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A Genomic Scan of Families with Prostate Cancer Identifies Multiple Regions of Interest

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A 10-cM genomewide scan of 94 families with hereditary prostate cancer, including 432 affected men, was used to identify regions of putative prostate cancer–susceptibility loci. There was an average of 3.6 affected, genotyped men per family, and an overall mean age at diagnosis of 65.4 years. A total of 50 families were classified as early onset (mean age at diagnosis <66 years), and 44 families were classified as later onset (mean age at diagnosis ⩾66 years). When the entire data set is considered, regions of interest (LOD score ⩾1.5) were identified on chromosomes 10, 12, and 14, with a dominant model of inheritance. Under a recessive model LOD scores ⩾1.5 were found on chromosomes 1, 8, 10, and 16. Stratification by age at diagnosis highlighted a putative susceptibility locus on chromosome 11, among the later-onset families, with a LOD score of 3.02 (recombination fraction 0) at marker ATA34E08. Overall, this genomic scan suggests that there are multiple prostate cancer loci responsible for the hereditary form of this common and complex disease and that stratification by a variety of factors will be required for identification of all relevant genes.

Introduction

Prostate cancer is the most common solid tumor and the second leading cause of cancer deaths among men in the United States. In 2000, ~180,400 men will be diagnosed with prostate cancer, and 31,900 will die of the disease (Greenlee et al. 2000). Case-control, cohort, and twin studies (Steinberg et al. 1990; Grönberg et al. 1994, 1996; Whittemore et al. 1995; Page et al. 1997), as well as segregation analyses (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998), all suggest strong evidence for prostate cancer–susceptibility genes in the population. Although data from two studies are most consistent with an X-linked or recessive model of inheritance (Monroe et al. 1995; Narod et al. 1995), three independent segregation analyses (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998) support an autosomal dominant model of inheritance. Dominant alleles are estimated to have a low population frequency (0.36%–1.67%) and to account for ~9% of all prostate cancer cases at age ⩽85 years and for as much as 43% of disease at age ⩽55 years (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998). The autosomal dominant alleles are hypothesized to be highly penetrant; by age 85 years, 63%–89% of men carrying a mutation are likely to incur a clinical diagnosis of disease (Carter et al. 1992; Grönberg et al. 1997*a;* Schaid et al. 1998).

To date, genomewide screens of families with prostate cancer have identified four chromosomal regions of putative linkage. The first, a locus on chromosome 1q24-25, termed "*HPC1*" (MIM 601518), was originally proposed to account for disease in 34% of families with prostate cancer in a data set defined by families with three or more first-degree affected relatives, prostate cancer in three generations, or two affected siblings diagnosed at age ⩽60 years (Smith et al. 1996). Additional studies suggest that families most likely to have linkage to the *HPC1* locus have an early mean age at diagnosis (<65 years), four or more close relatives with the disease, and proportionately more advanced-stage disease (Grönberg et al. 1997*b,* 1999). Although two studies provide weak confirmatory evidence of linkage to *HPC1* (Cooney et al. 1997; Hsieh et al. 1997), several others, using large data sets comparable to those used to map *HPC1,* report no evidence of linkage in any stratified subset of families (McIndoe et al. 1997; Ber-

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thon et al. 1998; Eeles et al. 1998; Berry et al. 2000; Goode et al.2000). A combined analysis of 772 families has suggested that 6% of families with hereditary prostate cancer have linkage to *HPC1* (Xu 2000). A second prostate cancer–susceptibility locus, *PCAP* (MIM 602759), at 1q 42.2-43, was reported in 1998 by Berthon and colleagues (Berthon et al. 1998). Three other studies of this region found no or only weak evidence for linkage (Gibbs et al. 1999*a;* Whittemore et al. 1999; Berry et al. 2000). Significant linkage to a third prostate cancer–susceptibility locus, at Xq27-28, termed "*HPCX*" (MIM 300147), was identified using a set of 360 Finnish, Swedish, and North American families (Xu et al. 1998), and the results of two independent studies, of 153 and 186 families, were consistent with linkage to this locus in families that show likely maternal inheritance of prostate cancer (Lange et al. 1999; Peters et al., in press). Finally, linkage to a fourth prostate cancer–susceptibility locus, at chromosome 1p36, has been reported in families with a history of both prostate and primary brain cancers (Gibbs et al. 1999*b*). Supportive evidence for this locus, termed "*CAPB*" (MIM 603688), has been reported in families with early-onset prostate cancer, regardless of family history of brain cancer (M. Badzioch, G. Leblanc, R. Eeles, W. D. Foulkes, J. Hopper, S. Edwards, and D. Goldgar, unpublished data).

The lack of strong confirmatory evidence of linkage for susceptibility loci described thus far, even in studies using seemingly similar prostate cancer data sets, highlights the difficulties in mapping genes associated with a disease that is both complexly inherited and common. Multiple prostate cancer–susceptibility genes clearly exist, and the presence of both genetic and sporadic cases within single families makes linkage analysis difficult (Jarvik et al. 1999). In our own data set of families at high risk for prostate cancer, we have observed, at best, modest evidence of linkage to any of the loci mentioned above, with the four loci, in aggregate, likely accounting for only a small portion of the total incidence of the disease (McIndoe et al. 1997; Gibbs et al. 1999*a,* 1999*b;* Goode et al. 2000; Peters et al., in press). This, together with the collective observations in this field of research, suggests that additional prostate cancer loci remain to be found. In this report, we summarize our results from a complete genomewide screen of 94 families with prostate cancer.

Subjects and Methods

Selection of Families with Prostate Cancer

Families in this genome screen were participants in the Prostate Cancer Genetic Research Study (PROGRESS). This Seattle-based study ascertained families with three or more first-degree relatives with prostate cancer, three generations with prostate cancer, or two first-degree relatives with prostate cancer diagnosed at age <65 years. Eligible families were recruited through national advertising of a toll-free number (1-800-777-3035) for self-referrals and communications with urologists, prostate cancer support groups, and other health-related publications. Participating family members were enrolled from throughout North America and several other countries. Details, including blood collection and DNA isolation, have been reported elsewhere (McIndoe et al. 1997). The institutional review board of the Fred Hutchinson Cancer Research Center approved all study procedures and material.

Markers and Genotyping

A total of 380 microsatellite markers from the Human Screening Sets 6 and 8 (Research Genetics) were analyzed. The mean marker heterozygosity was .7. Map distances were from the 1998 Marshfield Medical Research Foundation map (Broman et al. 1998; also see the Center for Medical Genetics, Marshfield Medical Research Foundation, Web site). The average spacing between markers was 9.4 cM, with 99.1% of the contained distance being <7.5 cM from a marker. When distances to terminal map markers are included, 97.1% of the Marshfield map is <7.5 cM, and 98.9% is <10 cM, of a marker included in this analysis. PCR amplification and genotyping has been described elsewhere (Gibbs et al. 1999*b*).

Statistical Methods

PedCheck 1.1 (O'Connell and Weeks 1998) and Unknown from the ANALYZE software package (Wellcome Trust Center for Human Genetics) were used to test the data set for Mendelian errors. Because the majority of pedigrees contained ungenotyped founders, and, consequently, rare alleles of many markers were present only in nonfounders, allele frequencies were estimated from all genotyped individuals by the use of *downfreq* from ANALYZE. In this data set of 94 families, the maximum contribution to the total pool of genotypes from related individuals in any single family was <2.5% of genotypes. Thus, we expected that frequencies calculated from the entire data set would not differ significantly from frequencies calculated from a data set of unrelated individuals, not accounting for any racial differences. The ANALYZE software package and the FASTLINK 4.1P version of LINKAGE (Lathrop et al. 1984; Cottingham et al. 1993) were used for the two-point parametric analysis. Multipoint parametric and nonparametric linkage (NPL) analyses used GENEHUNTER version 1.2 (Kruglyak et al. 1996).

The genetic model (age- and genotype-specific pene-

trance) used for LOD-score analysis followed the method of Easton et al. (1995) and defined 11 liability classes for a rare (q = .003) dominant gene. This model exactly follows model B of Grönberg et al. (1997*c*), except for the addition of a nonsusceptible liability class for women and unaffected men of age <30 years. Liabilities for gene carriers also were as in model B of Grönberg et al. (1997*c*), culminating with a lifetime risk of 88%. These risks are based on segregation analysis of familial prostate cancer ascertained through patients undergoing prostatectomy (Carter et al. 1992). For non–gene carriers, the risk increased with age, to a maximum of 16%. In this model, penetrance ratios (i.e., gene carriers/non–gene carriers) decreased from 47 for affected men under 50 years of age to 1.7 for men diagnosed at age ⩾80 years. The corresponding ratios for unaffected men were 48.4 and 5.5. This model was adapted for X-linked inheritance, for the scan of the X chromosome. Because repeating a parametric linkage scan under both a dominant and recessive model has been proposed as a method to avoid false negatives due to model misspecification (Greenberg et al. 1998), a recessive model also was tested. For this purpose, we implemented the recessive model reported by Carter et al. (1993), which specifies a disease-allele frequency of .341, with lifetime penetrance of 79% in homozygote carriers, and a lifetime risk of 25% for men of age >30 years who have other genotypes.

Results

Two-Point Analysis

The 94 families in this study included 1,517 individuals. There were 432 affected men, of which 340 were surveyed and 339 provided blood samples. There was an average of 3.6 affected men per family (range 2–12). The age at diagnosis of surveyed affected men was 42–85 years (mean 65.4 years) (table 1). Ninety of the 94 families are White. Diagnosis was confirmed by medical records for 333 of the 340 affected men (97.9%); records for the remaining 7 were unavailable.

The 94 families were analyzed as a single set and then were stratified by mean age at diagnosis, which was defined a priori by use of the mean ages at diagnosis of the affected men in each family. This resulted in data sets of 50 families in which the mean age at diagnosis was <66 years (early-onset families) and 44 families in which the mean age at diagnosis was ⩾66 years (later-onset families). Within the 50 early-onset families, there was a subset of 16 families in which the mean age at diagnosis was <61 years (earliest-onset families).

Dominant Model

Three regions of interest, which had two-point LOD scores ⩾1.5, were defined in a genomewide scan of 94 families, by use of the dominant model (fig. 1 andtable 2). On chromosome 12, a LOD score of 1.76 (recombination fraction [θ] .14) was observed with marker D12S1045. Flanking markers several centimorgans centromeric to D12S1045 also were positive, although the closest telomeric marker (D12S392), which is <1 cM from D12S1045, was not. When considered alone, the 50 early-onset families (mean age at diagnosis <66 years) gave a LOD score of 1.89 at θ = .10 (fig. 2).

A second region of interest, located on chromosome 10, was defined by a LOD score of 1.68 (θ = .08) at marker D10S1223 (fig. 1). Markers flanking D10S1223 were positive, with a LOD score of 0.91 observed at marker D10S1237 (θ = .18), which is located 21.6 cM centromeric to D10S1223. The 50 early-onset families contributed disproportionately to the result, with a LOD score of 2.35 (θ = .02).

A LOD score of 1.74 (θ = .10) with marker D14S588 defined the final region of interest under the dominant model in the 94-family data set. Markers flanking D14S588 were positive only at high values of θ. As with the other regions of interest, stratification by age at diagnosis indicated that the majority of likely linked families were early onset (upper section oftable 2).

Additional regions of interest with LOD scores ⩾1.5 in stratified subsets of the families were identified on chromosomes 6, 9, and 11 (figs. 2 and 3). The strongest result seen for any analysis and any stratification was on chromosome 11, where a LOD score of 3.02 (θ =

Table 1

Characteristics of 94 Families with Prostate Cancer, by Mean Age at Diagnosis

		Men Whose Mean Age at Diagnosis Was (years)	
	Overall	<66 years	⩾66 years
No. of families	94	50	44
No. of affected men sampled[a]	340	185	155
Average no. of affected men sampled/family	3.6 (2–12)	3.7	3.5
Mean age at diagnosis of affected men sampled (range)	65.4 years (42– 85 years)	62.3 years	69.1 years

[a] Includes one affected man who was surveyed but who did not provide a blood sample.

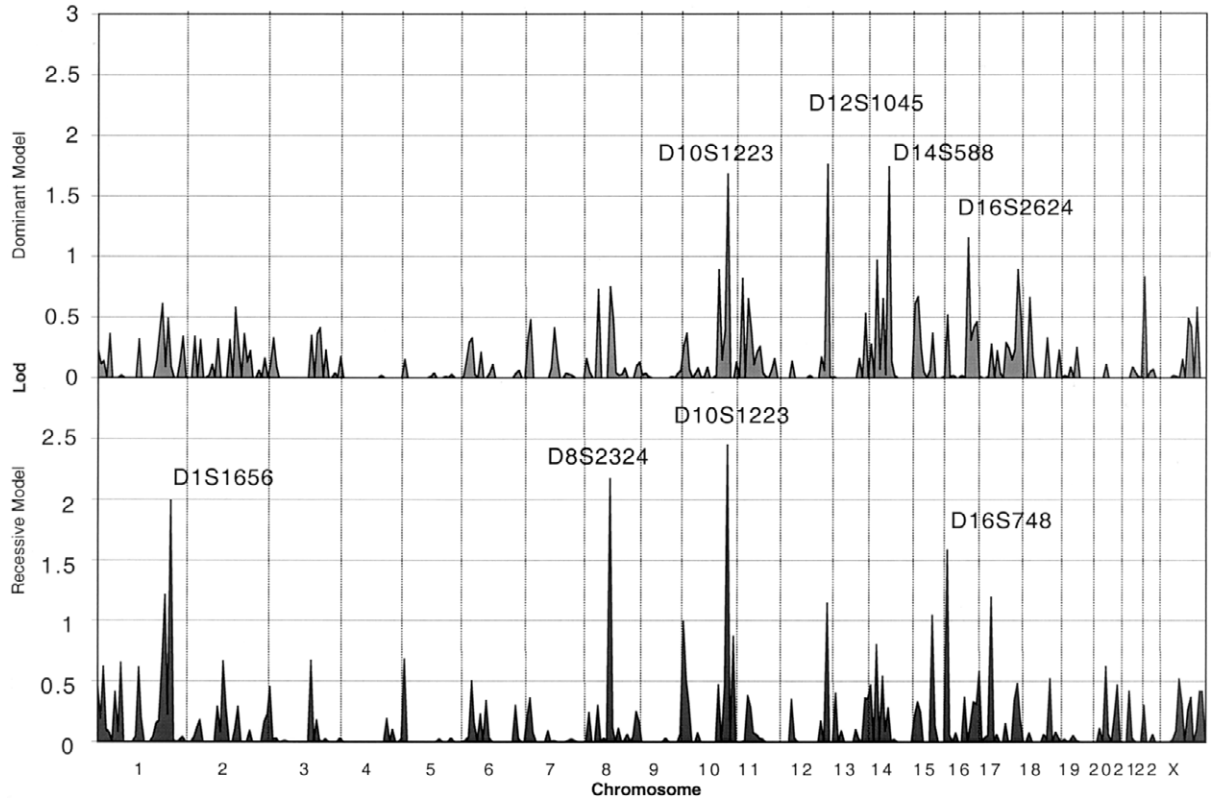

Figure 1 Two-point LOD scores of total data set, dominant and recessive models. Maximum LOD scores for each marker are plotted in order of chromosomal position.

.00) was observed in the 44 later-onset families, at marker ATA34E08 (fig. 3). Flanking markers were positive and included a LOD score of 1.02 at D11S1999. Only low LOD scores were observed, however, in either the total data set or the early-onset stratifications (upper section oftable 2). The majority of the LOD score in the later-onset men was contributed by 25 families whose mean age at diagnosis was 66–69 years (LOD score 2.56).

Recessive Model

The genome screen was also analyzed under a recessive model. Two-point LOD scores ≥ 1.5 were seen on chromosomes 1, 8, 10, and 16 in the total data set (fig. 1) and on chromosomes 2, 11, 12, and 15 in the age-stratified groups (figs. 2 and 3 and the lower section oftable 2). The largest LOD score in the 94 families was at D10S1223, with a maximum of 2.46 ($\theta = .04$) (lower section oftable 2). Three regions previously identified in the dominant analysis also were seen when the recessive model was used. Of these, the LOD score at D10S1223 was higher with the recessive model, and LOD scores at ATA34E08 and D12S1045 were lower. At D8S2324, with LOD scores of 2.17 ($\theta = .10$) in all families and 2.05 ($\theta = .00$) in the later-onset families when the recessive model was used, the corresponding LOD scores for the dominant model were 0.75 ($\theta = .20$) and 1.47 ($\theta = .02$). The other results, on chromosomes 1, 2, 15, and 16 (lower section oftable 2), are unique to the recessive model.

Multipoint Analysis

Multipoint NPL analyses of the total data set, by GENEHUNTER (Kruglyak et al. 1996), highlighted four regions with $P < .10$. Two of these, at D10S1223 (NPL 1.61; $P = .057$) and ATA34E08 (NPL 1.30; $P = .099$) corresponded to regions also identified by the two-point parametric analyses. Multipoint analyses of these two regions revealed a peak NPL score of 1.45 ($P = .08$) at D10S1223 in the early-onset families and a peak NPL of 1.90 ($P = .03$) at ATA34E08 in the later-onset families. The two further regions found in the total data set were an NPL peak of 1.48 ($P = .073$) between markers D3S1744 and D3S1763 on 3q (this peak increased to 1.72 [$P = .048$] for later- onset families) and an NPL peak of 1.45 ($P = .077$) at the position of marker D1S1597 in the putative CAPB region. Age group–specific multipoint analysis of the CAPB region

Table 2

Two-Point and Multipoint LOD Scores, for Dominant and Recessive Models, and NPL Scores for All Regions of Interest (Two-point LOD Score ⩾1.5)

	Two-Point Score		Multipoint Score				
			Parametric			Nonparametric	
Model, Marker, and Age Group (No.)[a]	LOD	θ	LOD	HLOD	α	NPL	*P*
Dominant:							
D12S1045 (160.7 cM):							
All (94)	1.76	.14	−3.29	.57	.26	.48	.31
<66 years (50)	1.89	.10	−1.66	.57	.31	.72	.23
⩾66 years (44)	.09	.26	−1.62	.04	.16	−.07	.52
<61 years (16)	1.05	.04	−.05	.30	.50	.58	.27
D14S588 (75.6 cM):							
All (94)	1.74	.10	−2.21	.71	.31	.43	.33
<66 years (50)	1.03	.10	−1.97	.36	.27	.70	.24
⩾66 years (44)	.71	.08	−.25	.38	.41	−.12	.54
<61 years (16)	1.68	.00	−.61	.17	.34	.67	.25
D10S1223 (156.3 cM):							
All (94)	1.68	.08	−1.32	.96	.39	1.61	.06
<66 years (50)	2.35	.02	1.41	1.79	.69	1.45	.08
⩾66 years (44)	.00	.50	−2.73	.00	.01	.81	.21
<61 years (16)	.51	.00	1.00	1.00	.93	.61	.26
ATA34E08[b] (33.0 cM):							
All (94)	.65	.18	−2.91	.29	.25	1.30	.10
<66 years (50)	.00	.50	−4.02	.00	.01	.01	.48
⩾66 years (44)	3.02	.00	1.12	1.14	.82	1.89	.03
<61 years (16)	.17	.18	−.52	.14	.37	.33	.36
D9S925 (32.2 cM):							
All (94)	.04	.30	−4.08	.03	.08	.21	.41
<66 years (50)	.72	.12	−1.36	.27	.28	.67	.24
⩾66 years (44)	.00	.50	−2.72	.00	.00	−.41	.65
<61 years (16)	1.60	.00	1.14	1.14	1.00	1.43	.08
D6S1019 (53.8 cM):							
All (94)	.03	.36	−4.24	.28	.19	.49	.30
<66 years (50)	.00	.50	−5.55	.00	.00	−.52	.69
⩾66 years (44)	1.62	.00	1.31	1.35	.79	1.28	.10
<61 years (16)	.00	.50	−1.83	.00	.00	−.04	.50
Recessive:							
D10S1223 (156.3 cM):							
All (94)	2.46	.04	−.23	1.15	.48	1.61	.06
<66 years (50)	1.28	.06	.68	1.02	.62	1.45	.08
⩾66 years (44)	1.17	.02	−.91	.26	.31	.81	.21
<61 years (16)	.35	.02	.08	.26	.54	.61	.26
D8S2324 (94.1 cM):							
All (94)	2.17	.10	−3.92	.18	.16	−.05	.51
<66 years (50)	.51	.18	−4.17	.00	.00	−1.00	.84
⩾66 years (44)	2.05	.00	.25	.82	.50	1.00	.16
<61 years (16)	.04	.26	−1.54	.00	.00	.06	.46
D1S1656 (245.1):							
All (94)	1.99	.12	−5.26	.05	.09	.33	.36
<66 years (50)	1.46	.10	−2.87	−.01	.02	.01	.48
⩾66 years (44)	.61	.16	−4.23	.00	.01	−.45	.66
<61 years (16)	.30	.10	−1.63	.00	.00	−1.24	.90
D16S748 (22.7 cM):							
All (94)	1.58	.12	−2.68	.28	.23	1.12	.13
<66 years (50)	1.22	.10	−1.40	.13	.22	.80	.21
⩾66 years (44)	.42	.18	−1.28	.15	.25	.78	.21
<61 years (16)	.10	.12	−1.20	.00	.00	−.53	.69

(*continued*)

Table 2 Continued

Model, Marker, and Age Group (No.)[a]	Two-Point Score		Multipoint Score				
			Parametric			Nonparametric	
	LOD	θ	LOD	HLOD	α	NPL	P
D12S1045 (160.7 cM):							
All (94)	1.14	.16	−6.14	.01	.05	.48	.31
<66 years (50)	1.71	.08	−2.44	.17	.19	.72	.23
⩾66 years (44)	.00	.50	−3.71	.00	.00	−.07	.52
<61 years (16)	.51	.04	−.88	.00	.11	.58	.27
D15S652 (90.0 cM):							
All (94)	1.04	.16	−1.10	.72	.38	1.23	.11
<66 years (50)	.06	.30	−2.80	.00	.00	−.23	.58
⩾66 years (44)	1.65	.02	1.70	1.76	.81	2.04	.03
<61 years (16)	.27	.12	−.08	.20	.49	.67	.24
ATA34E08[b] (33.0 cM):							
All (94)	.38	.24	−3.44	.12	.17	1.30	.10
<66 years (50)	.00	.50	−4.42	.00	.00	.01	.48
⩾66 years (44)	1.58	.04	.98	1.18	.68	1.89	.03
<61 years (16)	.00	.50	−1.61	.00	.00	.33	.36
D2S1790 (103.2 cM):							
All (94)	.29	.26	−4.63	.27	.18	−.01	.49
<66 years (50)	.30	.20	−2.21	.22	.22	−.18	.56
⩾66 years (44)	.04	.32	−2.43	.07	.14	.18	.42
<61 years (16)	1.58	.00	.72	.78	.74	.45	.31

[a] Markers are ordered on the basis of two-point LOD scores in all families; positions are from the Marshfield map (Broman et al. 1998; also see the Center for Medical Genetics, Marshfield Medical Research Foundation, Web site). The 16 families with mean age <61 years are a subset of the 50 early-onset families.

[b] On chromosome 11.

identified, in the earliest-onset group (<61 years), an ~28-cM region, between D1S468 and GATA29A05, defined by an NPL score >1.75 and with $P < .05$. The maximum NPL score in this region, 2.28 ($P = .016$), was at D1S1612. This NPL score was the largest found in any analysis of this family set.

Several additional prominent regions ($P < .05$) that were not highlighted by two-point calculations were found by multipoint analyses of the age strata. In the 44 families with a mean age at diagnosis ⩾66 years, there was a 19-cM region on chromosome 8p that had a maximum NPL of 2.02 ($P = .026$) at D8S1106 and an NPL score of 2.04 ($P = .025$) at D15S652. In the 50 early-onset families, a maximum NPL of 2.06 ($P < .03$) at D4S2366 identified a 2-cM length with $P < .05$, and an NPL score of 1.93 ($P = .032$) at D2S1399 identified a 2-cM segment of chromosome 2.

Discussion

The findings from our genome scan, which used both the dominant model and the recessive model in the entire data set of 94 families, identify several regions of interest, including regions on chromosomes 1, 8, 10, 12, 14, and 16. None of these meet the usual criteria for significance, however, and further analysis will be necessary to determine whether these regions truly contain susceptibility genes. Additional regions were revealed by stratifications based on age at diagnosis. The most provocative result found was on chromosome 11, where, for marker ATA34E08, we observed a LOD score of 3.02 ($\theta = .0$) and an NPL score of 1.9 ($P = .03$) in the 44 later-onset families. Those families in the 66–69-year mean-age group contributed the majority of the evidence of linkage.

Interestingly, marker ATA34E08 also defined a locus of interest in later-onset families in the genome scan by Suarez et al. (2000). Their analysis involved 504 brothers with prostate cancer who were from 230 multiplex sibships. A GENEHUNTER-PLUS (Kong and Cox 1997) likelihood-ratio LOD score (Z_{lr}) score of 1.87 ($P = .031$) was found in the 115 families with mean age at onset above the 65.4-year median. Together, these studies suggest that a locus at or near ATA34E08 may be responsible for some proportion of familial prostate cancer, particularly in men diagnosed at older ages. This finding challenges the common paradigm of using early-onset families to identify cancer-susceptibility loci and highlights the importance of not limiting the search for hereditary prostate cancer genes to patients diagnosed

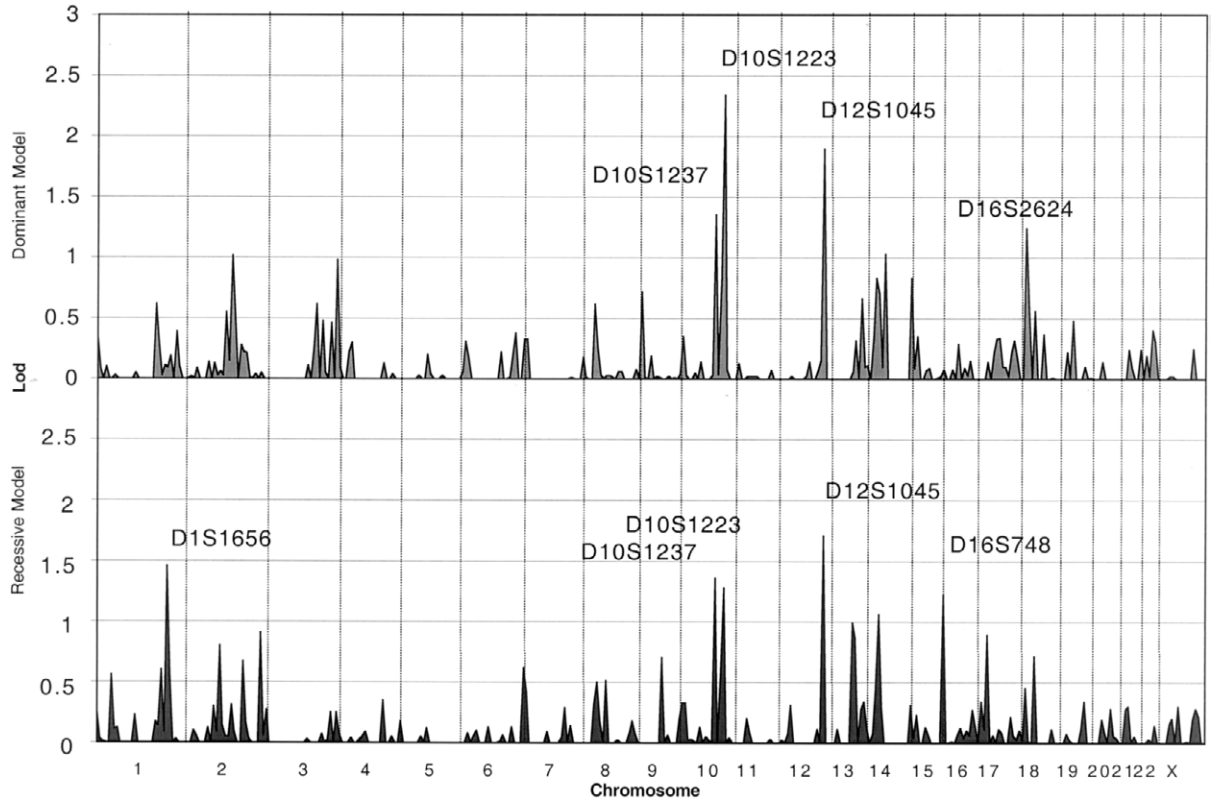

Figure 2 Two-point LOD scores of early-onset group (mean age at diagnosis in family <66 years), dominant and recessive models

at young ages. It is possible that the locus at 11p is associated with less-aggressive disease, which has a longer preclinical phase and is diagnosed at later ages. From a public-health standpoint, the 11p locus may prove to be equally as important as are loci linked solely to early-onset disease, since the age at diagnosis of the majority (78%) of patients with clinical prostate cancer is >65 years (Stanford et al. 1999).

Linkage studies have suggested the locations of four prostate cancer–susceptibility loci, at 1q24-25 (*HPC1*), 1q42.2-43 (*PCAP*), Xq27-28 (*HPCX*), and 1p36 (*CAPB*) (Smith et al. 1996; Berthon et al. 1998; Xu et al. 1998; Gibbs et al. 1999*b*). All were localized through analysis of "high risk" families that show an excess of early-onset disease, compared with the population expectation. To date, however, no causative gene has been cloned from any region. Our previous analyses of PROGRESS families found no significant evidence of linkage to the *HPC1* locus at 1q24 (McIndoe et al. 1997; Goode et al. 2000) and weak evidence of linkage at the 1q42.2-43 (Gibbs et al. 1999*a*) and *HPCX* loci (Peters et al., in press). We previously had reported linkage to a putative new locus at 1p36 (Gibbs et al. 1999*b*), which our initial analysis suggested was most important in a limited group of PROGRESS families with a history of both prostate and primary brain cancers.

The findings from our genome scan, for both the dominant model and the recessive model, are consistent with the studies cited above. In the 94 families studied here, when the dominant model was used, we did not detect linkage to *HPC1* (maximum positive LOD scores 0). Significant evidence of linkage to the *PCAP, HPCX,* and *CAPB* loci was not seen (LOD scores 0.01–0.39 at high values of θ) in the unstratified data sets. Evidence of these putative loci is also sparse under the recessive model, although a LOD score of 1.00 was seen, in the 44 early-onset families, at D1S1660, a marker within the *HPC1* region. Also, a LOD score of 1.99 (θ = .12) in all 94 families was seen at D1S1656, a marker situated between the *HPC1* and *PCAP* regions. Multipoint NPL analysis of all families revealed a peak NPL score of 1.45 (P = .077) at marker D1S1597 in the *CAPB* region. This finding was expected, since these PROGRESS families include 7 of the 12 families used to define the *CAPB* locus. However, since the evidence for linkage to this region increased to an NPL score of 2.28 (P = .016) when all very-early-onset families (i.e., without regard to the presence of brain cancer) were tested, the detailed phenotypic expression of this gene remains unclear.

Results from two other genome scans for prostate cancer loci have been reported. In an analysis of 66

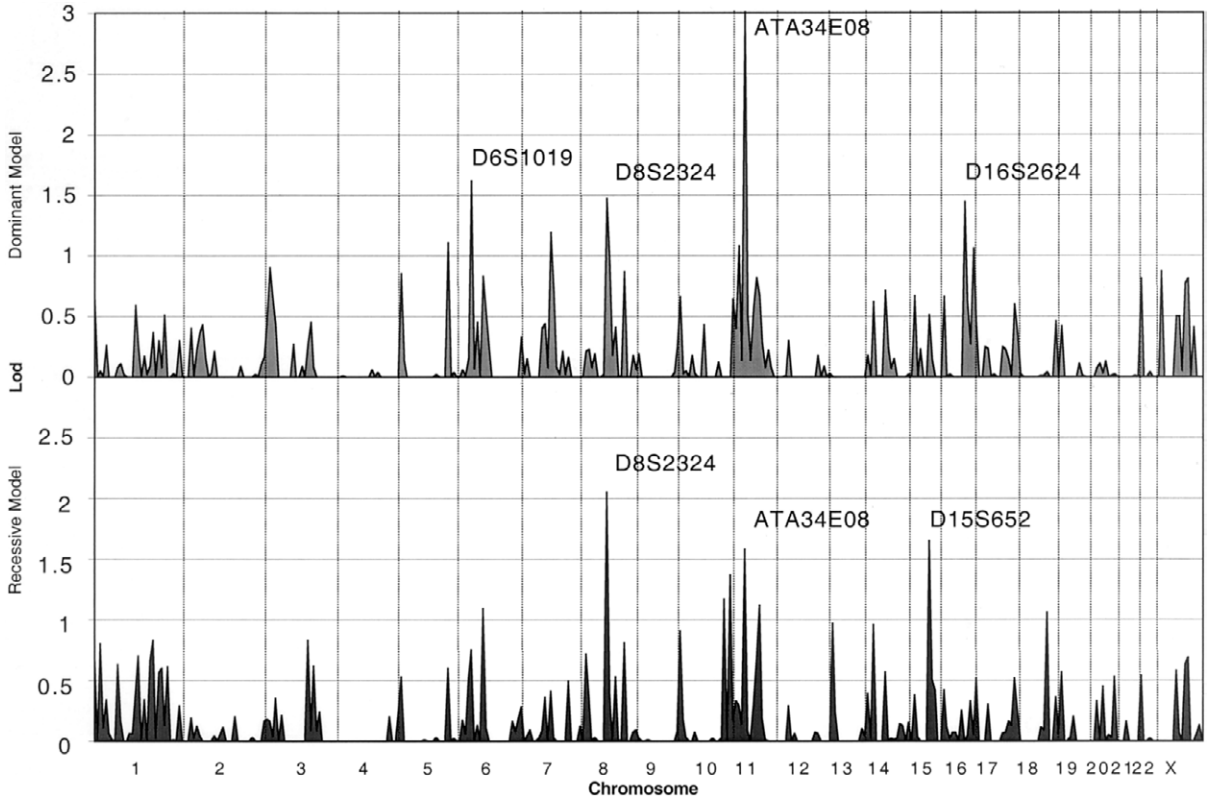

Figure 3 Two-point LOD scores of later-onset group (mean age at diagnosis in family ⩾66 years), dominant and recessive models

high-risk families, Smith et al. (1996) reported evidence of linkage to *HPC1* and observed LOD scores >1.5 at only one other marker, D4S430. We saw no evidence for linkage to markers in that region. In addition to the 11p locus defined by ATA34E08 in later-onset families, a complete genome scan by Suarez et al. (2000) also defined areas of interest on chromosomes 2q, 12p, 15q, 16p, and 16q, using an unstratified data set of 230 affected sibships. Stratifications based on family history of prostate cancer, age at onset, and family history of breast cancer revealed further regions, including 1p35.1 (in families with a history of breast cancer) and 8q22.3 (in families that meet criteria for "hereditary" prostate cancer) (Suarez et al. 2000).

Some similar regions were identified between this study and that of Suarez et al. (2000). The locus on chromosome 1 is immediately adjacent to the region that we have identified as containing the putative *CAPB* locus (Gibbs et al. 1999*b*), and, conceivably, these could be the same. Interestingly, a group including one of the authors of the present study has found data supporting a locus at 1p36 in early-onset families but has found no association between this region and either brain- or breast-tumor history (M. Badzioch, G. Leblanc, R. Eeles, W. D. Foulkes, J. Hopper, S. Edwards, and D. Goldgar, unpublished data). The 8q22.3 locus that Suarez et al. defined by using marker GAAT1A4 is ~16 cM from the locus that we have defined by using marker D8S2324, where, with the recessive model, we observed LOD scores of 2.17 (θ = .10), in all 94 families, and 2.05, in the families with age at onset ⩾66 years. However, marker GAAT1A4 in our analysis showed no evidence of linkage in either the total or the stratified data sets when the recessive model was used. Analysis of additional markers in both data sets may be needed to provide clarification as to the exact position of this putative locus.

The strongest signals found by Suarez et al. were for linkage to broad regions of 16p and 16q, with a peak multipoint Z_{lr} of 3.15 at D16S3096. We saw no evidence of linkage to 16p when the dominant model was used, but we did see a LOD score of 1.58 in the total data set at marker D16S748 when the recessive model was used. Conversely, we saw the most evidence for linkage to 16q when the dominant model was used. Weak positive LOD scores, both in the total data set (0.31–1.15) and in the later-onset families (0.27–1.44), were found at four consecutive markers across the 16q region that was identified by the Suarez et al. study and that included D16S3096.

It is clear from the work thus far presented by re-

searchers in this field that, unlike the situation in inherited susceptibility to breast cancer, there are more than two or three major loci that increase susceptibility to inherited prostate cancer. Successful identification of prostate cancer–susceptibility loci necessarily will involve categorization or stratification of the data set, to reduce the complexities associated with locus heterogeneity. Avenues currently under pursuit in our ongoing study, as well as within the field as a whole, include stratification by clinical features and the organization of metanalyses with larger data sets for regions suggested by genomewide screens.

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Electronic-Database Information

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

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.marshmed.org/genetics

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

Wellcome Trust Center for Human Genetics, ftp://ftp.well.ox.ac.uk/pub/genetics

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