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Predisposing Gene for Early-Onset Prostate Cancer, Localized on Chromosome 1q42.2-43

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Summary

There is genetic predisposition associated with ⩾10% of all cancer of the prostate (CaP). By means of a genomewide search on a selection of 47 French and German families, parametric and nonparametric linkage (NPL) analysis allowed identification of a locus, on chromosome 1q42.2-43, carrying a putative predisposing gene for CaP (PCaP). The primary localization was confirmed with several markers, by use of three different genetic models. We obtained a maximum two-point LOD score of 2.7 with marker D1S2785. Multipoint parametric and NPL analysis yielded maximum HLOD and NPL scores of 2.2 and 3.1, respectively, with an associated *P* value of .001. Homogeneity analysis with multipoint LOD scores gave an estimate of the proportion of families with linkage to this locus of 50%, with a likelihood ratio of 157/1 in favor of heterogeneity. Furthermore, the 9/47 families with early-onset CaP at age <60 years gave multipoint LOD and NPL scores of 3.31 and 3.32, respectively, with *P* = .001.

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Introduction

Since the first description, in 1956 (Morganti et al. 1956), of familial aggregation of prostate cancer (CaP) cases, several reports (Woolf 1960; Skolnick et al. 1979; Cannon et al. 1982; Meikle et al. 1985; Spitz et al. 1991) have confirmed that ~10% of all CaPs are hereditary, with an autosomal dominant inheritance (Carter et al. 1992; Grönberg et al. 1997*a*). Recent investigations by linkage analysis have proposed one susceptibility locus for CaP on chromosome 1q24-25 (Smith et al. 1996). This locus, called "HPC1" by the investigators, is still a matter of controversy. It has been confirmed both by two other groups (Cooney et al. 1997; Hsieh et al. 1997) and through reanalysis and extension of the original study (Grönberg et al. 1997*b*). Conversely, HPC1 has remained unconfirmed by other investigations, including those by a U.K./Canada/Texas consortium (Eeles et al. 1997) and three North American groups (Cannon-Albright and Neuhausen 1997; McIndoe et al. 1997; Thibodeau et al. 1997).

To identify the genes predisposing for CaP (PCaP genes), we have initiated an independent linkage study, using a set of European families (French and German) with three or more CaP patients per family (Valeri et al. 1996). In the present study we demonstrate a localization for a PCaP gene, on chromosome 1q42.2-43, significantly distant from the proposed locus on 1q24-25 (Smith et al. 1996).

Families and Methods

Family Collection

A family study of CaP has been undertaken since 1995, first identifying and collecting families in France

Table 1

Characteristics of Genotyped CaP Families

Category	Result
No. of families analyzed	47
Total no. of individuals genotyped	194
Total no. of affecteds genotyped	122
Average no. of CaP cases/family (range)	3.31 (3–8)
Average no. of genotyped CaP cases/family (range)	2.60 (2–5)
Mean age ± SD (in years) at diagnosis (range)	65.9 ± 8.8 (41–85)

that have at least two CaP cases; this study is named the "ProGène" study (Valeri et al. 1996). A total of 924 families have been collected, 293 of which have at least three affected members. With the same procedure, a set of 30 well-documented German hereditary-CaP families was added. Data were processed by use of a laboratory-developed database for pedigree, clinical, and epidemiological information. From this collection of families, a set meeting the minimum criteria for genetic analysis were selected. In brief, and in accordance with the criteria defined by Carter et al. (1992), only families with at least three confirmed CaP cases, two of whom were living at the time of the present study, were sampled for genotyping. The pathological record or the radical-prostatectomy report was the absolute requirement for inclusion of families in the final selected set. Prostate-specific–antigen assays were systematically performed in every supposedly nonaffected male family member age >40 years, to confirm his nonaffected status. This family selection allowed 47 families, including 10 families of German origin, to be studied (table 1).

Genotyping

DNA was prepared from lymphocytes and was used for PCR. In parallel, collections of serum and immortalized lymphoblastoid-cell lines have been set up for every individual sampled. Microsatellite markers (n = 364) were selected, on the basis of the Généthon map (Dib et al. 1996), to provide an average spacing of 10 cM.

Two successive methods have been used. The first method, developed at Généthon by Vignal et al. (1993), used a semiautomated microsatellite PCR genotyping. With this method, 216 markers were analyzed. In brief, 50-μl PCR reactions with 60 ng of DNA/sample were prepared in 96-well microtiter plates by use of a robotic dispensing station. This allows a large number to be set up rapidly and insures accuracy. The products from 16 markers were pooled and coprecipitated before being loaded on 6% polyacrylamide gels, for separation under denaturing conditions. After electrophoresis, the amplified fragments were transferred to Hybond N^+ membranes (Amersham) and then were fixed by UV cross-linking. PCR, coprecipitation, denaturating PAGE, and transfer to membranes were performed at Généthon (France). Subsequently, membranes were hybridized with as many as three nonoverlapping probes and were stripped and rehybridized as many as 10 times. CEPH family member 134702 was typed with each marker, to provide a positive control and size reference (Dib et al. 1996). Allele assignment was made by comparison with this individual. Membranes were read by at least two people independently, prior to computer processing.

The second method was accomplished to complete the marker set ($\geqslant$364 markers) by use of semiautomated ABI sequencer 377. PCR reactions (total volume 15 μl) contained 30 ng DNA, 4–50 pmol of each fluorescently labeled primer, according to individual marker-optimization parameters, 0.6 U of *Taq* polymerase, 0.25 mM each dNTP, 2.5 mM $MgCl_2$, and additional buffer components. PCR conditions included initial denaturation at 95°C for 10 min; 10 cycles of denaturation (94°C for 15 s), annealing (55°C for 15 s), and elongation (72°C for 30 s); 20 cycles of denaturation (89°C for 15 s), annealing (55°C for 15 s), and elongation (72°C for 30 s); and a final 10-min elongation period at 72°C. Three to five PCR reactions were multiplexed. Twelve aliquots were pooled into multiplexed nonoverlapping panels and were analyzed on a semiautomated sequencer. Allele assignment was performed by use of the Genescan and Genotyper II package, on the basis of comparison with CEPH family members 134702 and 88415.

Linkage Analysis

Two-point parametric LOD scores were computed by use of MLINK from the FASTLINK 3.0P package (Lathrop et al. 1984; Cottingham et al. 1993). Multipoint parametric LOD scores and nonparametric LOD scores (Whittemore and Halpern 1994) were computed by use of GENEHUNTER (Kruglyak et al. 1996). Some controls using LINKMAP (Cottingham et al. 1993) or VITESSE (O'Connell and Weeks 1995) showed no significant differences in multipoint parametric LOD scores. We used three genetic models. All models were chosen on the basis of autosomal dominant inheritance of a gene whose disease allele has a frequency of .003 and an

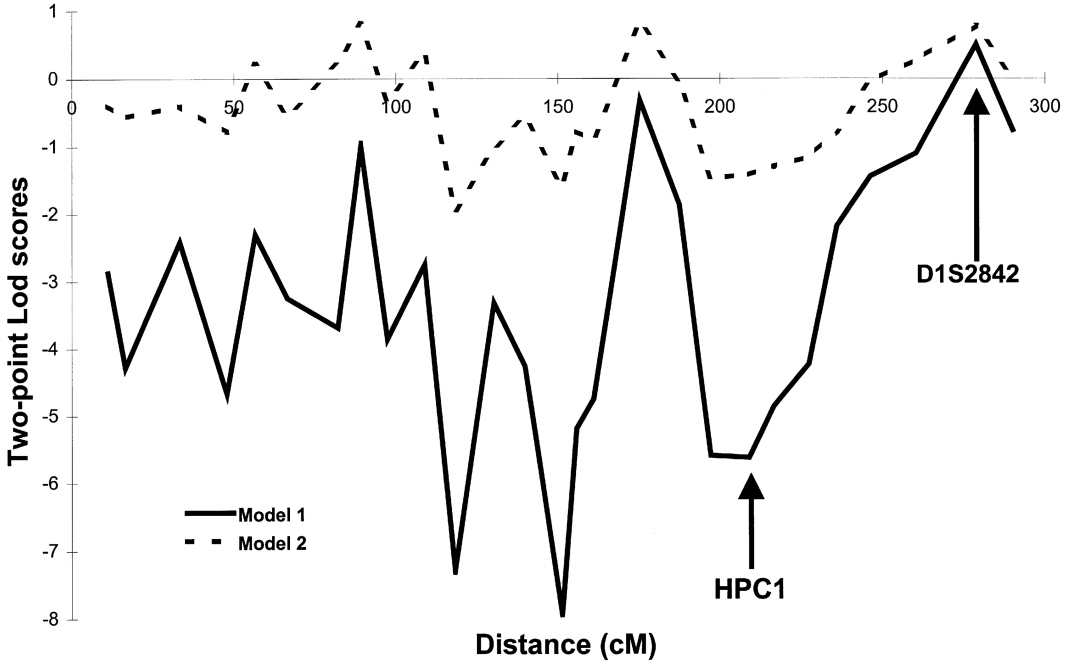

Figure 1 Chromosome 1 scan of 47 families. Maximal two-point LOD scores at a $\theta \leqslant .05$, computed for models 1 and 2, is plotted against genetic distance.

overall penetrance of .88 by 85 years of age (Carter et al. 1992). In these models we used age-dependent penetrance classes, with the following penetrances for the susceptible genotypes—for example, heterozygote and eventual homozygote—based on the data in Carter et al. (1992): .01 at age <40 years, .1 at age 40–55 years, .5 at age 55–70 years, and .9 at age >70 years. The difference between these three models was the penetrance of the nonsusceptible genotype—for example, the phenocopy rate—which was .01, in all age classes, for the first model; 10% of the susceptible-genotype penetrance, in all age classes, for the second model; and similar to that used by Smith et al. (a constant phenocopy rate of 15%), in the third model. Women were coded as unknown. Allelic frequencies were computed on the basis of 50 independent individuals in our sample. Comparison with frequencies published by Dib et al. (1996) showed no striking differences.

Results and Discussion

To select families displaying a potential hereditary pattern of CaP, we originally referred to the monogenic autosomal dominant model described by Carter et al. (1992). In brief, CaP was considered to be hereditary in families if at least three first-degree relatives were affected or if two relatives had been diagnosed at age <55 years. Although one third of the families identified in the French ProGène study (Valeri et al. 1996) have at least three affected members, only a subset (table 1) has been considered informative for linkage analysis, as a consequence of (i) missing pathology records, (ii) few affected members alive and/or available for blood sampling, or (iii) absence of consent. Therefore, a genome-wide screening has been performed on 47 families, including 10 families of German origin. Interestingly, the mean age at diagnosis of CaP in these 47 families (65.9 years) appeared to be lower than that in a control population of sporadic cases (68.9 years). No associated pathology, including other cancers, appeared to be significantly associated with hereditary CaP.

We analyzed 122 affected and 72 unaffected individuals (table 1) with 364 highly polymorphic microsatellite markers (including 27 makers on chromosome 1), taken from the Généthon human linkage map (Dib et al. 1996), which were spaced 10 cM apart. Preliminary evidence for linkage was obtained with marker D1S2842 (fig. 1 and table 2) on chromosome 1q42.2-43. Two-point linkage analysis (table 2) and multipoint parametric and NPL analysis were performed by use of 14 markers spanning 40.3 cM of the region of interest, confirming the localization. We used three different genetic models to address the problem of the phenocopy rate. Hereditary CaP represents 5%–10% of all CaP, and the annual age-adjusted incidence of clinical CaP in the general population rises dramatically, from age 40 (1–2/100,000/

Table 2

Two-Point LOD Scores with 1q42.2-43 Markers for 47 Families

Model and Marker	Distance[a] (cM)	LOD Score at θ = .0	.01	.05	.1	.2	.3	.4
1:								
D1S2827		−9.32	−7.42	−3.92	−2.06	−.54	−.07	.02
D1S490	3.1	−14.03	−11.57	−6.76	−3.93	−1.34	−.37	−.06
D1S2758	2.5	−8.56	−7.16	−4.40	−2.75	−1.13	−.40	−.09
D1S2631	3.5	−4.47	−3.81	−2.45	−1.58	−.65	−.22	−.05
D1S251	1.4	−11.69	−9.48	−5.18	−2.77	−.79	−.18	−.03
D1S2709	2.2	−8.70	−7.35	−4.52	−2.71	−1.00	−.32	−.07
D1S446	4.9	−9.61	−7.72	−4.13	−2.15	−.53	−.06	−.01
D1S235	2.6	−6.36	−5.04	−2.49	−1.05	.03	.20	.09
D1S2678	1.6	−3.03	−2.50	−1.33	−.57	.03	.12	.05
D1S2850	0	−5.76	−4.51	−2.24	−1.01	−.09	.07	.02
D1S2785	9.4	.16	.99	2.34	2.70	2.22	1.27	.42
D1S321	2.3	−5.88	−4.76	−2.50	−1.16	−.09	−.13	.07
D1S2842	5.3	−2.04	−1.12	.50	1.14	1.18	.72	.25
D1S2811	1.5	−9.46	−7.40	−3.42	−1.32	.18	.39	.20
2:								
D1S2827		−1.06	−.96	−.65	−.39	−.11	−.01	.01
D1S490	3.1	−3.09	−2.87	−2.14	−1.47	−.63	−.22	−.05
D1S2758	2.5	−2.18	−2.07	−1.66	−1.25	−.65	−.27	−.07
D1S2631	3.5	−1.37	−1.29	−1.03	−.76	−.38	−.16	−.04
D1S251	1.4	−1.90	−.75	−1.26	−.83	−.34	−.12	−.03
D1S2709	2.2	−1.85	−1.73	−1.30	−.89	−.40	−.15	−.04
D1S446	4.9	−1.24	−1.14	−.80	−.50	−.16	−.04	.00
D1S235	2.6	−.51	−.44	−.21	−.03	.09	.08	.03
D1S2678	1.6	−.19	−.14	−.02	.08	.12	.08	.02
D1S2850	0	−1.12	−1.02	−.70	−.43	−.14	−.04	−.01
D1S2785	9.4	2.10	2.08	1.95	1.73	1.17	.61	.19
D1S321	2.3	−.90	−.80	−.49	−.24	.01	.05	.02
D1S2842	5.3	.75	.76	.77	.73	.54	.30	.10
D1S2811	1.5	−1.04	−.91	−.49	−.16	.13	.16	.08

[a] Between the marker immediately to the left and that directly above it.

year) to a peak during the 80s (1,600/100,000/year), which gives an estimated overall lifetime risk of 10% (Boyle et al. 1996). Since it is impossible to estimate the phenocopy rate in our population of families with multiple cases, we have designed three different models. Model 1 considers a low, constant phenocopy rate of 1%. Because hereditary cases are often associated with an early age at onset (see discussion above), it seems reasonable to use a further model (model 2), which has a phenocopy number that increases with age. We used age-dependent penetrance classes to extract information for unaffected men. A third model, close to the model used by Smith et al. (1996), yielded similar profiles, with magnitude lower than that in our models 1 and 2 (two-point LOD score of 1.33 at a recombination fraction (θ) of 0, multipoint LOD score of 1.55 for maker D1S2785).

Our data show a two-point LOD score of 2.7 at θ = .1 (model 1), with D1S2785 (table 2). A multipoint LOD score of 1.89 is obtained under model 2 (fig. 2), and, under the hypothesis of heterogeneity, model 1 gives an HLOD score of 2.2 (fig. 2). The NPL-all statistic (Whittemore and Halpern 1994), which is independent of the genetic model, confirms these findings, reaching 3.1, with P = .001 (fig. 2). The value of α, proportion of families with linkage to this locus, was determined in two ways. GENEHUNTER was used to compute HLOD (Smith 1963), which is a parametric LOD score maximized on α (Kruglyak et al. 1996). Under model 1, α = 48%. Model 2 does not show heterogeneity near the maximum LOD score. A homogeneity analysis, using the program HOMOG (Morton 1956; Ott 1986) with multipoint LOD scores, gave a similar α (50%), with a of 157/1 likelihood ratio in favor of heterogeneity, for model 1. Model 2 showed no clear evidence in favor of heterogeneity. However, the lower limit of the conditional probability of linkage showed that families could be divided into two groups. Furthermore, information on heterogeneity, in both our current linkage analysis and that of others (Smith et al. 1996), suggests that several genes may account for all cases of inherited CaP.

In nine families, the age at diagnosis of all affected members in the last generation was <60 years (range 48–60 years). We analyzed this subset of families for heterogeneity of the recombination frequency, by com-

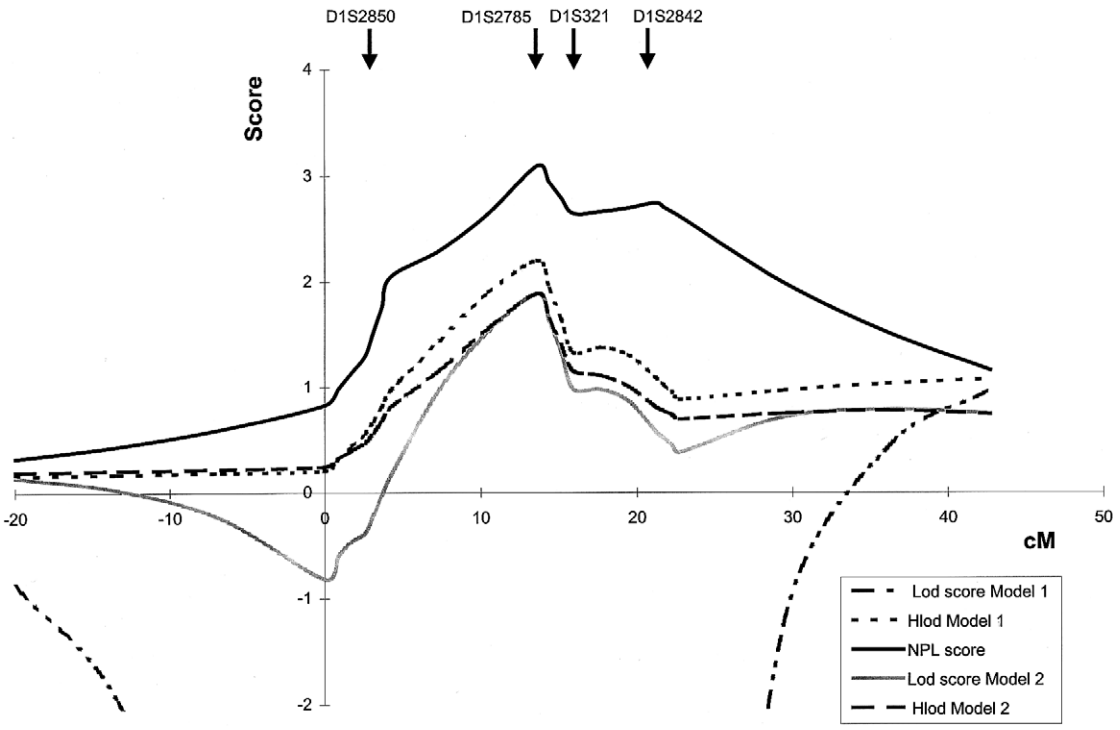

Figure 2 Multipoint LOD scores and NPL scores for 47 families, computed with GENEHUNTER, on a map of four markers. HLODs are maximized on α.

parison with the other families. For this analysis, we used the predivided sample test (Morton 1956) with the Mtest program and multipoint, instead of two-point, LOD scores. A highly significant χ^2 (1 df) of 16.25 ($P < .0001$) is obtained with model 1. Two-point (table 3) and multipoint LOD scores and NPL scores were computed for this subset of families. An identical value of 3.3 for multipoint LOD and NPL scores was reached, at marker D1S2785, by model 1 (fig. 3). Haplotypes reconstructed with GENEHUNTER showed, in each of these nine families, one haplotype segregating in all affected individuals. However, no critical recombinant allowing a narrowing of the candidate region was characterized. These data are suggestive of familial clustering with the age at diagnosis, since we have observed in our populations (Valeri et al. 1996) an earlier age at diagnosis is correlated with an increase in the number of CaP cases observed per family: 68.5 years for one CaP case/family, 67.0 years for two CaP cases/family, 65.6 years for three CaP cases/family, and 60.6 for four or more CaP cases/family (in both 579 families with sporadic cases and 924 families with two or more cases).

Although the two-point LOD scores do not reach the critical threshold value of 3, these data are obtained with multiple LOD scores (model 1). Furthermore, a LOD score of 3.3 is reached with early-onset families (parametric and nonparametric scores). The two-point and multipoint LOD-score results obtained do not rule out the possibility of false-positive values. Génin et al. (1995) showed that, for a certain family structure and for a dominant disease, the posterior probability of no linkage, with a two-point LOD score of 3.0, is 8%–16%.

Table 3

Two-Point LOD Scores with 1q42.2–43 Markers for Nine Early-Onset Families

Model and Marker	Distance[a] (cM)	LOD Score at θ = .0	.01	.05	.1	.2	.3	.4
1:								
D1S235		.36	.36	.33	.29	.20	.10	.03
D1S2678	1.6	−.73	−.57	−.25	−.08	.04	.05	.02
D1S2785	9.4	2.06	2.15	2.17	1.97	1.39	.77	.27
D1S2842	7.6	−.93	−.43	.40	.71	.71	.45	.17
2:								
D1S235		−.51	−.44	−.21	−.03	.09	.08	.03
D1S2678	1.6	.24	.24	.21	.18	.12	.06	.02
D1S2785	9.4	1.75	1.70	1.51	1.27	.81	.42	.14
D1S2842	7.6	.66	.67	.66	.61	.44	.25	.09

[a] As defined in the footnote to table 2.

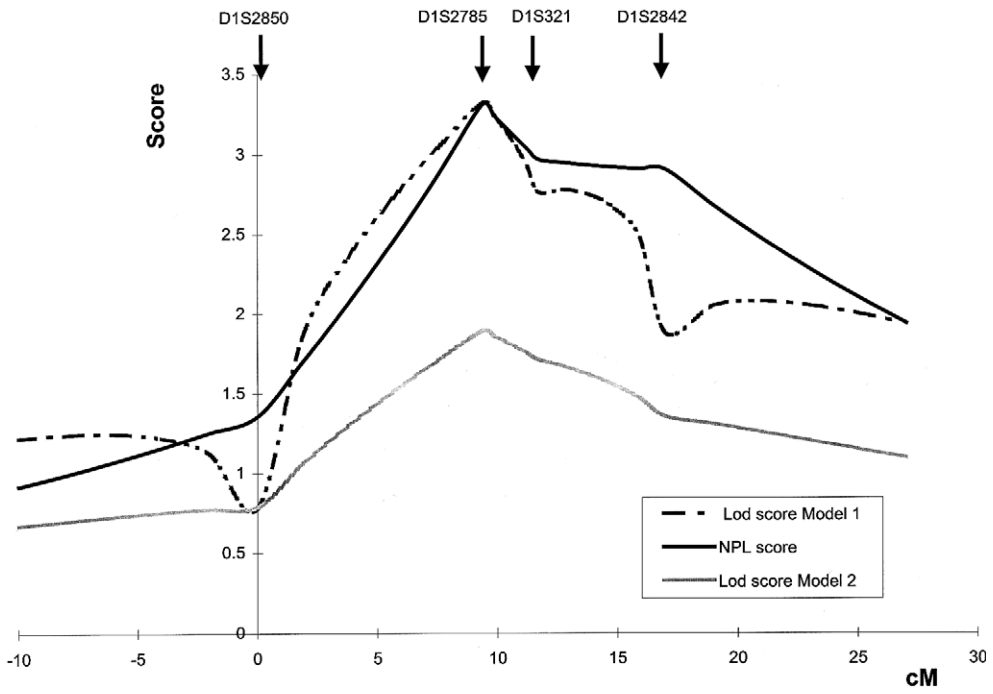

Figure 3 Multipoint LOD scores and NPL scores for nine families with early-onset familial CaP, computed with GENEHUNTER, on a map of four markers.

However, this result is strongly dependent on the family structure and the genetic model. A first cause of errors could be a misspecification of genetic parameters at the disease locus. However, Clerget-Darpoux et al. (1986) showed that this leads more likely to false-negative errors. Another well-known cause of false-positive results is the use of wrong allelic frequencies at marker loci (Freimer et al. 1993). Since we have used allelic frequencies derived from the population under study, which correlate well with published values, we can rule out this cause of errors. We have also addressed this problem by running simulations at $\theta = .5$ and $\alpha = 0$, for two- and three-point LOD scores, thus modeling no linkage. Despite the fact that run-time limitations did not allow us to analyze enough replicas to achieve full statistical significance, the data in the present study show that the probability of false-positive results above a LOD-score value of 3.0 is <5%–10%.

With regard to heterogeneity, the 50% estimate found by homogeneity analysis is probably an overestimation partly due to the number of families with only two fully informative meioses. A lower limit for α (~20%) is derived from the 9/47 ratio of families with early-onset CaP cases to the total number of families with CaP cases. A better estimation of α would require a metanalysis of a worldwide collection of families. Taken together, these results allow us to propose that PCaP is localized on chromosome 1q42.2-43 and accounts for $\leqslant$50% cases of hereditary CaP.

Smith et al. (1996) have described a locus on chromosome 1q24-25 that has evidence of linkage, after an analysis of a set of North American and Swedish families. This locus maps 60 cM centromeric to the region on 1q42.2-43, described in the present report. A linkage analysis was performed on the 1q24-25 locus, and, in agreement with the data recently published by others (Cannon-Albright and Neuhausen 1997; Eeles et al. 1997; McIndoe et al. 1997; Thibodeau et al. 1997), we found no evidence of linkage within this region (table 4). Several reasons for discrepancy between our data and the data of Smith et al. (1996) could include the differences in the number of families (47 vs. 91), in the mean number of affected individuals (3.3/family vs. 4.9/family), and in the mean number of genotyped individuals (4.1/family vs. 6.6/family). The differences in the ethnic composition of the samples also could be responsible for different results. Since both populations have similar but also different origins, it seems very difficult to further analyze that matter. Also interesting is the fact that, in the chromosome 1 scan by Smith et al. (1996, fig. 1), they observed a hit at marker D1S235. This marker is centromeric (table 2) to the locus that we have studied and in effect may have presaged our findings.

We have recently examined the 1q24-25 region for

Table 4

Two-Point LOD Scores with 1q24-25 (HPC1) Markers for 47 Families

Model and Marker	Distance[a] (cM)	LOD Score at θ = .0	.01	.05	.1	.2	.3	.4
1:								
D1S218		−13.05	−10.41	−5.59	−3.02	−.88	−.16	.03
D1S238	11.9	−13.12	−10.48	−5.62	−3.02	−.89	−.19	−.01
D1S413	7.6	−10.4	−8.55	−4.86	−2.75	−.91	−.24	−.03
2:								
D1S218		−2.07	−1.93	−1.47	−1.01	−.42	−.13	−.01
D1S238	11.9	−2.11	−1.95	−1.42	−.95	−.39	−.14	−.02
D1S413	7.6	−1.89	−1.76	−1.30	−.89	−.39	−.14	−.03

[a] As defined in the footnote to table 2.

loss of heterozygosity (LOH) in sporadic prostate tumors, and LOH has been found in 9/55 tumors (Latil et al. 1997). We have further supplemented this previous study, with microsatellite markers, to analyze the 1q42.2-43 region in sporadic tumors. In five of the nine 1q24-25–deleted tumors, the deletion overlapped with the distal 1q42.2-43 region. Furthermore, allelic loss at 1q42.2-43 was seen in six tumors without any alteration within the 1q24-25 region. Taken together, these results suggest that chromosome 1q could harbor two genes involved during progression of CaP.

A small number of genes of interest are known to map to the candidate locus; they include PCTA-1, a member of the galectin family (Su et al. 1996); the poly (ADP-ribose) polymerase (Lyn et al. 1993); and the RAS-related GTP-binding protein RAB-4 (Rousseau-Merck et al. 1991). Also, a fragile site (Feichtinger and Schmid 1989) and replication-error–type genetic instability have been observed within the 1q42-43 region (Murty et al. 1994); the last reveals a potential association with hereditary nonpolyposis colorectal cancer. Also, this region has been shown to be involved in translocations in glioblastomas (Li et al. 1995).

Although screening in the general population is still under debate in Western countries, evidence of familial inheritance should be the basis for genetic screening of this population at risk (Narod et al. 1995). As a matter of fact, the relative risk could rise to 11 when three first-degree relatives are affected (Steinberg et al. 1990; McWorther et al. 1992; Tulinius et al. 1992; Sellers et al. 1994; Aprikian et al. 1995; Monroe et al. 1995; Whittemore et al. 1995; Lesko et al. 1996). Therefore, the development of reliable tests could greatly help clinicians in genetic counseling.

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