1S1609* were within the range 0.76–0.90 at $\theta = .0$, when α was assumed to be .29–.22 (table 5). Multipoint analysis of this group resulted in a maximum NPL score of 1.23 ($P = .11$) at a position corresponding to *D1S1609* (table 6). Under the assumption of heterogeneity, multipoint LOD scores at this position were within the range 0.46–0.57 (α of .12–.15).

Given that the strongest evidence for linkage was found in families with at least five affected men, we next considered the possibility that the families most likely to show linkage would be those that shared a young mean age at onset and a significant number of affected men. We therefore analyzed the 22 white families with a mean age at diagnosis of <66.0 years and with at least five affected men (data not shown). The results were less suggestive than those described above for the 46 white families. Under the assumption of heterogeneity, markers *D1S2785, D1S547,* and *D1S1609* yielded LOD scores within the range 0.102–0.619 at θ values of .0–.26, when all three models were used. The maximum LOD score of 0.619 at $\theta = .18$ was observed with *D1S547*. NPL scores were negative across the entire region (data not shown).

As an additional subset analysis, we selected those six white families that had at least five affected men and a mean age at onset of <61.0 years, representing a refined stratification of families in which disease is most likely due to genetic causes. With *D1S1609,* LOD scores were within the range 0.87–1.11 at $\theta = .0$, for the three models (data not shown). However, no evidence for linkage was observed at the intervening marker, *D1S547,* at any θ value, and the maximum NPL score was −0.12 ($P = .5$; data not shown).

Exclusion of Families with Potential Linkage to Other Loci

Currently, there are no defined clinical criteria to distinguish sporadic from genetic prostate cancer or *HPC1*-associated disease from that induced by other susceptibility loci. Until *HPC1* is cloned, prediction of the families potentially with linkage and those potentially without linkage is only possible on the basis of individual family LOD scores and haplotype sharing. We previously had shown that the first 150 PROGRESS families contain few families with potential linkage to *HPC1* (McIndoe et al. 1997; authors' unpublished data) but that there is evidence for a rare putative prostate/brain cancer locus at 1p36 (provisionally termed "*CAPB*") in

Table 3

Two-Point LOD Scores with 1q42.2-43 Markers, for 20 White Families with Mean Age at Diagnosis <61.0 Years

Model and Marker	Distance (cM)	LOD Score at $\theta = .0$	Maximum LOD Score (θ)	Maximum HLOD Score (θ)	α
S1:					
D1S235	...	−2.720	.000 (.50)	.010 (.00)	.05
D1S2785	11.63	−3.009	.008 (.38)	.008 (.38)	1.00
D1S547	1.24	−1.424	.112 (.26)	.112 (.26)	1.00
D1S1609	8.26	−.644	.362 (.16)	.429 (.00)	.42
B1:					
D1S235	...	−3.977	.000 (.50)	.011 (.00)	.04
D1S2785	11.63	−3.997	.048 (.32)	.048 (.32)	.99
D1S547	1.24	−3.150	.073 (.30)	.073 (.30)	1.00
D1S1609	8.26	−.675	.464 (.16)	.542 (.00)	.44
B2:					
D1S235	...	−1.552	.000 (.50)	.000 (.50)	1.00
D1S2785	11.63	−.367	.141 (.20)	.141 (.20)	1.00
D1S547	1.24	−.705	.058 (.26)	.058 (.26)	1.00
D1S1609	8.26	1.176	1.176 (.00)	1.176 (.00)	1.00

a small subset of the PROGRESS families (Gibbs et al. 1999). To minimize the effects of locus heterogeneity on our analysis, the entire data set was stratified to exclude families that had greater evidence of linkage to either the *HPC1* or *CAPB* loci, based on comparison of the maximum absolute LOD scores at each locus. Eighty-eight families had stronger evidence of linkage to *HPC1* or *CAPB*, leaving a subset of 64 families that were either negative at all three loci ($n = 28$) or had the greatest positive score at *D1S2785* ($n = 34$). When these families were analyzed by use of the four markers that define the *PCAP* locus, we observed a maximum LOD score for *D1S2785* of 1.90 at $\theta = .0$. However, at the closest adjacent marker, *D1S547*, a maximum LOD score of 0.365 at $\theta = .28$ was observed, and LOD scores at *D1S235* and *D1S1609* also were low (0.0 and 0.038, respectively), suggesting that the result for *D1S2785* likely reflects bias imposed by stratification based on LOD scores for that individual marker, rather than identification of a linked subset.

Therefore, a more conservative stratification to remove the families likely to show linkage to *CAPB* was the removal of families with a large positive LOD score at *D1S407*. A total of eight families that had LOD scores $\geq$0.4 (range, 0.43–1.09) at *D1S407* were excluded from the 46 with at least five affected men. Analysis of the remaining 38 families found LOD scores at *D1S1609* that were higher than those observed for the original 46 families (table 5), with all three models (table 7), but less difference was observed at the other three loci. Similarly, multipoint analysis revealed a higher maximum NPL score of 1.4 ($P = .09$) at *D1S1609* but less evidence for linkage over the rest of the region (table 7).

Discussion

Analysis of 152 families at high risk for prostate cancer found overall evidence against linkage of prostate cancer to markers at chromosome 1q42.2-43. This rejection of linkage to *PCAP* may reflect locus heterogeneity. Pedigrees, therefore, were stratified into homogeneous subsets based on race, mean age at diagnosis of prostate cancer, and number of affected men. Although analyses of these subsets also did not support linkage,

Table 4

Multipoint Analyses of 20 White Families with Mean Age at Diagnosis <61.0 Years

	Parametric Model									Nonparametric Model	
	S1			B1			B2				
Marker Position	LOD Score	HLOD Score	α	LOD Score	HLOD Score	α	LOD Score	HLOD Score	α	NPL Score	*P* Value
0	−2.085	.056	.112	−3.630	.063	.100	−.914	.021	.130	−.418	.652
11.63	−4.257	−.001	.000	−6.010	−.001	.001	−1.336	−.002	.004	−.229	.578
12.87	−3.757	−.001	.000	−5.364	−.001	.001	−1.335	−.002	.004	−.147	.546
19.89	−1.611	.123	.234	−2.154	.220	.256	.077	.198	.503	.399	.335

Note.—Results shown correspond to the positions of the markers described in table 3 (*D1S235*, *D1S2785*, *D1S547*, and *D1S1609*, respectively).

Table 5

Two-Point LOD Scores with 1q42.2-43 Markers, for 46 White Families with at Least Five Affected Men

Model and Marker	Distance (cM)	LOD Score at $\theta = .0$	Maximum LOD Score (θ)	Maximum HLOD Score (θ)	α
S1:					
D1S235	...	−16.276	.000 (.50)	.000 (.50)	1.00
D1S2785	11.63	−10.493	.403 (.30)	.459 (.00)	.15
D1S547	1.24	−8.271	.229 (.30)	.229 (.30)	1.00
D1S1609	8.26	−8.133	.432 (.28)	.775 (.00)	.23
B1:					
D1S235	...	−24.739	.000 (.50)	.000 (.50)	1.00
D1S2785	11.63	−18.827	.412 (.32)	.469 (.00)	.12
D1S547	1.24	−15.258	.098 (.36)	.098 (.36)	1.00
D1S1609	8.26	−14.635	.288 (.32)	.900 (.00)	.22
B2:					
D1S235	...	−10.103	.000 (.50)	.000 (.50)	1.00
D1S2785	11.63	−5.326	.307 (.30)	.441 (.00)	.17
D1S547	1.24	−4.883	.087 (.32)	.087 (.32)	.94
D1S1609	8.26	−3.044	.378 (.26)	.758 (.00)	.29

positive—albeit small—LOD scores were found at larger θ values (in general, >.2). This is the pattern expected when a small proportion of families have linkage to the region of interest. The most suggestive evidence for linkage was in those families with at least five affected men, although statistical significance was not achieved. The estimated α in this subset of 46 families was .12–.29, corresponding to ~4%–9% of the total data set of 152 families. Given the overall lack of significance and the model dependence of these estimates, however, this result should be treated with caution. Further stratification of this group by mean age at diagnosis did not improve the evidence for linkage. As expected from the size and structure of the pedigrees analyzed, no single family generated a significant LOD score. The most suggestive was a family with a mean age at diagnosis of 67.0 years, which had a maximum LOD score of 1.3 at *D1S2785* and a maximum NPL score of 5.03 ($P = .004$), unadjusted for 152 comparisons.

The original report of linkage between inherited prostate cancer and 1q42.2-43 was found by analysis of 47 families. These families included 194 genotyped individuals, of whom 122 were affected, for an average of 2.6 affected individuals per family (Berthon et al. 1998). The proportion of families with linkage was estimated to be 50%. The 152 families analyzed here included 1,189 genotyped individuals, including 522 genotyped affected men, for an average of 3.4 affected men per family. It is likely, therefore, that linkage of the magnitude seen by Berthon et al. (1998) could be detected in our data set. Berthon et al. (1998) noted, however, that the proportion of families with linkage of 50% was likely to be an overestimate, given the number of families with only two informative meioses, and they suggested a lower figure of 20%, based on the proportion of families with early onset.

SIMLINK analyses performed on subsets of PROGRESS families, under the assumptions of marker informativeness (polymorphic information content [PIC]) of .7, penetrance of 88% for carriers, and penetrance of 5% for noncarriers, suggested sufficient power to detect linkage if, as estimated by Berthon et al. (1998), 50%

Table 6

Multipoint Analysis of 46 White Families with at Least Five Affected Men

	Parametric Model									Nonparametric Model	
	S1			B1			B2				
Marker Position	LOD Score	HLOD Score	α	LOD Score	HLOD Score	α	LOD Score	HLOD Score	α	NPL Score	*P* Value
0	−18.868	.000	.000	−28.084	.000	.000	−11.512	.000	.000	−.936	.824
11.63	−15.871	.192	.068	−26.047	.188	.055	−8.687	.195	.085	1.034	.151
12.87	−15.148	.192	.069	−25.007	.182	.055	−8.855	.177	.080	1.009	.156
19.89	−11.379	.569	.145	−19.067	.571	.121	−6.369	.461	.152	1.228	.113

Note.—Results shown correspond to the positions of the markers described in table 5 (*D1S235*, *D1S2785*, *D1S547*, and *D1S1609*, respectively).

Table 7

Two-Point and Multipoint Analyses for 38 Families with at Least Five Affected Men and LOD Scores <0.4 at the *CAPB* Locus

		Two-Point Analysis				Multipoint Analysis				
Marker	Distance (cM)	LOD Score at $\theta = .0$	Maximum LOD Score (θ)	Maximum HLOD Score (θ)	α	LOD Score	HLOD Score	α	NPL Score	*P* Value
D1S235	...	−6.514	.000 (.50)	.216 (.46)	.71	−15.935	.000	.000	−.776	.775
D1S2785	11.63	−10.882	.149 (.34)	.150 (.34)	.92	−14.691	.096	.046	.656	.245
D1S547	1.24	−6.513	.216 (.30)	.216 (.30)	1.00	−13.683	.105	.050	.686	.237
D1S1609	8.26	−4.868	.708 (.24)	1.214 (.00)	.33	−8.245	.840	.202	1.396	.088

Note.—Distance is from the preceding marker. LOD scores shown were calculated by use of model S1; other models gave similar results. Multipoint scores are shown only for positions corresponding to markers.

of the families show linkage (G. P. Jarvik, J. L. Stanford, E. L. Goode, L. Hood, E. A. Ostrander, unpublished data). These estimates are conservative for the analysis at *PCAP,* because the 1q24-25 markers analyzed in this study had PIC values ⩾.7. If 30% of families overall show linkage, the expected LOD scores at $\theta = .00$ and .05 are estimated to be 0.286 and 0.297, respectively. If 10% of families show linkage, the expected LOD scores at $\theta = .00$ and .05 are estimated to be 0.116 and 0.137, respectively. We estimate, therefore, that if <10% of families show linkage, the power to detect linkage with a significant LOD score is low, but a positive overall LOD score would be expected. Instead, large negative LOD scores were seen. Therefore, the fact that some stratified subsets of these families gave low positive LOD scores is consistent with the notion that a small proportion of families that have at least five affected men are likely to have disease due to germ-line mutations at *PCAP.* In contrast, our linkage analysis of the *HPC1* region, with the same subset of families, found consistently negative LOD scores (authors' unpublished data), suggesting very little evidence for linkage at the *HPC1* locus.

It is difficult to compensate for locus heterogeneity by stratification, in the absence of defined characteristics to classify *HPC1* or *PCAP* families. Segregation of families on the basis of LOD scores or haplotype sharing should enrich for families with linkage but will naturally include false-positive results and exclude false-negative results. This has been aptly demonstrated by the comparison of *BRCA1* and *BRCA2* linkage and mutation-detection results. In one small analysis of 10 families with a high risk for breast cancer, all characterized by multipoint LOD scores of <−1.0 at the *BRCA1* locus, 3 families were found to carry germ-line mutations in the *BRCA1* gene (Narod et al. 1995). Similarly, not all families with positive LOD scores at the *BRCA1* or *BRCA2* locus appear to carry germ-line mutations in these genes, after careful examination of the entire coding region by means of even the most stringent mutation-detection methods (Ford et al. 1998). The cloning of any prostate cancer–susceptibility gene, anxiously awaited by both the basic science and the clinical communities, or the identification of a biochemical marker to identify homogeneous subsets of families would greatly facilitate further analyses to define other loci.

The proportion of families in this analysis that appear to have linkage to the *HPC1* and *PCAP* regions was less than that predicted from initial estimates of frequency (Smith et al. 1996; Berthon et al. 1998) and suggests that other prostate cancer–susceptibility loci, possibly including the recently identified *HPCX* locus (Xu et al. 1998), account for disease in most of these families. It is interesting to consider why both the *HPC1* (Smith et al. 1996) and *PCAP* (Berthon et al. 1998) loci subsequently have not been found to account for a similar proportion of prostate cancer in other, seemingly similar data sets (McIndoe et al. 1997; Berthon et al. 1998; Eeles et al. 1998; authors' unpublished data). This may simply reflect the existence of multiple prostate cancer–susceptibility loci, any one of which may be abundant in some family collections and much rarer in others, owing to stochastic variation or subtle differences in the family collections. Because heterogeneity weakens power to detect linkage, a locus must account for a reasonable proportion of families, to yield significant evidence of linkage. The exact proportion varies, depending on the sample. When this is considered, given the fact that the recent localizations of *HPCX* (Xu et al. 1998) and *CAPB* (Gibbs et al. 1999) bring the number of putative prostate cancer–susceptibility loci to four, it is not surprising that the original estimates of proportions of families with linkage were substantially higher than those in follow-up studies of other samples. If the loci had not been well represented in the original sample (because of chance or study design), significant evidence for linkage could not have been shown.

Our data are not inconsistent with a prostate cancer locus at 1q42.2-43. Rather, any prostate cancer–susceptibility locus in this region likely accounts for less than the original estimate of 20%–50% of families with prostate cancer. The exact proportion of families with disease that can be attributed to this locus can be determined only when a gene is found and mutation-detection studies are completed.

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Electronic-Database Information

URLs for data in this article are as follows:

Genome Database, http://gdbwww.gdb.org (for allele frequencies used for comparison)
Marshfield Medical Research Foundation, http://www.marshmed.org/genetics/ (for genetic maps)

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