Linkage Analysis of Chromosome 1q Markers in 136 Prostate Cancer Families

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Summary

Prostate cancer shows evidence of familial aggregation, particularly at young ages at diagnosis, but the inherited basis of familial prostate cancer is poorly understood. Smith et al. recently found evidence of linkage to markers on 1q, at a locus designated "*HPC1*," in 91 families with multiple cases of early-onset prostate cancer. Using both parametric and nonparametric methods, we attempted to confirm this finding, in 60 affected related pairs and in 76 families with three or more cases of prostate cancer, but we found no significant evidence of linkage. The estimated proportion of linked families, under a standard autosomal dominant model, was 4%, with an upper 95% confidence limit of 31%. We conclude that the *HPC1* locus is responsible for only a minority of familial prostate cancer cases and that it is likely to be most important in families with at least four cases of the disease.

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Introduction

Prostate cancer is a significant public health problem. In the United States, it is the most common malignancy and the second most common cause of cancer-related deaths; 209,900 cases and 41,480 deaths were estimated to have occurred in the United States in 1997 (von Eschenbach et al. 1997). Approximately 14,000 cases/year and 8,742 deaths/year are reported in England and Wales (Office for National Statistics 1991, 1996). Prostate cancer has traditionally been considered a cancer of elderly men; however, 13% of cases occur in men <65 years of age; this is just over the total number of testicular cancers reported per year.

Epidemiological studies have clearly demonstrated that prostate cancer has an inherited component. The first piece of evidence is the presence of familial clustering. The best examples are the large Utah kindreds (Cannon et al. 1982; Eeles and Cannon-Albright 1996). Many other groups have reported familial clusters; interestingly, these are, with few exceptions, small clusters of three or four cases. The second piece of evidence is the results of epidemiological studies of prostate cancer risk among relatives of patients. Woolf (1960) first described an increased incidence of prostate cancer in the relatives of patients. He studied the incidence of prostate cancer among first-degree relatives of 228 individuals with prostate cancer and among age-matched controls. Using data from death certificates, he found that, among first-degree relatives of prostate cancer patients, the relative risk (RR) of developing the disease was 3. This RR is similar to those for other common cancers for which there is a genetic component.

There have been two types of case-control studies; one

(eight studies) compares the incidence of prostate cancer among relatives of cases versus controls, and the other (five studies) compares the percentage of cases versus controls with positive family histories of prostate cancer (summarized in Eeles et al. 1997). Among first-degree relatives of cases, the RRs of developing prostate cancer are 1.76–11.00, in the first type of case-control study, and 0.64–7.50, in the second. Only one study (Steele et al. 1971) reported a lower RR in relatives, but that study included only 39 cases. Two cohort studies have been reported; these showed RRs of 2.20 (95% confidence interval [CI] 2.00–2.40) and 1.70 (95% CI 1.51–1.90) (Goldgar et al. 1994; Grönberg et al. 1996).

The increase in RR, evident from the case-control studies, as clustering becomes more dramatic suggests a genetic effect; RR markedly increases (up to sevenfold) as the age of the proband decreases (Cannon et al. 1982), as the closeness and number of affected members in the family increases (Steinberg et al. 1990), or when both factors are taken together (Carter et al. 1992). A change, of this magnitude, in RR as clustering increases cannot be explained solely by a common environmental effect in each cluster.

A segregation analysis of nuclear families suggested that familial prostate cancer is due to a rare, highly penetrant, dominant gene or genes, the first of which has been named *"HPC1"* (Carter et al. 1992). The gene frequency was estimated to be .0033. This gene is thought to cause 43% of cases that occur by the age of 55 years and 9% of cases that occur by the age of 80 years.

At present, there is considerable debate about the genetic model for prostate cancer predisposition. Narod et al. (1995) have suggested that, because the risk of prostate cancer is higher among brothers than among fathers of affected individuals, a recessive-genetic model should be used. However, this finding could be explained by a screening effect that leads to a higher rate of diagnosis among brothers of affected individuals. Other studies have suggested an X-linked model (Monroe et al. 1995), but male-to-male transmission, demonstrated in some Utah clusters, has refuted this suggestion, at least in some pedigrees (Cannon-Albright and Eeles 1995). The observation that, in general, prostate cancer clusters are smaller than those observed for other common cancers (e.g., breast and colon cancers) could be explained either by a lower recall of family history among males or by the model that prostate cancer predisposition is due to a more common, lower-penetrance gene than that predicted in the model of Carter et al. (1992). H. Grönberg (as discussed in Smith et al. 1996) has estimated a lower penetrance (63%), with a similar gene frequency. Model-free methods are therefore very important in linkage analysis in this disease.

The first prostate cancer–susceptibility locus to be mapped was reported by Smith et al. (1996), who performed a genomic search in 91 families and found linkage to chromosome 1q24-25, in prostate cancer clusters of $\geqslant 3$ cases/family. Smith et al. (1996) estimated that 34% of familial cases were attributable to this locus. The maximum multipoint LOD score was 5.43. In an attempt to confirm this linkage, we performed genetic-linkage analysis of 136 prostate cancer families, using microsatellite markers in the chromosomal region 1q24-25, as suggested by Smith et al. (1996).

Families and Methods

Families

One hundred thirty-six families with multiple family members affected with prostate cancer were ascertained by collaborating urologists in the United Kingdom, Quebec, and Texas. The majority (95%) of the U.K. families were ascertained as a result of clinical presentation; 37.5% of U.S. and Canadian families were ascertained as a result of clinical presentation. The remaining U.S. and Canadian families were ascertained as a result of prostate-specific–antigen serum screens. Diagnoses of all affected individuals typed by the U.K. and U.S. groups were confirmed by either medical report or death certificate. All familial cases in the Canadian group were reported by the patients; 50% of these were also reported by physicians. Characteristics of the families are summarized in table 1.

Genotyping

All genotyping was performed on DNA extracted from lymphocytes. All research groups typed markers that flank the best estimate (Smith et al. 1996) of the position of *HPC1*. A total of six markers, spanning *D1S2883*, *D1S158*, and *D1S422*, were typed. The markers (with distance [cM] to adjacent marker) were *D1S212* (2 cM), *D1S2883* (6.5 cM), *D1S158* (3.5 cM), *D1S238* (3 cM), *D1S422* (6 cM), and *D1S413* (18 cM). All groups typed *D1S422* and *D1S413*. The Canadian group also typed *D1S2883*, and the Texan group also typed *D1S212* and *D1S158*. The U.K. group typed all markers except *D1S212*. Primer sequences and conditions are shown in table 2.

Fifty nanograms of genomic DNA was amplified. In the United Kingdom, amplification was performed with fluorescently labeled primers, and PCR products were submitted to electrophoresis and were sized by an automatic ABI 377 (PE-ABI), using the programs GENESCAN and GENOTYPER to allocate alleles. In Texas and Quebec, PCR products were submitted to manual electrophoresis, in 6% polyacrylamide denaturing gels, with end-labeled ^{32}P primers. Three control individuals were typed by each group, on each gel, as a sizing check.

Table 1

Characteristics of Prostate Cancer Families

	No. of Prostate Cancer Cases in Family						
	2	3	4	5	6	7+	Total
Center:							
United Kingdom	26	11	7	2	. . .	. . .	46
Quebec	31	26	11	7	1	1	77
Texas	3	4	1	2	2	1	13
Total	60	41	19	11	3	2	136
Average no. of affecteds typed	2.00	2.25	2.38	2.45	2.67	3.00	
⩾2 Cases diagnosed at age:							
<60 years	1	4	4	1	1	1	
<70 years	32	28	17	8	3	2	

Note.—One hundred twenty-seven families had at least one pair of affected first-degree relatives, seven families had at least one pair of affected second-degree relatives, and two families had pairs of affected cousins only.

Statistical Methods

Linkage of prostate cancer to chromosome 1q was first assessed by parametric LOD-score analysis, based on the prostate cancer–susceptibility model suggested by Carter et al. (1992). In this model, susceptibility to prostate cancer was assumed to be due to a dominant susceptibility allele with population frequency .0033, which confers a prostate cancer risk, by age 70 years, of 85% among carriers, compared with a risk of 2% among noncarriers. Multipoint heterogeneity LOD (HLOD) scores were computed over the 21-cM region suggested by Smith et al. (1996) and defined by the markers *D1S212–D1S413*.

To guard against the possibility that evidence for linkage might be missed because of misspecification of the genetic model, we also analyzed the data by the nonparametric haplotype-sharing method that is implemented in the program GENEHUNTER (Kruglyak et al. 1996). This analysis is based on computation of haplotype sharing among affected relatives and, thus, is not model dependent. Results are summarized in terms of a statistic, Z, which estimates the excess (over that expected by chance) haplotype sharing, divided by its SD, under the null hypothesis of no linkage. Statistical significance is assessed by relating Z to a standard normal distribution. To assess the contribution of *HPC1* to brothers with prostate cancer, haplotype sharing among affected sibling pairs was also assessed, by use of the program MAPMAKER/SIBS (Kruglyak and Lander 1995), with the "all pairs" option.

Results

The nonparametric analysis by the program GENEHUNTER found no significant evidence for linkage to the 1q region defined by Smith et al. (1996), either for all families combined ($Z = -0.56$ at *D1S422*, $P = .71$) or, separately, for families with fewer than four cases ($Z = -1.09$, $P = .86$) or with at least four cases ($Z = 0.72$, $P = .22$) (tables 3 and 4).

Results of the multipoint heterogeneity analysis are summarized in tables 3 and 4. Our analysis found no

Table 2

Primers Used for 1q Markers Genotyped

Marker	Upstream Primer	Downstream Primer	Annealing Temperature (°C)
D1S212	5′ cagcaagactctgcctctac	5′ ccaggctgattttgtgtatg	55
D1S2883	5′ gtgtctgtatgcagtttg	5′ gtgtctcctctcacatatacaaa	50
D1S158	5′ ggaaagactggaccaaagag	5′ gtttctgggccttcttatattgcttc	59
D1S238	5′ tcatgXctagatcctgtgcc	5′ tggaggcagtttagattgtg	58
D1S422	5′ catggggtatagcaacagac	5′ tgatttcctgcaaacatttt	50
D1S413	5′ gccaagcctgagatcaaaat	5′ acttgaacagattgggattg	50

Note.—All PCRs were performed with 1.5 mM Mg^{2+}. PCR cycle conditions were as follows: Initial denaturation step for 2 min at 94°C, followed by 40 cycles of 1 min at 94°C, 1 min at annealing temperature, and 1 min at 72°C. The appropriate annealing temperature was chosen for each primer pair. PCR was concluded by a final polymerization for 10 min at 72°C.

Table 3

Analysis of All Prostate Cancer Families

Marker and Relative Position (cM)	Two-Point LOD Score[a]	α	Multipoint HLOD Score	Multipoint NPL Score	*P*
D1S212:					
.00	−3.08	.00	.00	−1.17	.88
.40		.00	.00	−1.16	.88
.80		.00	.00	−1.15	.88
1.20		.00	.00	−1.14	.87
1.60		.00	.00	−1.13	.87
D1S2883:					
2.00	−11.42	.00	.00	−1.13	.87
3.30		.00	.00	−1.06	.86
4.60		.00	.00	−.99	.84
5.90		.00	.00	−.93	.82
7.20		.00	.00	−.86	.81
D1S158:					
8.50	−5.64	.00	.00	−.80	.79
9.20		.00	.00	−.75	.77
9.90		.00	.00	−.70	.76
10.60		.00	.00	−.65	.74
11.30		.00	.00	−.60	.72
D1S238:					
12.00	−2.49	.04	.01	−.55	.71
12.60		.04	.01	−.55	.71
13.20		.04	.01	−.55	.71
13.80		.04	.01	−.55	.71
14.40		.04	.01	−.56	.71
D1S422:					
15.00	−8.07	.04	.01	−.56	.71
16.20		.04	.01	−.60	.72
17.40		.04	.01	−.64	.74
18.60		.04	.01	−.67	.75
19.80		.04	.01	−.71	.76
D1S413:					
21.00	−7.82	.04	.01	−.75	.77

[a] At tight linkage to each marker ($\theta = .00$).

significant evidence of linkage to 1q. The overall HLOD score, for all 136 families, was 0.01, with the estimated proportion of linked families, α, being 4% (95% CI 0%–31%). For families with at least four cases, the HLOD score was 0.20, with $\alpha = 20\%$ (95% CI 0%–63%); for families with three or fewer cases, the HLOD score was 0.00, with $\alpha = 0\%$ (95% CI 0%–27%) (table 4). Analysis according to age at diagnosis indicated that 90 families had at least two family members diagnosed at age <70 years; the HLOD for these families was 0.02 ($\alpha = 6.5\%$), and the HLOD for the remaining 46 families was 0.00 ($\alpha = 0\%$).

The affected-sibling-pair MAPMAKER/SIBS analysis showed that the best estimates of the proportion of sibling pairs that share no (z_0), one (z_1), or both haplotypes (z_2) at *HPC1* were .25, .50, and .25 (i.e., their null expectations), respectively; the lower 95% confidence limit for z_0 was .20, at *D1S422*, and .16, over the entire region. This would imply that the 1q locus is likely to explain a sibling RR of <1.56, which compares with the familial RR, based on epidemiological studies, of 2–3.

Discussion

In our collection of 136 prostate cancer families, we found no evidence of linkage to the disease, using markers on chromosome 1q24-25 (two-point LOD = −2.49 to −11.42, across the region of the maximum multipoint LOD reported by Smith et al. 1996). Overall, only 4% of families are estimated to be linked (upper 95% confidence limit of 31%). The discrepancy between some of our results and those of Smith et al. (1996) could be explained, in part, by differences in ethnic background; all of the families in the present study are Caucasian, whereas two families reported by Smith et al. were African American, and these families contributed a total LOD of 1.4; this locus may therefore be more important in families of African origin. A recent study by Cooney et al. (1997) provides evidence for linkage at DIS466 (between DIS2883 and DIS158) in 20 families with an average of 4.4 prostate cancer cases per family; 4 of these families were African American. In contrast, McIndoe et al. (1997) reported negative two-point LOD

Table 4

Multipoint Analysis by Number of Prostate Cancer Cases per Family

Marker and Relative Position (cM)	⩽3 Cases (101 Families)				⩾4 Cases (35 Families)			
	α	HLOD	NPL Score	*P*	α	HLOD	NPL Score	*P*
D1S212:								
.00	.00	.00	−1.36	.91	.00	.00	−.01	.49
.40	.00	.00	−1.35	.91	.00	.00	−.00	.49
.80	.00	.00	−1.35	.91	.00	.00	.00	.48
1.20	.00	.00	−1.34	.91	.00	.00	.00	.48
1.60	.00	.00	−1.33	.91	.00	.00	.01	.48
D1S2883:								
2.00	.00	.00	−.33	.91	.00	.00	.02	.48
3.30	.00	.00	−1.28	.90	.04	.01	.06	.46
4.60	.00	.00	−1.22	.89	.05	.01	.10	.44
5.90	.00	.00	−1.17	.88	.06	.01	.15	.42
7.20	.00	.00	−1.12	.87	.07	.02	.19	.41
D1S158:								
8.50	.00	.00	−1.08	.86	.08	.02	.24	.39
9.20	.00	.00	−1.06	.86	.10	.04	.30	.36
9.90	.00	.00	−1.04	.85	.12	.06	.37	.34
10.60	.00	.00	−1.02	.85	.15	.09	.44	.32
11.30	.00	.00	−1.00	.84	.17	.12	.50	.29
D1S238:								
12.00	.00	.00	−.98	.84	.19	.15	.57	.27
12.60	.00	.00	−1.00	.84	.19	.16	.60	.26
13.20	.00	.00	−1.02	.85	.20	.17	.63	.25
13.80	.00	.00	−1.04	.85	.20	.18	.66	.24
14.40	.00	.00	−1.07	.86	.20	.19	.69	.23
D1S422:								
15.00	.00	.00	−1.09	.86	.20	.20	.72	.22
16.20	.00	.00	−1.06	.86	.20	.18	.60	.26
17.40	.00	.00	−1.04	.85	.20	.16	.49	.30
18.60	.00	.00	−1.02	.85	.19	.14	.37	.34
19.80	.00	.00	−.99	.84	.17	.12	.26	.38
D1S413:								
21.00	.00	.00	−.97	.83	.16	.10	.15	.42

scores across the 1q24-25 region in a series of 49 families, none of which were African American.

A more important factor that might explain the discrepancy between our results and those of Smith et al. (1996) is the fact that the families in the present study included fewer prostate cancer cases; 73% of the families in our analysis include ⩽3 affecteds, whereas the average number of affecteds in Smith's analysis was 4.9 (3–15). When our data were analyzed according to the number of affecteds in each cluster, α rose to 20% for clusters of four or more cases and fell to 0 for clusters of three or fewer cases. This finding is further supported by the data reported by Cooney et al. (1997): the evidence for linkage to 1q is stronger in families with an average of 4.4 prostate cancer cases than in those with an average of 2.4 cases (nonparametric linkage [NPL] score 1.72, $P = .0451$, vs. NPL score 0.809, $P = .208$, respectively). This difference is analogous to that for *BRCA1* and *BRCA2* in breast cancer clusters; these highly penetrant genes account for 80%–90% of larger clusters (six or more cases), but they account for a much lower proportion of families with fewer than four cases (D. Easton, personal communication). However, in contrast to *BRCA1* and *BRCA2*, the 1q locus does not account for such a high proportion of families, even among those with very large clusters of prostate cancer cases. Predisposing mutations in *HPC1* would therefore be predicted to cause a high risk of the disease and to explain a proportion of families with numerous cases, whereas families with fewer cases will more often be explained by more common, lower-penetrance genes and/or environmental effects.

The MAPMAKER/SIBS analysis of our data estimates the familial RR of prostate cancer due to *HPC1* (under the assumption that *HPC1* acts multiplicatively on risk, with respect to other loci) to be 1.0, with an upper 95% confidence limit of 1.56. This compares to an RR of ⩾3, determined by epidemiological studies, for relatives of individuals diagnosed at <65 years of age. Moreover, the familial risks that are due to *HPC1* are overestimated by this method, because many of the families in this study were selected because they had three or more cases

of the disease. We conclude that *HPC1* is likely to explain only a small fraction of the overall familial aggregation of prostate cancer.

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