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Combined Analysis of Hereditary Prostate Cancer Linkage to *1q24-25*: Results from 772 Hereditary Prostate Cancer Families from the International Consortium for Prostate Cancer Genetics

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A previous linkage study provided evidence for a prostate cancer–susceptibility locus at 1q24-25. Subsequent reports in additional collections of families have yielded conflicting results. In addition, evidence for locus heterogeneity has been provided by the identification of other putative hereditary prostate cancer loci on Xq27-28, 1q42-43, and 1p36. The present study describes a combined analysis for six markers in the 1q24-25 region in 772 families affected by hereditary prostate cancer and ascertained by the members of the International Consortium for Prostate Cancer Genetics (ICPCG) from North America, Australia, Finland, Norway, Sweden, and the United Kingdom. Overall, there was some evidence for linkage, with a peak parametric multipoint LOD score assuming heterogeneity (HLOD) of 1.40 ($P = .01$) at D1S212. The estimated proportion of families (α) linked to the locus was .06 (1-LOD support interval .01–.12). This evidence was not observed by a nonparametric approach, presumably because of the extensive heterogeneity. Further parametric analysis revealed a significant effect of the presence of male-to-male disease transmission within the families. In the subset of 491 such families, the peak HLOD was 2.56 ($P = .0006$) and $\alpha = .11$ (1-LOD support interval .04–.19), compared with HLODs of 0 in the remaining 281 families. Within the families with male-to-male disease transmission, α increased with the early mean age at diagnosis (<65 years, $\alpha = .19$, with 1-LOD support interval .06–.34) and the number of affected family members (five or more family members, $\alpha = .15$, with 1-LOD support interval .04–.28). The highest value of α was observed for the 48 families that met all three criteria (peak HLOD = 2.25, $P = .001$, $\alpha = .29$, with 1-LOD support interval .08–.53). These results support the finding of a prostate cancer–susceptibility gene linked to 1q24-25, albeit in a defined subset of prostate cancer families. Although *HPC1* accounts for only a small proportion of all families affected by hereditary prostate cancer, it appears to play a more prominent role in the subset of families with several members affected at an early age and with male-to-male disease transmission.

Introduction

Prostate cancer has significant international public-health importance, with a worldwide estimate of 239,000 deaths resulting from this disease annually (WHO); in the United States, it is the most common malignancy diagnosed in men. With over 175,000 new cases diagnosed annually (Landis et al. 1999), prostate cancer causes a tremendous social and economic burden to patients, their families, and society. Despite the significance of the disease, progress in understanding the molecular determinants of prostate cancer susceptibility is still in the initial stages. Genetic epidemiological studies supporting the existence of hereditary forms of prostate cancer have led to the initiation of genomewide searches for loci contributing to hereditary prostate cancer. A previous genomewide scan for hereditary prostate cancer (HPC) loci in prostate cancer families ascertained at the Johns Hopkins University and Umeå University in Sweden resulted in an indication of a prostate cancer–susceptibility locus at 1q24-25 (*HPC1* [MIM 601518]). The maximum multipoint parametric LOD score was 3.65 at D1S2883 (Smith et al. 1996). There was significant evidence for locus heterogeneity, with an estimate of 34% of the families being linked to *HPC1* (LOD assuming heterogeneity [HLOD] = 5.43 at D1S422). Subsequent stratification analysis revealed that families linked to *HPC1* tended to have an early mean age at diagnosis and a large number of affected family members (Grönberg et al. 1997). The maximum HLOD was 4.88 for 40 families whose members had a mean age at diagnosis of <65 years, but the maximum HLOD was only 0.28 for 39 families whose members had a mean age at diagnosis of ≥65 years. The maxi-

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mum HLOD was 5.45 for 45 families with five or more affected members in a family, but it was only 0.18 and 0.83 for families with three affected members (10 families) and four affected members (24 families), respectively.

Although two subsequent studies have corroborated linkage to *HPC1* (Cooney et al. 1997; Hsieh et al. 1997), three additional studies found no clear evidence for *HPC1*-predisposed disease within their study populations (McIndoe et al. 1997; Berthon et al. 1998; Eeles et al. 1998). Cooney et al. (1997) reported a linkage study of 1q24-25 in 59 families affected by prostate cancer, each with two or more affected individuals. The peak nonparametric linkage (NPL) score was 1.58 at D1S466 ($P = .057$) in the 59 families, but was 1.72 ($P = .045$) in the subset of 20 families that met the criteria for HPC—operationally defined as having three or more affected individuals within one nuclear family, affected individuals in three successive generations, or clustering of two or more individuals affected before age 55 years. Hsieh et al. (1997) reported further evidence to support *HPC1*. In 92 unrelated families with three or more affected individuals, the NPL score was 1.71 ($P = .046$). The evidence for linkage was stronger in the 46 families with mean age at diagnosis of <67 years. The NPL score was 2.04 ($P = .023$). McIndoe et al. (1997) reported no evidence for linkage in this region, in 49 families with a high risk for prostate cancer, either by a parametric LOD score approach assuming homogeneity or by nonparametric analysis. There was also no evidence for linkage in the 18 families whose members had an early mean age at diagnosis (<65 years). Berthon et al. (1998) reported results of a genomewide screen as well as results from the 1q24-25 region in 47 French and German families. For the three markers in the 1q24-25 region, they found negative two-point LOD scores, assuming a dominant model. No results, however, were reported for the families whose members had an early age at diagnosis or a large number of affected individuals. Eeles et al. (1998) reported a linkage study of 1q24-25 in 136 families associated with prostate cancer ascertained in United Kingdom, Quebec, and Texas, 76 of which had three or more affected individuals. They found negative NPL scores in this region in the total sample, but they found positive NPL scores in a subset of 35 families with four or more affected members.

Recently, a prostate cancer–susceptibility gene linked to the Xq27-28 region (*HPCX* [MIM 300147]) was reported in a combined study population of 360 families affected by HPC collected at four different sites in North America, Finland, and Sweden (Xu et al. 1998). The peak two-point LOD score was 4.6 at DXS1113, and the peak multipoint LOD score was 3.85 between DXS1200 and DXS297. Significant evidence for locus heterogeneity was observed. The proportion of families linked to *HPCX* was estimated to be 16% in the combined study population and was similar in each separate family collection. The linkage of a prostate-cancer gene to the X chromosome is consistent with the results of several population-based studies suggesting an X-linked mode of inheritance of prostate cancer (Woolf 1960; Hayes et al. 1995; Monroe et al. 1995; Narod et al. 1995). Although further replication studies in independent populations are warranted, this finding provides a unique tool to facilitate a locus heterogeneity study; that is, families can be stratified into two subgroups before performing linkage analysis, with one group of families being consistent with an X-linked mode of inheritance (without male-to-male disease transmission within a family), and the other group of families with male-to-male disease transmission within a family. By using this approach, evidence for *HPC1* was strengthened in 79 HPC families ascertained at the Johns Hopkins Hospital. The maximum HLOD was 4.27 in 49 families with male-to-male disease transmission but was only 0.43 in 29 families without male-to-male disease transmission (one family's mode of transmission could not be unequivocally classified as male to male).

Further evidence for locus heterogeneity was observed in two other prostate cancer linkage studies. Berthon et al. (1998) reported a linkage (*PCaP* [MIM 602759]) at 1q42-43 in 47 French and German prostate cancer families, and most recently, Gibbs et al. (1999) reported evidence for a third locus on chromosome 1 (1p36 [MIM 603688]) that predisposes its carrier to both prostate and brain cancer.

The observations in all of these studies emphasize the common set of obstacles for linkage detection in HPC—most prominently, a significant degree of locus heterogeneity, a high phenocopy rate, and the late age at onset of the disease. Because of the significant degree of locus heterogeneity, any single HPC locus may be responsible for only a small proportion of families affected by HPC in general, although a single locus may be responsible for a larger proportion of families affected by HPC in different family collections or in defined subsets of a study population or sample. The high age-dependent phenocopy rate in prostate cancer further masks the ability to detect HPC loci. These barriers are compounded by the late age at onset of the disease, making it difficult to ascertain families that may provide information for linkage studies. Therefore, it is difficult to have sufficient power to detect and localize HPC loci in a single data set with a limited number of HPC families. For this reason, the International Consortium for Prostate Cancer Genetics (ICPCG) was formed to establish a larger data set of HPC families. Currently, data from 772 prostate cancer families ascertained from seven countries are available for linkage analysis. This

is a valuable resource for identification and localization of prostate cancer–susceptibility loci.

The present report describes the results of the combined analysis for linkage data on six markers in the 1q24-25 region using the resource of 772 families affected by HPC from ICPCG. Specifically, four questions were addressed: (1) Is there any evidence for linkage between the prostate cancer–susceptibility locus (*HPC1*) and markers at the 1q24-25 region in the overall 772 HPC families? (2) Is the *HPC1* locus more prominent in the subset of families with male-to-male disease transmission? (3) Is the *HPC1* locus more prominent in families with an early mean age at diagnosis (<65 years)? (4) Is the *HPC1* locus more prominent in families with more affected members (five or more)?

Subjects and Methods

Ascertainment of Families

Families with three or more prostate cancer cases (not necessarily all available for genotyping) were eligible for inclusion in this study. Families with fewer than three cases were excluded, as they are more likely to represent chance clustering of the disease and have little power to detect linkage. Families were defined as having male-to-male disease transmission when there was evidence of paternal disease transmission in the families, including the following: (1) presence of affected father and affected son or sons; (2) presence of prostate cancer cases on the paternal side of the family, with no evidence of affected relatives on the maternal side; or (3) presence of prostate cancer cases on the maternal side of the family and male-to-male disease transmission on the maternal side. The remaining families were defined as non–male-to-male disease transmission families. They have either an unknown mode of inheritance (insufficient data to determine inheritance pattern) or are consistent with X-linked mode of inheritance.

The families under study in this report were collected by a variety of research groups in several countries. The ACTANE (Anglo, Canada, Texas, Australia, Norway, EU Biomed) Group, which is a multinational consortium of research groups, has members from the United Kingdom, the state of Texas in the United States, Canada, Norway, and Australia. Families were recruited for study in these regions.

The United Kingdom Group recruited 35 families for study. All families were assessed for inclusion through collaborating urologists, geneticists, or oncologists via the British Prostate Group; 97% of the cases were clinically detected, and the remaining 3% were detected through a prostate specific antigen (PSA) screen. All reports of cancer were confirmed by a histopathology report or by medical records.

The Texas group recruited six families. The probands in these families were patients referred to the University of Texas M. D. Anderson Cancer Center in Houston, and were subsequently diagnosed with prostate cancer.

The Canada group recruited 43 families. Fourteen families were recruited through prostate and hereditary cancer clinics in Montreal; two were recruited from the Prostate Clinic in Halifax, Nova Scotia; and 27 were recruited after an advertisement was placed inviting participation in a prostate cancer–susceptibility gene study in a magazine produced by the Patient Advocates for Advanced Cancer Treatment, a prostate cancer–advocate organization founded in Grand Rapids, MI. In 12 of these families, at least one affected member was assessed by a PSA screen.

The Norway group studied three families. Families were referred to the cancer genetics clinic at the Norwegian Radium Hospital because of their high incidence of prostate cancer. All cases of prostate cancer were clinical presentations.

The Australia group studied 13 families. These families were recruited from the Risk Factors for Prostate Cancer study, a population-based, case-control study of 1,600 cases and controls conducted in Melbourne, Sydney, and Perth. Probands were aged 40–69 years and reported a family history of prostate cancer.

The BC/CA/HI resource consists of 97 unrelated families in British Columbia, California, and Hawaii containing three or more medically verified diagnoses of prostate cancer in first- or second-degree relatives. Eighty-two of these families fulfilled one or more of the proposed criteria for families whose prostate cancer is likely to be hereditary (i.e., three or more affected individuals within one nuclear family; affected individuals in three successive generations; or two or more individuals affected before age 55 years). Seven families were African-American, four were Japanese-American, and three were Chinese-American. The families were identified from several sources (described by Hsieh et al. 1997). The mean number per family of affected and genotyped individuals was 2.6 (range 2–5), and the mean age at diagnosis of all affected individuals was 66.9 years (67.0 years in white families, 64.1 years in African-American families, and 69.2 years in Asian-American families).

The 150 families in the Fred Hutchinson Family Collection analysis are participating in the Prostate Cancer Genetic Research Study (PROGRESS) and met at least one of three criteria: three or more first-degree relatives with prostate cancer, three generations with prostate cancer, or two affected siblings with prostate cancer diagnosed at ⩽60 years of age. PROGRESS is based in Seattle, was initiated in 1995, has participants from North American and several other countries, and has ascertained eligible families through national media for

Table 1

Markers Used in the Combined Analysis

Marker	Heterozygosity	Estimated Distance from pter (cM)
D1S452	.75	187.5
D1S212	.80	194.9
D1S466	.77	200.7
D1S158	.89	202.8
D1S422	.76	206.6
D1S413	.76	211.8

NOTE.—The marker order and distances were estimated from 121 HPC families ascertained at Johns Hopkins, and they are consistent with the LDB map (Collins et al. 1996) and the Marshfield map.

self-referrals and through communication with urologists, prostate cancer support groups, and health-related publications. Medical records received for 95% of the genotyped affected men in these families confirm the diagnosis in all but one man.

In the Johns Hopkins Family Collection, 101 families affected by HPC were ascertained and genotyped for the *HPC1* analysis. The first 79 families with HPC were included in the initial *HPC1* report and thus are not included in the current replication study (Smith et al. 1996). The remaining 22 families with HPC were included. Families were ascertained at the Brady Urology Institute at Johns Hopkins Hospital, Baltimore, MD. A majority of these families were ascertained through referrals from physicians; some families were recruited from earlier epidemiological studies (Carter et al. 1992) and through news articles. Age at diagnosis of prostate cancer was confirmed either through medical records or from two other independent sources. All individuals in this study gave full informed consent.

The 159 North American families in the Mayo Clinic Family Collection were ascertained by a cancer family-history survey sent to >5,000 men who underwent a radical prostatectomy for clinically localized prostate cancer in the Department of Urology at the Mayo Clinic during 1966–1995. Further results are provided elsewhere (Schaid et al. 1998). Prostate cancer diagnosis and the age of its occurrence was confirmed through medical records at the Mayo Clinic and elsewhere.

The 56 families reported by the Michigan Family Collection are participants in the University of Michigan Prostate Cancer Genetics Study, which was established to define the molecular determinants of inherited prostate cancer susceptibility. Collection strategy and *HPC1* linkage results for a subset of these families (26 of 56) have been previously reported (Cooney et al. 1997). Written consent was obtained from all participants, and research protocols were approved by the Institutional Review Board at the University of Michigan. The diagnosis of prostate cancer was confirmed, in all men that were available for genotyping, by review of pathology reports and medical records. For the affected men who were unavailable for genotyping, the diagnosis of prostate cancer was confirmed by medical records or by two independent family members.

In Finland, 302 families linked to prostate cancer with two or more affected family members of the Tampere Family Collection were identified through referrals from physicians; family questionnaires sent to patients; a nationwide registry-based search; and advertisements in newspapers, radio, and television. Of this group, 32 families that met the criteria of HPC and provided information for linkage analyses were included in this study. Diagnosis of all prostate cancer patients was confirmed through hospital records or from the Finnish Cancer Registry. All individuals participating in this study gave full informed consent.

Since 1995, families with three or more relatives affected with prostate cancer have been collected at the Department of Oncology of Umeå University, Sweden, in their Umeå Family Collection, mainly from referrals from urologists throughout the country. From ~300 referrals, 40 families that provide information for linkage analysis have been selected. Twelve of these families were included in the initial report and thus were not included in the current study (Smith et al. 1996). The remaining 28 HPC families were included. If blood samples were unavailable, tissue samples were collected from affected men whenever possible. Tissue samples were reviewed by an experienced pathologist, and microdissection was performed to separate normal and tumor tissue. For genotyping, only normal tissue was used. All prostate cancer diagnoses in the families were confirmed by the National Cancer Registry and medical records.

The Utah pedigrees that make up the Utah Family Collection were ascertained from the Utah Population Database, which combines a genealogy containing approximately eight generations of Utah pioneers and their descendants with a cancer registry containing ~30 years of complete cancer registration for the state of Utah (Skolnick et al. 1979). Approximately 298 families have been ascertained by observation of a significant excess of prostate cancer cases among descendants of a single founder, with no age-at-diagnosis criteria. Of these, genotyping has been completed on ~100 pedigrees. Because the Utah pedigrees are considerably larger than those submitted by the rest of the Consortium, they were split into independent subpedigrees having at least three prostate cancer cases and small enough to be analyzed by GENEHUNTER (Kruglyak et al. 1996), the analysis tool that had been chosen for the consortium data set. We used an algorithm to split pedigrees; the algorithm ascends three generations from affected individuals at

Table 2

Genetic Models Used in the Parametric Linkage Analysis

Model[a] and Liability Class	Penetrance			Description
	dd	Dd	DD	
A:				
1	.001	1	1	All affected men
2	.5	.5	.5	Unaffected men aged <75 years and all women
3	.84	.37	.37	Unaffected men aged ⩾75 years
B:				
1	.00038	.0018	.0018	Affected men aged ⩽49 years at diagnosis
2	.00061	.0084	.0084	Affected men aged 50–59 years at diagnosis
3	.0032	.03	.03	Affected men aged 60–69 years at diagnosis
4	.0082	.04	.04	Affected men aged 70–79 years at diagnosis
5	.0086	.015	.015	Affected men aged ⩾80 years at diagnosis
6	.99981	.9908	.9908	Unaffected men aged ⩽49 years
7	.9968	.94	.94	Unaffected men aged 50–59 years
8	.978	.75	.75	Unaffected men aged 60–69 years
9	.921	.39	.39	Unaffected men aged 70–74 years
10	.84	.12	.12	Unaffected men aged ⩾75 years
11	.5	.5	.5	Unknown and all women

[a] For both model A and model B, disease-gene frequency f_D = .003.

the bottom of the pedigree. Subpedigrees that were small enough to be analyzed by GENEHUNTER were then selected from this set. We thus created a total of 128 subpedigrees from the 81 complete pedigrees that yielded at least one subpedigree.

Genotyping and Markers

The core markers utilized in the study are listed in table 1. When one of the core markers was not available in an individual family collection, two alternative approaches were used in the analysis. First, a substitute marker was used if there was a marker within 2 cM of the missing core marker in that family collection. Second, a missing data point was assumed when there was no marker data available near the missing core marker. Although these two approaches may have had some impact on the linkage results, we believe the impact will have been small, since all the analyses were multipoint and since we are, in essence, studying the linkage curves (LOD and NPL) of each family in this chromosomal region, not the marker per se.

Analytical Methods

The linkage analyses were performed by both parametric and nonparametric approaches, with analyses implemented by the computer software package GENEHUNTER (Kruglyak et al. 1996). Two genetic models describing the inheritance of a prostate cancer–susceptibility gene were used in the parametric analyses (table 2). Both models assumed an autosomal dominant disease allele with an allele frequency of .003. The first (model A) was the same model used by Smith et al. (1996) in analysis in which the *HPC1* was initially mapped. In this model, affected men were assumed to be carriers of a rare autosomal dominant gene with a fixed 15% phenocopy rate, whereas all unaffected men aged <75 years and all women were assumed to be of an unknown phenotype. In men over age 75 years, the lifetime penetrance of gene carriers was estimated to be 63%, and the lifetime risk of prostate cancer for noncarriers was 16% in this age class. The second model (model B) assumed variable penetrances and phenocopy rates for different age groups. The age- and genotype-specific penetrances for the 11 liability classes were derived from complex segregation analysis (Carter et al. 1992) and surveillance, epidemiology, and end results (SEER) in a fashion similar to the method used by the Breast Cancer Linkage Consortium (Easton et al. 1993).

HLOD scores were calculated by the admixture test (Ott 1991). In this model, two types of families are assumed, one type linked to the disease locus, with a proportion of α, and the other type not linked, with the proportion $1-\alpha$. A maximum-likelihood approach was used to estimate the proportion of linked families (α) by maximizing HLOD. The 1-LOD support interval of the maximized α was determined as the range of α values that gave likelihoods within 1 LOD unit of the maximized α. This approach does not accommodate the possibility that multiple prostate cancers in some members of the families may have occurred by chance, and, therefore, estimates of α are crude approximations.

The NPL was calculated on the basis of observed and expected identical-by-descent allele sharing among affected relative pairs. Families were weighted equally, and the score function "all" was used (Whittemore and Halpern 1994).

A multipoint approach was applied in the analyses to increase the information content of the markers in HPC families and to decrease the impact of misspecification of marker allele frequencies on the linkage results. This is necessary because the genotype data of the parental generation are usually not available. A multipoint approach is also the method of choice because not all the genotyped groups had the same core markers, although replaced markers are, in general, in the vicinity of the core markers. It is inappropriate to add a two-point LOD score from each family when different markers are used; however, it is less problematic to add the LOD score curve of the same chromosomal region from each family. The misspecification of the intermarker distances may affect the linkage results, but the impact is small in this situation because the marker distances are relatively large (the range of intermarker recombination fractions is .03–.08). Marker allele frequencies were calculated by each research group on the basis of their own family data, using the information from pedigree founders only.

The combined analysis was implemented by combining intermediate results by pedigree from each research group. Each research group analyzed data from their study families by use of the same procedure, intermarker distances, software package, and options as described above. They then submitted the LOD scores and NPL scores by pedigree, as well as the characteristics (male-to-male transmission, mean age at diagnosis, number of affected members in a family) of each pedigree to the coordinating center. For the parametric analyses, the computer program HOMOG (Ott 1991) was used to calculate HLOD scores. For the nonparametric method, the overall NPL scores were calculated by the sum of each individual pedigree NPL score divided by the square root of the total number of families. To ensure uniformity of the analysis in each group, a test file was distributed, and the results were checked among the research groups where the same results required the exact procedure in coding liability classes and in running the program.

LOD scores assuming heterogeneity can be converted to a χ^2 ($\chi^2 = 4.6 \times$ HLOD). Although the true distribution of the χ^2 value under the null hypothesis of no linkage is unknown, especially in the situation of multipoint analysis, we assume that the distribution is a mixture of one that is degenerate at zero and one that can be approximated by the distribution of the maximum of two independent χ^2 variables, each with 1 degree of freedom (Faraway 1993). *P* values were thus calculated by $.5 \times [1 - (1 - P_1)(1 - P_1)]$, where P_1 is the *P* value of χ^2 with 1 df.

When evidence for linkage was observed in the whole sample, likelihood-ratio tests were performed to test the hypotheses of different values of α among subsets of families (i.e., among families with or without male-to-male transmission, among families with five or more or four or fewer affected members, and among families with mean age at diagnosis <65 or ⩾65 years). To increase the power of detecting the difference, the recombination fraction was restricted to be the same for both subsets, which is the maximum-likelihood estimate of the recombination fraction in the whole sample. A $\chi^2 = 4.6 \times (HLOD_1 + HLOD_2 - HLOD_{total})$ is calculated that has 1 df, where $HLOD_1$, $HLOD_2$, and $HLOD_{total}$ are the HLODs for the first and second subsets of families and the whole sample, respectively.

Results and Discussion

Characterization of Families with ICPCG

A summary of the features of the 772 families studied is presented in table 3. Some of these families have been included in previous publications by the members of the ICPCG. Of the 100 families from the ACTANE Group, 76 were included in the study by Eeles et al. (1998). Of the 97 families from the BC/CA/HI Group, 92 were included in the study by Hsieh et al. (1997). Of the 150 families from the Fred Hutchinson Group, 49 were included in the study of McIndoe et al. (1997). Of the 56 families from the Michigan Group, 20 were included in the study of Cooney et al. (1997). All 28 families from the Umeå Group were included in the linkage report by Grönberg et al. (1999). The rest of the families—507 of 772—have not been reported in previous linkage studies for the 1q24-25 region.

These 772 families contain an average of 4.2 affected individuals diagnosed at an average age of 66.8 years. Of the families, >20% had five or more affected individuals, and ~33% had an average age at diagnosis <65 years. Sixty-four percent of the families showed evidence of male-to-male disease transmission.

Linkage of the HPC1 Locus and Markers at 1q24-25

Multipoint HLOD scores and maximum-likelihood estimates α for the six markers in each family collection and in the combined sample of 772 families are shown in table 4. Two groups had HLOD values >1; the rest of the seven groups provided little evidence for linkage. However, there is some evidence for linkage in the combined sample. The peak HLOD was 1.4 at D1S212 ($P = .01$), with an estimated proportion of linked families $\alpha = .06$ (1-LOD support interval .01–.12). These results provided a weak confirmation for the linkage between the *HPC1* locus and markers at 1q24-25 region in a subset of the HPC families. The estimated proportion of families linked to *HPC1* in this set of families was much lower than the initial estimate of $\alpha = .34$ (Smith et al. 1996).

It is worth noting that there are 21 African American

Table 3

Characteristics of HPC Families in the ICPCG Combined Analysis

Group	Total No. of Pedigrees	Total No. of Individuals	Pedigrees with Male-to-Male Transmission		No. of Affected Family Members		Pedigrees with ⩾5 Affected Family Members		Age at Diagnosis		Pedigrees with Age at Diagnosis <65 Years		Pedigrees Meeting All Three Criteria[a]	
			No.	%	Range	Mean	No.	%	Range	Mean	No.	%	No.	%
ACTANE	100	948	64	64.0	3–9	3.7	18	18.0	52.7–78.7	67.1	31	31.0	2	2.0
BC/CA/HI	97	748	41	42.3	3–6	3.3	7	7.2	53.7–80.3	66.9	37	38.1	2	2.0
Fred Hutchinson	150	2,174	83	55.3	3–10	4.3	47	31.3	50.8–78.0	65.9	56	37.3	15	10.0
Johns Hopkins	22	206	15	68.2	3–17	5.5	13	59.1	52.2–75.0	65.8	8	36.4	4	18.2
Mayo	159	1,141	113	71.1	3–11	4.4	56	35.2	47.3–76.8	66.3	62	39.0	17	10.7
Michigan	56	360	28	50.0	3–9	3.4	4	7.1	51.0–77.5	64.5	29	51.8	2	3.6
Tampere	32	1,091	13	40.6	3–6	3.6	4	12.5	58.5–77.7	68.2	8	25.0	1	3.1
Umeå	28	366	23	82.1	3–10	4.1	6	21.4	57.6–74.5	67.4	9	32.1	1	3.6
Utah	128	2,173	111	86.7	3–8	3.8	19	14.8	54.0–77.3	68.8	23	18.0	4	3.1
Total	772	9,207	491	63.6	3–17	4.2	174	22.5	47.3–80.3	66.8	263	34.1	48	6.2

[a] The three criteria are male-to-male transmission, age at diagnosis of <65 years, and ⩾5 affected individuals per family.

families in the total 772 families (2.7%). The peak HLOD for these families was 0.61 (α = .39 at D1S413). The overall HLOD was unchanged when these families were omitted from the analysis—that is, for the remaining 751 families, the peak HLOD was 1.38 (α = .06 at D1S212). We intend to further investigate the HPC1 linkage in African American families when additional families become available.

Linkage in Families and Male-to-Male Disease Transmission

The 772 families with HPC were stratified into families with male-to-male disease transmission (n = 491), and families without evidence for male-to-male disease transmission (n = 281). Parametric multipoint linkage analyses were performed by using model A (table 5). For the families with male-to-male disease transmission, the peak HLOD was 2.56 at D1S212 (P = .0006), with α = .11 (1-LOD support interval .04–.19). By contrast, families without male-to-male disease transmission did not provide any evidence for linkage. The HLODs were 0 (α = 0) for all six markers. The difference in α between the two subsets of families was statistically significant (χ^2 = 4.51, P = .03). To exclude possible confounding factors leading to the negative *HPC1* finding in the families without male-to-male disease transmission, these families were stratified by mean age at diagnosis (<65 or ⩾65 years) and the number of affected family members (four or fewer and five or more). No evidence for linkage was observed in any of these groups. The stronger evidence for linkage of the *HPC1* locus and markers at 1q24-25 in the families with male-to-male disease transmission is consistent with the initial finding in the 79 HPC families ascertained at Johns Hopkins (Xu et al. 1998).

Presumably the increased evidence for linkage in this group reflects several factors: first, there is an enrichment in families having an autosomal dominant mode of inheritance, as opposed to X-chromosome or recessive linkage; and, second, families with male-to-male transmission by definition have affected individuals in more than one generation, possibly reducing the number of families in which the disease clustering is due to nongenetic mechanisms (e.g., shared environment) or more complex genetic mechanisms.

Linkage in Family Members with Early and Late Mean Age at Diagnosis

The 772 HPC families were stratified into 263 families that had members with an early mean age at diagnosis (<65 years) and 509 families with members that had a late mean age at diagnosis (⩾65 years). Parametric multipoint linkage analyses were performed by using model A (table 5). Families that had members with an early mean age at diagnosis had a peak HLOD of 1.32 at *D1S212* (P = .01), with α = .11 (1-LOD support interval .02–.22). Families that had members with a later age at diagnosis had a peak HLOD of 0.39 at the same marker (P = .16), with α = .04 (1-LOD support interval .01–.12). The difference in the α values between the two subsets of families, however, was not statistically significant (χ^2 = 1.43, P = .23). When the stratified analysis was limited to the 491 HPC families with male-to-male disease transmission, the 161 families that had members with an early mean age at diagnosis had a peak HLOD of 2.28 at D1S212 (P = .001), with α = .19 (1-LOD support interval .06–.34), whereas the 330 families that had members with a late mean age at diagnosis had a maximized HLOD of 0.79 at D1S212 (P = .05), with α = .07 (1-LOD support interval .01–.16). The difference in

Table 4

Parametric Multipoint Analysis (LOD Assuming Heterogeneity, Model A)

	D1S452		D1S212		D1S466		D1S158		D1S422		D1S413	
GROUP (NO. OF FAMILIES)	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α
ACTANE (100)	.03	.06	.05	.05	.03	.05	.03	.04	.06	.06	.01	.03
BC/CA/HI (97)	.28	.10	.16	.07	.00	.00	.00	.00	.00	.00	.00	.00
Fred Hutchinson (150)	.00	.00	.01	.01	.08	.04	.05	.03	.00	.00	.00	.00
Johns Hopkins (22)	.00	.00	.35	.20	.4	.20	1.19	.32	1.16	.31	1.1	.32
Mayo (159)	.12	.04	.12	.04	.15	.20	.01	.01	.09	.03	.29	.07
Michigan (56)	.07	.09	.1	.09	.19	.12	.12	.09	.06	.07	.10	.10
Tempere (32)	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
Umeå (28)	.03	.07	.12	.14	.20	.17	.37	.21	.22	.17	.15	.16
Utah (128)	1.55	.15	1.32	.13	.88	.11	.56	.08	.06	.06	.02	.01
Combined (772)	1.00	.06	1.40	.06	.76	.05	.41	.03	.25	.03	.34	.03

the α values between the two subsets of families was not statistically significant ($\chi^2 = 2.35$, $P = .12$). These results suggest a trend: families affected by HPC with members that have an early age at diagnosis, especially in the families with male-to-male disease transmission, are more likely to be linked to *HPC1* than are families not meeting these criteria. This effect of age at diagnosis is consistent with earlier findings by Grönberg et al. (1997).

Age at diagnosis for prostate cancer is a problematic variable in that, in some cases, it is strongly related to age at first screening for the disease, particularly since the widespread use of PSA began over a decade ago (at least in North America). As the populations studied here vary widely with respect to frequency of disease screening and testing by PSA, age at diagnosis is an inconsistent indicator of age at onset. For this reason, until a more standardized approach is implemented, the impact of age at diagnosis on the linkage result across different study populations is difficult to fully evaluate.

Effect of Number of Affected Individuals in Families

The 772 HPC families were stratified into 174 families with five or more affected family members and 598 families with four or fewer affected family members. Parametric multipoint linkage analyses were performed by using model A (table 5). Families with five or more affected family members had a peak HLOD of 1.11 at D1S212 ($P = .02$), with $\alpha = .09$ (1-LOD support interval .01–.21). Families with four or fewer affected family members had a peak HLOD of 0.42 at the same marker ($P = .15$), with $\alpha = .05$ (1-LOD support interval .01–.13). The difference in the α values between the two subsets of families, however, was not statistically significant ($\chi^2 = .60$, $P = .44$). When the stratified analysis was limited to the 491 families with male-to-male disease transmission, the 141 families with five or more affected family members had a peak HLOD of 2.01 at D1S212 ($P = .002$), with $\alpha = .15$ (1-LOD support interval .04–.28), whereas 350 families with four or fewer affected family members had a maximized HLOD of 0.71 at D1S212 ($P = .07$), with $\alpha = .08$ (1-LOD support interval .01–.19). These results suggest the trend that a higher proportion of HPC families are linked to 1q24-25 when the families have more affected members, especially in families with male-to-male disease transmission. The finding of an effect of number of affected individuals within a family is consistent with the earlier findings by Grönberg et al. (1997).

Evidence of the HPC1 Locus and Estimate of Families Linked to the HPC1 Locus in All Available HPC Families

Since the above results provided some confirmation for the *HPC1* linkage, it was of interest to estimate the overall evidence for the *HPC1* locus and the proportion of the families linked to the *HPC1* locus for all available families. This was done by combining the current 772 HPC families with the previous 79 HPC families ascertained at Johns Hopkins University and 12 HPC families from Sweden. Among all 863 HPC families available for study, there was strong evidence for linkage in the 1q24-25 region; the peak HLOD was 4.3 at D1S212 ($P = 8.59 \times 10^{-6}$), with $\alpha = .09$ (1-LOD support interval .05–.15) (table 6). The evidence for linkage was greater in the following subsets of families: the 550 families with male-to-male disease transmission (peak HLOD = 5.65, $P = 3.38 \times 10^{-7}$, $\alpha = .14$, 1-LOD support interval .07–.21); the 306 families with early mean age (<65 years) at diagnosis (peak HLOD = 5.23, $P = 9.22 \times 10^{-7}$, $\alpha = .18$, 1-LOD support interval .09–.28); and the 224 families with five or more affected family members (peak HLOD = 3.6, $P = 4.67 \times 10^{-5}$, $\alpha = .12$, 1-LOD support interval .05–.22). There were statistical differences in the proportions of families linked to *HPC1* between the 550 families with male-to-male disease transmission and the remaining 313 families ($\chi^2 = 6.21$, $P = .01$); between the 306 families with early mean age at diagnosis and 557 families with late mean age at diagnosis ($\chi^2 = 6.30$, $P = .01$). There was no statistical difference, however,

Table 5

Parametric Multipoint Analysis

Group (No. of Families)	D1S452		D1S212		D1S466		D1S158		D1S422		D1S413	
	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α
Male-to-male transmission (491)	2.24	.11	2.56	.11	2.24	.11	1.81	.09	1.4	.08	1.45	.09
Non–male-to-male transmission (281)	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
Age at diagnosis <65 years (263)	.72	.09	1.32	.11	.59	.07	.14	.03	.09	.03	.21	.03
Age at diagnosis ≥65 years (509)	.39	.04	.39	.04	.25	.03	.27	.03	.15	.03	.15	.03
≥5 affected family members per family (174)	.78	.08	1.11	.09	.87	.08	.66	.07	.48	.06	.92	.10
≤4 affected members per family (598)	.34	.05	.42	.05	.11	.02	.02	.01	0	.00	0	.00
Male-to-male transmission:												
Age at diagnosis <65 years (161)	1.27	.16	2.28	.19	1.22	.13	.45	.07	.68	.08	.5	.09
Age at diagnosis ≥65 (330)	1.08	.09	.79	.07	1.08	.09	1.39	.10	.9	.08	.96	.09
≥5 affected family members (141)	1.35	.13	2.01	.15	1.68	.14	1.25	.11	.9	.10	1.49	.14
≤4 affected family members (350)	.91	.10	.71	.08	.68	.08	.61	.07	.53	.07	.24	.05

between 224 families with five or more affected members and 639 families with four or fewer affected members ($\chi^2 = 1.10$, $P = .29$). The evidence for linkage was strongest for the 66 families that met all three criteria: male-to-male disease transmission, early mean age at diagnosis, and five or more affected family members. For this group, the peak HLOD was 7.01 at D1S212 ($P = 3.31 \times 10^{-9}$, $\alpha = .39$, 1-LOD support interval .08–.53). Of these 66 families, 48 were from the current combined analysis. For these 48 families, a peak HLOD of 2.25 was observed at the same marker ($P = .001$), with $\alpha = .29$ (1-LOD support interval .08–.53).

These results suggest an important role for *HPC1* only in a relatively small, highly defined subset of all families affected by HPC. To put this result in perspective, it is interesting to examine the results of previous linkage analyses for another common cancer, breast cancer. In the analyses performed by the Breast Cancer Consortium (Easton et al. 1993), it is clear that the primary evidence of linkage to *BRCA1,* although much greater overall than that observed for *HPC1,* was restricted to two main subsets of families: (1) those with breast and ovarian cancer, and (2) among breast-cancer-only families, those with large numbers of affected individuals diagnosed at an early age. Breast-cancer-only families with average ages of diagnoses >45 years or with fewer than four affected individuals contributed little evidence of linkage to *BRCA1*.

It is worth noting the large difference in the evidence for *HPC1* linkage between the data from the current combined analysis and the data from Smith et al. (1996). The peak multipoint HLOD in the current combined analysis of 772 HPC families was 1.4, whereas the peak HLOD (using the same model) in the study of Smith et al. (91 HPC families) was 3.65. Even in the families that met all three criteria (male-to-male disease transmission, early mean age at diagnosis [<65 years], and five or more affected family members), the 48 families with HPC from the current study only had a peak HLOD of 2.25, whereas the 18 such families from Smith et al. (1996) had a peak HLOD of 5.53. Although this is most likely attributable to numerous factors, differences in the characteristics of the families in the two studies may be important. In the study by Smith et al., there was a higher proportion of families with more than four affected members or with a mean age at diagnosis of <65 years (57.0% or 50.6%, respectively) than in the current study (22.5% or 34.1%, respectively). Within the subgroup of families with an average age of diagnosis of <65 years, five or more affected members, and male-to-male transmission, there were differences in power and informativity; for example, there was a higher average number of affected individuals genotyped in the group of 18 families from the study by Smith et al. versus the 48 families from this combined analysis (3.8 vs. 3.3, respectively), and the highest LOD scores observed in each group varied considerably (2.61 vs. 1.20, respectively). Other explanations for differences between the studies might include differential use of PSA screening within the study populations, which, in turn, could affect the age at diagnosis and possibly the phenocopy rate. Furthermore, the random variation of the proportions of linked families in different study populations may contribute to the difference. It is possible that in the initial linkage study, the linked families were overrepresented by chance, which led to the initial finding of linkage. Overrepresentation of linked families, however, does not happen often in replication studies by the trend of regression to the mean.

Results of Parametric Multipoint Linkage Analyses, by Use of Model B

Parametric multipoint linkage analyses by model B were performed by the same procedure as that for model A. Results for model B are summarized in table 7. In general, the results were similar to those for model A, although the LOD scores were always lower and the α

Table 6

Parametric Multipoint Analysis in 772 Combined ICPCG and 91 Johns Hopkins University and Swedish Families Affected by HPC

	D1S452		D1S212		D1S466		D1S158		D1S422		D1S413	
GROUP (NO. OF FAMILIES)	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α
All (863):	2.98	.08	4.3	.09	3.41	.08	2.81	.07	2.57	.06	1.56	.07
Male-to-male transmission (550)	4.51	.13	5.65	.14	5.2	.13	4.78	.12	4.1	.11	2.78	.12
Age at diagnosis <65 years (306)	3.51	.15	5.23	.18	3.93	.14	3.03	.11	3.09	.12	2.06	.13
⩾5 affected members per family (224)	2.69	.11	3.6	.12	3.28	.11	3.11	.11	2.91	.11	1.94	.12
Families with all three criteria:												
Current combined analysis (48)	1.29	.23	2.25	.29	1.09	.20	.15	.06	.21	.08	.24	.09
Smith et al. 1996 (18)	5.22	.61	5.23	.58	4.88	.52	5.53	.59	5.14	.58	2.76	.56
Total (66)	5.72	.37	7.01	.39	5.33	.31	3.85	.24	3.89	.26	1.91	.22

value was always higher than those for model A. These differences may be explained by the genotypic penetrances specified in the two models. The penetrance values specified by model A were such that affected individuals had a very high probability of being gene carriers (penetrance ratios of gene carriers to noncarriers were high); thus, they are very informative for linkage. This does not seem to represent families with HPC in general but may represent a subset of HPC families, which is certainly appropriate when combined with the assumption of heterogeneity. The penetrance ratios between gene carriers and noncarriers specified in model B were lower; thus, affected individuals are not very informative. This causes the LOD score to approach 0. Another explanation for the lower LOD scores for model B could be model misspecification. If model A were closer to truth than model B is, then model B would overestimate the recombination fraction, which decreases the LOD score. Also, since the recombination fraction and α are positively correlated, an increased estimate of recombination fraction would cause the α value to be increased.

Results of Nonparametric Multipoint Linkage Analyses

Nonparametric analyses were performed in parallel to the parametric analyses. Results are shown in table 8. There was no evidence for linkage of a prostate cancer–susceptibility locus to the 1q24-25 region in the combined 772 HPC families; the NPL scores were negative for all six markers. The NPL scores were negative in general in all the stratified analyses, except in the subset of 491 families with evidence for male-to-male disease transmission (NPL = 0.32 at D1S452) and in the 48 families that met all three criteria: male-to-male disease transmission, mean age at diagnosis <65 years, and five or more affected family members (NPL = 0.14 at D1S452). There are two possible explanations for the difference between the parametric and nonparametric analyses. First, the NPL scores were calculated by weighting each family equally, regardless of the size (number of informative meioses) of the families. Second, and perhaps more important, nonparametric analyses in general have lower power (compared with the parametric analyses) to detect linkage when the model of the

Table 7

Parametric Multipoint Analysis (LOD Assuming Heterogeneity, Model B)

	D1S452		D1S212		D1S466		D1S158		D1S422		D1S413	
STRATIFICATION (NO. OF FAMILIES)	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α	HLOD	α
All (772)	.31	.08	.50	.10	.39	.09	.17	.05	.17	.06	.39	.10
Male-to-male transmission (491)	.84	.17	1.50	.22	1.61	.23	1.02	.17	.54	.13	.83	.18
Non–male-to-male transmission (281)	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
Onset at age <65 years (263)	.31	.17	.50	.16	.39	.06	.17	.00	.17	.00	.39	.05
Onset at age ⩾65 years (509)	.00	.00	.04	.04	.33	.11	.44	.12	.06	.16	.43	.14
⩾5 affected family members (274)	.44	.16	.90	.22	1.26	.26	.93	.21	.45	.15	.54	.19
⩽4 affected family members (598)	.02	.03	.02	.02	.00	.00	.00	.00	.00	.00	.03	.04
Male-to-male transmission, age at onset <65 years (161)	.84	.23	.92	.23	.23	.12	.00	.01	.00	.00	.04	.06
Male-to-male transmission, ⩾5 affected family members (141)	.61	.20	1.33	.30	1.82	.35	1.31	.28	.70	.22	.90	.27
Male-to-male transmission, age at onset <65 years, ⩾5 affected family members (48)	.52	.25	.86	.33	.41	.22	.02	.05	.00	.01	.03	.06

Table 8

Nonparametric Multipoint Linkage Analysis (NPL Scores)

Stratification (No. of Families)	NPL Scores at Marker					
	D1S452	D1S212	D1S466	D1S158	D1S422	D1S413
All (772)	−1.06	−1.57	−1.83	−2.68	−1.85	−1.12
Male-to-male transmission* (491)	.32	−.15	−.19	−.95	−.23	.05
Non–male-to-male transmission (281)	−2.18	−2.40	−2.78	−3.19	−2.76	−1.93
Age at onset <65 years (263)	−.87	−1.33	−1.57	−2.28	−1.73	−1.13
Age at onset ⩾65 years (509)	−.68	−.98	−1.13	−1.66	−1.04	−.57
⩾5 affected family members (274)	−.90	−1.90	−1.40	−1.81	−.93	−.60
⩽4 affected family members (598)	−.72	−.76	−1.33	−2.07	−1.60	−.95
Male-to-male transmission, age at onset <65 years (161)	−.07	−.27	−.49	−.98	−.50	−.44
Male-to-male transmission, ⩾5 affected family members (141)	−.13	−.80	−.49	−1.03	−.40	.08
Male-to-male transmission, age at onset <65 years, ⩾5 affected family members (48)	.14	−.10	−.51	−1.52	−.82	−.86

disease transmission is approximately correct (Greenberg et al. 1998). (Importantly, on the basis of theoretical and simulation studies [Hodge and Elston 1994; Greenberg et al. 1998], the use of an incorrectly specified model in the parametric analyses will not increase the false-positive rate as long as marker allele frequencies are correctly specified.) Additionally, analyses assuming heterogeneity can be readily implemented in the parametric analysis, which greatly increases the power to detect linkage when there is a substantial degree of heterogeneity. Nonparametric analyses, however, do not have this property. An examination of the LOD scores and the NPL scores for each family in the group of 48 families that met all three criteria illustrates this point. In this group, 21 families had positive LOD scores; all but one of these 21 also had a positive NPL score (the remaining family had a NPL score of -0.06). Similarly, among the remaining 27 families with negative LOD scores, all but two had negative NPL scores. Thus, both approaches would seem to provide similar evidence for linkage. In spite of this concordance for the individual families, the summary statistics gave rather distinct results: an HLOD of 2.25 and a NPL score of −.10 in this group. It is worth noting that the summary LOD score assuming homogeneity is highly negative (−16.41) for this group, which is not surprising, since there is still a significant proportion of heterogeneity even in this subset. This further emphasizes the need to perform the analysis assuming heterogeneity.

Summary and Conclusion

Overall weak evidence of linkage to *HPC1* was observed in a combined international study population of 772 HPC families, with the estimated proportion of linked families being 6%. Stronger evidence of linkage was observed in subsets of families, varying by the presence or absence of apparent male-to-male disease transmission, mean age at diagnosis, and number of affected individuals. We did not correct *P* values for having multiple tests (two genetic models and multiple stratification of the data set) in reporting the significance levels of the linkage results for the following two reasons. First, the current analysis is a replication study; we primarily used the same genetic model (model A) and the same stratification as implemented in the initial studies. Second, the two models are related and thus are not independent. In fact, these two models are very similar: both assume a dominant mode of inheritance and a rare disease allele. We applied model B in this analysis mainly to investigate the impact of a more general model (estimates from segregation analyses) on the LOD scores. As expected, this model is less informative because it allows higher phenocopy rates and lower penetrances.

Although these data support the linkage to *HPC1*, this study indicates that most HPC families will not provide evidence for this locus. Further, it suggests that efforts for gene identification should focus on the restricted subset of HPC families characterized by male-to-male disease transmission and by large numbers of affected individuals with an early age at diagnosis. This international study suggests that such families represent only ~8% of families associated with multiplex prostate cancer.

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Electronic-Database Information

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

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for HPC1 [MIM 601518], HPCX [MIM 300147], PCaP [MIM 602759], and 1p36 [MIM 603688])

World Health Organization World Health Report (WHO), http://www.who.org/whr/1999

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