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Linkage Analysis of 49 High-Risk Families Does Not Support a Common Familial Prostate Cancer–Susceptibility Gene at 1q24-25

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Summary

Linkage of a putative prostate cancer–susceptibility locus (HPC1) to chromosome 1q24-25 has recently been reported. Confirmation of this linkage in independent data sets is essential because of the complex nature of this disease. Here we report the results of a linkage analysis using 10 polymorphic markers spanning ~37 cM in the region of the putative HPC1 locus in 49 high-risk prostate cancer families. Data were analyzed by use of two parametric models and a nonparametric method. For the parametric LOD-score method, the first model was identical to the original report by Smith and coworkers ("Hopkins"), and the second was based on a segregation analysis previously reported by Carter and coworkers ("Seattle"). In both cases, our results do not confirm the linkage reported for this region. Calculated LOD scores from the two-point analysis for each marker were highly negative at small recombination fractions. Multipoint LOD scores for this linkage group were also highly negative. Additionally, we were unable to demonstrate heterogeneity within the data set, using HOMOG. Although these data do not formally exclude linkage of a prostate cancer–susceptibility locus at HPC1, it is likely that other prostate cancer–susceptibility loci play a more critical role in the families that we studied.

Introduction

Prostate cancer is a complex disease marked by varying rates of progression, response to therapies, age at onset, and time interval to diagnosis. It is the most frequently diagnosed noncutaneous cancer and the second most common cause of cancer-related deaths in American men (Parker et al. 1997). Several studies have demonstrated familial clustering of prostate cancer, suggesting a heritable form of the disease (Steinberg et al. 1990; Carter et al. 1992, 1993). Segregation analysis based on data from 691 prostate cancer probands suggested that inherited forms of this disease are best explained by a rare, highly penetrant, autosomal dominant allele (Carter et al. 1992). This analysis also predicted that the inheritance of this allele accounts for ~43% of early-onset prostate cancers, defined as diagnosis at age ≤ 55 years, and for ~9% of prostate cancers diagnosed by age 85 years. Although inherited factors appear to account for only a small subset of all prostate cancers, the identification of such a disease gene(s) is considered crucial to an understanding of the molecular and cellular mechanisms that contribute to the development of prostate cancer.

The genetic etiology responsible for the neoplastic transformation of normal prostate cells remains largely unknown, although research has identified several genes involved in the progression of prostate tumors; these include the MAX-interacting protein 1 (*MXI1*) on 10q25 (Eagle et al. 1995), a suppressor of the metastasis gene (*KAI1*) on 11p11.2 (Dong et al. 1996; Ichikawa et al. 1996), the androgen-receptor locus on Xq11-12 (Irvine et al. 1995), and a cell-cell adhesion system (E-cadherin/α-catenin) critical for tumor metastasis (Umbas et al. 1992; Morton et al. 1993). Mutations in tumor-suppressor genes shown to be important in other cancers, such as p53 and Rb1, can be detected in a proportion of advanced-stage prostate cancers (Bookstein et al. 1993; Massenkeil et al. 1994); nevertheless, these genes appear to be unimportant in the initiation of prostate cancer (Bookstein 1994; Brooks et al. 1996). Similarly, loss-of-heterozygosity studies have identified several regions that may contain unidentified tumor-suppressor genes, including 7q, 8p, 10p, 10q, 13q, 16q, 17p, 17q, and 18q (Carter et al. 1990; Bova et al. 1993; Massenkeil et al. 1994; Zenklusen et al.

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1994; Kagan et al. 1995; Macoska et al. 1995; Bova et al. 1996; Williams et al. 1996); but, as yet, there is no evidence that prostate cancer–susceptibility genes are in any of these candidate regions. Thus, known tumor-suppressor genes do not account for the majority of familial prostate cancer, and the identification of susceptibility loci remains a major goal of prostate cancer research.

Smith et al. (1996) recently screened 91 North American and Swedish families, with microsatellite markers. Two-point analysis of 66 North American families found suggestive linkage (LOD score 2.75) with D1S218, a marker in chromosome 1q24-25. Analysis of an additional 25 families and markers narrowed the region of linkage to an interval of ~15 cM defined by markers D1S2883 to D1S422. An admixture test for homogeneity suggested an estimated 34% of the families studied by Smith et al. were linked to this region. Given both the complex nature of this disease and the potential importance of this finding, we have attempted to verify this result in a similar group of families.

Subjects and Methods

Ascertainment of Prostate Cancer Families

The Prostate Cancer Genetic Research Study (PROGRESS) was initiated in July 1995 for the purpose of identifying familial clusters of prostate cancer and, ultimately, inherited susceptibility genes. National advertising, media events, and mailings to support groups and urologists were used to recruit families into the study. A toll-free number (800-777-3035) was established to screen potential participants for their suitability. For participation, families were selected on the basis of the number of first-degree relatives diagnosed with prostate cancer, the age at diagnosis of the affecteds, and the number of living affecteds from whom blood samples could be obtained. The study and its consent and medical record–release forms were approved by the institutional review board of the Fred Hutchinson Cancer Research Center. All consent and medical record–release forms were signed and returned to PROGRESS. Affected members of selected families were asked to give medical and family-history information and to donate a blood sample. Medical record confirmation of diagnosis was sought. Selected unaffected family members expected to be informative for linkage were then recruited.

DNA Isolation and Genotyping

Genomic DNAs were isolated from previously frozen buffy coats by standard methods. Genomic DNA from each individual was genotyped by PCR amplification of 10 microsatellite markers spanning the putative HPC1 locus on 1q24-25. Each reaction contained genomic DNA (50 ng), primers (0.2 μM each), 50 mM KCl, 10 mM Tris, 1–2.5 mM $MgCl_2$, 0.2 mM dNTPs, and 0.5 μM dATP-IRD40 or α^{32}P-dCTP. The samples were cycled 35 times at 94°C for 15 s, 50°C–58°C for 15 s, and 72°C for 15 s. Markers were optimized for both their annealing temperature (50°C–58°C) and $MgCl_2$ concentration (1.0–2.5 mM). Products were labeled during strand synthesis, with either an infrared dye (dATP-IRD40; Boehringer Mannheim) or α^{32}P-labeled dCTP (Redivue; Amersham). Products were resolved on denaturing polyacrylamide gels, with the dye-labeled products detected by use of a Li-Cor Model 4000S automated infrared DNA sequencer (Li-Cor), and the genotypes were determined by use of proprietary in-house genotyping software (SAGA). All radioactive gels were independently scored by at least two people. Estimated genotypic error rates were 0.22%.

Linkage Analysis

The parametric-LOD-method linkage analyses used two models for the inheritance of prostate cancer in these high-risk families (table 1). The first model (''Hopkins'') was identical to the model used by Smith et al. (1996) in their report of linkage to chromosome 1. This was used to ensure that result differences were not secondary to model differences. This model was autosomal dominant with a risk-allele frequency of .003 (q) and three liability classes (table 1). All affected men were in the first liability class, regardless of age, and the class had a phenocopy rate of .001 and a penetrance of 1.0 for carriers of the disease allele. All women and unaffected men <75 years of age were grouped together in the second liability class, whereas unaffected men ≥ 75 years of age were placed in the third liability class (table 1). The second model (''Seattle'') closely followed the results of Carter et al. (1993), by using age-dependent penetrance values for individuals >50 years of age. This model was also autosomal dominant with a risk-allele frequency of .003 (Carter et al. 1992). Unlike the Hopkins model, there were seven liability classes (table 1). Men <30 years of age and women were considered to have zero risk of currently having prostate cancer.

FASTLINK version 3.0P (Cottingham et al. 1993) and LINKAGE version 5.1 (Lathrop et al. 1984) were used for the two-point linkage analysis. Multipoint parametric and nonparametric linkage (NPL) analyses used GENEHUNTER version 1.1 (Kruglyak et al. 1996). In addition, nonparametric two-point analyses used the nonparametric option of the ANALYZE linkage computer package by Joseph Terwilliger. Allele frequencies were determined from the data set by use of *downfreq* from ANALYZE. An admixture test for heterogeneity in the data set was performed by use of HOMOG (Ott 1991).

Table 1

Parametric Models of Inheritance That Were Evaluated in Present Study

			Penetrance		
			Homozygous Normal	Heterozygous	Homozygous Disease
Hopkins:[a]					
1	Affected men	Affected	.001	1.0	1.0
2	Women	Unknown	.5	.5	.5
2	Unaffected men <75 years of age	Unknown	.5	.5	.5
3	Unaffected men ⩾75 years of age	Unaffected	.16	.63	.63
Seattle:					
1	Women	Unaffected	.0	.0	.0
1	Men <30 years of age	Unaffected	.0	.0	.0
2	Men 30–39 years of age	Unaffected or affected	.001	.0045	.0045
3	Men 40–49 years of age	Unaffected or affected	.001	.01	.01
4	Men 50–59 years of age	Unaffected or affected	.005	.05	.05
5	Men 60–69 years of age	Unaffected or affected	.01	.37	.37
6	Men 70–79 years of age	Unaffected or affected	.05	.76	.76
7	Men >79 years of age	Unaffected or affected	.05	.88	.88

[a] Model specifications kindly provided by Jianfeng Xu.

Table 2

Two-Point LOD Scores for 10 Chromosome 1q24-25 Markers, under the Seattle Model and under the Hopkins Model, for 46 Caucasian Families

	LOD Score at θ =							
Model and Locus	.00	.05	.10	.20	.30	.40	Z_{max}[a]	Z_{max} (α, θ)[b]
Seattle:								
D1S1677	−9.28	−5.46	−3.37	−1.24	−.38	−.07	.0 (∞)	.0 (1.0, ∞)
D1S1589	−8.07	−4.78	−2.95	−1.05	−.29	−.04	.0 (∞)	.0 (1.0, ∞)
D1S2883	−8.32	−4.49	−2.59	−.81	−.16	−.01	.001 (.46)	.001 (1.0, .46)
D1S212	−9.77	−5.42	−3.22	−1.08	−.26	−.03	.0 (∞)	.0 (1.0, ∞)
D1S2818	−6.20	−3.53	−2.22	−.89	−.31	−.06	.0 (∞)	.0 (1.0, ∞)
D1S2127	−8.43	−4.13	−2.18	−.44	.06	.06	.088 (.34)	.208 (.13, .0)
D1S191	−6.19	−2.99	−1.41	−.07	.2	.09	.194 (.30)	.194 (1.0, .3)
D1S518	−7.54	−3.73	−1.83	−.19	.18	.08	.180 (.32)	.180 (.93, .3)
D1S422	−2.16	−.56	.11	.49	.34	.11	.484 (.20)	.492 (.53, .10)
D1S1660	−8.94	−4.44	−2.33	−.51	−.02	.03	.036 (.36)	.036 (1.0, .36)
Hopkins:								
D1S1677	−22.63	−8.62	−4.77	−1.55	−.41	−.05	.0 (∞)	.0 (1.0, ∞)
D1S1589	−18.59	−7.62	−4.32	−1.41	−.35	−.04	.0 (∞)	.0 (1.0, ∞)
D1S2883	−20.86	−7.61	−3.78	−.77	.04	.07	.089 (.36)	.089 (1.0, .36)
D1S212	−13.58	−4.14	−1.60	.16	.37	.15	.388 (.28)	.388 (1.0, .28)
D1S2818	−13.71	−5.32	−3.05	−1.12	−.36	−.07	.0 (∞)	.0 (1.0, ∞)
D1S2127	−19.84	−7.19	−3.72	−.95	−.1	.03	.027 (.40)	.174 (.10, .0)
D1S191	−18.66	−5.88	−2.76	−.42	.11	.08	.133 (.34)	.159 (.12, .0)
D1S518	−22.26	−8.33	−4.24	−.93	−.02	.06	.073 (.36)	.073 (.95, .36)
D1S422	−13.35	−3.08	−1.02	.22	.31	.11	.332 (.26)	.415 (.23, .0)
D1S1660	−25.11	−8.62	−4.33	−1.06	−.15	.01	.009 (.42)	.009 (1.0, .42)

[a] Homogeneity is assumed.
[b] Heterogeneity is assumed.

Results

The 49 families included in this analysis had an average of 4.4 men affected with prostate cancer (range 3–9) and an average age at diagnosis of 65.9 years (range 39–94 years). The average number of living affected men genotyped per family was 3.5, with an average age at diagnosis of 64.9 years. A total of 364 individuals, including 169 affected men, were genotyped. Medical records were obtained for 165 (98%) of these affected men. In every case the diagnosis was confirmed. Forty-six of the 49 families were of Caucasian descent.

LOD scores from the two-point parametric analysis using both models of inheritance of prostate cancer for the Caucasian families in this study are given in table 2. Both the Hopkins model and the Seattle model gave strong evidence against linkage, for nearly all markers. The largest positive LOD score for the Seattle model is 0.484 at recombination fraction (θ) = .2, with D1S422, whereas that for the Hopkins model is 0.388 at θ = .28, with D1S212. Using an admixture test (HOMOG), we were unable to find significant evidence of locus heterogeneity in the data set. If heterogeneity is assumed, the largest LOD score obtained under the Seattle model is 0.492 at θ = .1, with an estimate of .53 (1.0 = homogeneity), whereas that for the Hopkins model is 0.415 at θ = .0, with an estimate of .23 for D1S422. An examination of each family showed no convincing evidence of linkage to these chromosome 1q markers.

Stratification of the dataset, by age at diagnosis, into "early"- and "late"-onset families did not yield significant evidence of linkage. Families were considered to have an early onset if their mean age of diagnosis was 65 years of age, whereas families whose mean age at diagnosis was >65 years were considered to have a late onset. Our dataset contained 18 Caucasian families having an early onset and 28 families having a late onset. Under the Seattle model, the LOD scores derived for the early-onset families were generally highly negative at small θ's, with maximum LOD score (Z_{max}) of 0.0 at $\theta = \infty$ for all markers tested. The Hopkins model also gave negative LOD scores at small θ's with Z_{max} also of 0.0 at $\theta = \infty$ for all markers. Similarly, under the Seattle model, the LOD scores for the late-onset families were again highly negative, with Z_{max} = 0.708 at θ = .16, for marker D1S422. However, the Hopkins model did give small positive LOD scores, with Z_{max} = 1.09 (12.6:1 likelihood ratio) at θ = .18, for marker D1S212.

The parametric analysis relies on having an approximately correct model defined for the mode of inheritance. To avoid any risk, secondary to model misspecification, of falsely rejecting linkage, we performed a nonparametric multipoint analysis, using the GENEHUNTER program (Kruglyak et al. 1996). A plot of the multipoint LOD and NPL scores across this region of chromosome 1q24-25, under both models, is shown in figure 1. As in the two-point analysis, there is no significant evidence for linkage of a prostate cancer–susceptibility locus to this region.

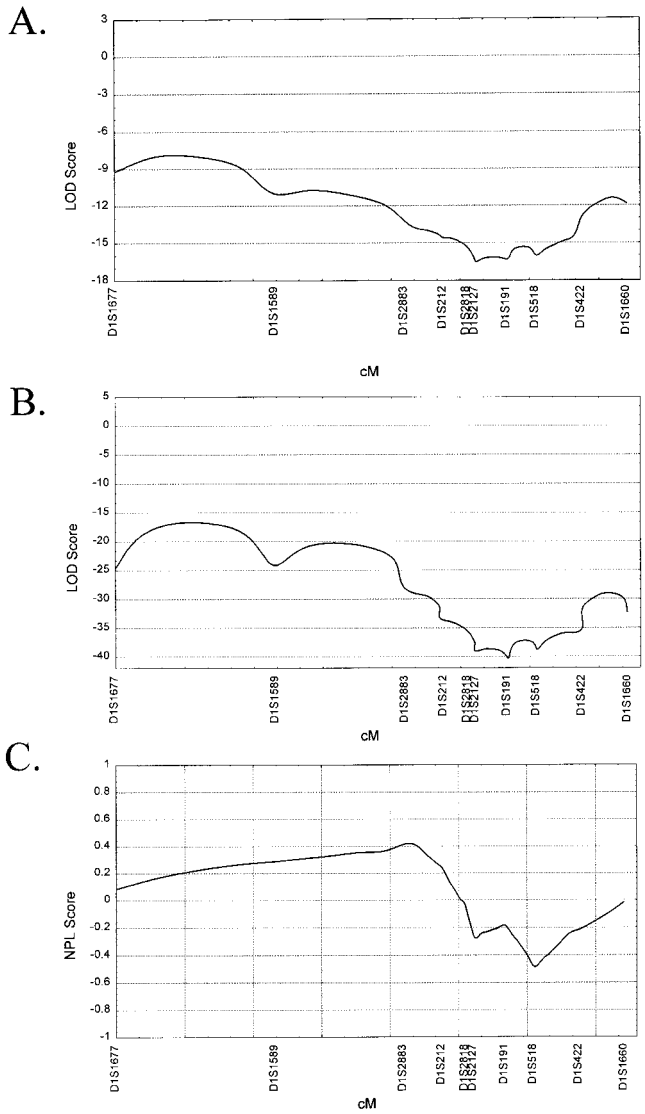

Figure 1 Plot of LOD and NPL scores from the multipoint analysis by GENEHUNTER (Kruglyak et al. 1996). *A,* Plot of LOD-score values obtained by the Seattle model. *B,* Plot of LOD-score values obtained by the Hopkins model. *C,* Plot of NPL-score values for this region of chromosome 1. The relative position and marker name are given on the *x*-axis.

The results for single Japanese, Latino, and Native-American pedigrees in our data set do not appear significantly different from those for the Caucasian families. The Japanese and Latino families generally yield low negative LOD scores, under either model. The Native-American pedigree gave negative LOD scores under both the Seattle model and the Hopkins model; however,

this pedigree did have two loci with LOD scores of 1.12 (D1S2883) and 1.36 (D1S212), at $\theta = .0$, under the Hopkins model.

Discussion

We found no evidence for linkage of prostate cancer to 1q24-25, using three models. Given the similarities (table 3) between our data set and that of Smith et al. (1996), our results are surprising. The 49 families analyzed here are expected to be typical of high-risk prostate cancer families. All of the families that we studied have three or more affected first-degree relatives; 21 (42.8%) of the 49 families have five or more affected individuals. In addition, 14 families reported disease in two generations. Eleven families meet two critical criteria: having an average age at diagnosis of <65 years and disease in at least two generations.

Conflicting evidence regarding linkage to a chromosomal region is not unexpected in common diseases and may be explained by one of the following reasons. First, it may represent a false-positive or false-negative linkage result, or it may represent sample differences in the presence of locus heterogeneity. In the absence of a biologically plausible candidate gene or alternative region of linkage, disputed linkages may be resolved either by evaluation of further families or by extension of the families originally reported to be linked. The evaluation of further families should improve the estimate of the proportion of families linked to the reported locus.

Second, in the presence of locus heterogeneity, it may be difficult to replicate a linkage that is correct but that represents an infrequent locus. This is especially true when the families studied by various groups differ in some way. In that case, the best method to show that the original linkage was correct is to extend the original pedigrees. A true linkage will result in an improved LOD score, and a false result should not withstand the scrutiny. An example of conflicting reports was the linkage of chromosome 21 to familial Alzheimer disease (FAD; St. George-Hyslop et al. 1987) and the subsequent report of the absence of that linkage (Schellenberg et al. 1988). The families found not to be linked to chromosome 21 were later found to show linkage to a more common FAD locus, on chromosome 14 (Schellenberg et al. 1992), whereas the chromosome 21 locus has been found to be linked to a small portion of FAD.

Third, the lack of agreement between our results and those of Smith and coworkers may also reflect study-population differences in the presence of locus heterogeneity. Despite the obvious similarities between the data sets, some differences can be shown to exist. The data set of Smith and coworkers contained two African American families that contributed approximately one-half of the LOD score for the North American pedigrees studied, whereas our data contained no African American families. Differences in prostate cancer morbidity and mortality have been reported between Caucasians and African Americans (Walker et al. 1995). Other, more subtle differences are likely to exist as well.

Finally, given our significant evidence against linkage, we must consider the hypothesis that either the linkage to 1q24-25 is spurious or the reported proportion of linked families (34%) is an overestimate. Whereas the report of linkage by Smith and coworkers is supported by their parametric and nonparametric analyses, the estimated proportion of families with linkage (α), .34, is model dependent. The Hopkins model is unusual and deviates from the segregation analysis performed by Carter et al. (1992, 1993). The segregation data of Carter et al. suggest that the penetrances of prostate cancer loci are age dependent. This is largely unaccounted for in the Hopkins model. Instead, unaffected men <75 years of age are considered to have an unknown diagnosis, and unaffected men >75 years of age are grouped separately (table 1). Furthermore, all affected men are

Table 3

Comparison of Prostate Cancer Families

	Smith et al. (1996)	Present Study
Average age (range) at diagnosis, of all affected	64.9 years (39–85 years)	65.9 years (39–94 years)
Average age (range) at diagnosis, if genotyped	NA	64.9 years (51–82 years)
Percentage of genotyped affected <55 years of age	10	9
Average number (range) of affected per family	4.9 (3–15)	4.4 (3–9)
Average number (range) of genotyped affected per family	3.7 (2–11)	3.5 (2–7)
Number of families with:		
Two affected sibs	NA	5
Three affected sibs	NA	28
Four affected sibs	NA	15
Five affected sibs	NA	1

[a] NA = not available.

assumed to have a very low probability (.001) of being sporadic cases.

We were unable to detect any evidence of locus heterogeneity in our data set, using an admixture test, under either the Hopkins model or the Seattle model, although a small fraction of linked pedigrees might have been undetectable. The number of informative families required for detection of heterogeneity increases dramatically at small values of α. The families analyzed here could be reasonably expected to allow detection of heterogeneity at a minimum value of .21–.28 (Cavalli-Sforza and King 1986). We observed a subset of families in which all affected individuals share haplotypes. However, the proportion of families observed did not differ significantly from that expected under random chance. One possible explanation for an overestimate of α by Smith et al. is that the model presented was the best fitting of several models tested. It would be of interest to learn what estimate of α would be derived from a nonparametric analysis of heterogeneity in their data.

It is likely that multiple groups will comment on the fraction of pedigrees possibly linked to chromosome 1q24-25 and that a better estimate of the proportion of families with prostate cancer linked to this region will be derived from the evaluation of larger pools of families. We believe that this estimate is likely to be significantly $<34\%$. It is clear that multiple loci will be involved in the etiology of prostate cancer and that these results illustrate the complexity and difficulties faced in the assessment of linkage in a complex disease.

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References

Bookstein R (1994) Tumor suppressor genes in prostatic oncogenesis. J Cell Biochem Suppl 19:217–223

Bookstein R, MacGrogan D, Hilsenbeck SG, Sharkey F, Allred DC (1993) p53 is mutated in a subset of advanced-stage prostate cancers. Cancer Res 53:3369–3373

Bova GS, Carter BS, Bussemakers MJ, Emi M, Fujiwara Y, Kyprianou N, Jacobs SC, et al (1993) Homozygous deletion and frequent allelic loss of chromosome 8p22 loci in human prostate cancer. Cancer Res 53:3869–3873

Bova GS, MacGrogan D, Levy A, Pin SS, Bookstein R, Isaacs WB (1996) Physical mapping of chromosome 8p22 markers and their homozygous deletion in a metastatic prostate cancer. Genomics 35:46–54

Brooks JD, Bova GS, Ewing CM, Piantadosi S, Carter BS, Robinson JC, Epstein JI, et al (1996) An uncertain role for p53 gene alterations in human prostate cancers. Cancer Res 56:3814–3822

Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC (1992) Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 89:3367–3371

Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, Walsh PC (1993) Hereditary prostate cancer: epidemiologic and clinical features. J Urol 150:797–802

Carter BS, Ewing CM, Ward WS, Treiger BF, Aalders TW, Schalken JA, Epstein JI, et al (1990) Allelic loss of chromosomes 16q and 10q in human prostate cancer. Proc Natl Acad Sci USA 87:8751–8755

Cavalli-Sforza LL, King MC (1986) Detecting linkage for genetically heterogeneous diseases and detecting heterogeneity with linkage data. Am J Hum Genet 38:599–616

Cottingham RW Jr, Idury RM, Schäffer AA (1993) Faster sequential genetic linkage computations. Am J Hum Genet 53:252–263

Dong JT, Suzuki H, Pin SS, Bova GS, Schalken JA, Isaacs WB, Barrett JC, et al (1996) Down-regulation of the KAI1 metastasis suppressor gene during the progression of human prostatic cancer infrequently involves gene mutation or allelic loss. Cancer Res 56:4387–4390

Eagle LR, Yin X, Brothman AR, Williams BJ, Atkin NB, Prochownik EV (1995) Mutation of the MXI1 gene in prostate cancer. Nat Genet 9:249–255

Ichikawa T, Nihei N, Kuramochi H, Kawana Y, Killary AM, Rinker-Schaeffer CW, Barrett JC, et al (1996) Metastasis suppressor genes for prostate cancer. Prostate Suppl 6:31–35

Irvine RA, Yu MC, Ross RK, Coetzee GA (1995) The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. Cancer Res 55:1937–1940

Kagan J, Stein J, Babaian RJ, Joe YS, Pisters LL, Glassman AB, von Eschenbach AC, et al (1995) Homozygous deletions at 8p22 and 8p21 in prostate cancer implicate these regions as the sites for candidate tumor suppressor genes. Oncogene 11:2121–2126

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Macoska JA, Trybus TM, Benson PD, Sakr WA, Grignon DJ, Wojno KD, Pietruk T, et al (1995) Evidence for three tumor suppressor gene loci on chromosome 8p in human prostate cancer. Cancer Res 55:5390–5395

Massenkeil G, Oberhuber H, Hailemariam S, Sulser T, Diener

PA, Bannwart F, Schafer R, et al (1994) P53 mutations and loss of heterozygosity on chromosomes 8p, 16q, 17p, and 18q are confined to advanced prostate cancer. Anticancer Res 14:2785–2790

Morton RA, Ewing CM, Nagafuchi A, Tsukita S, Isaacs WB (1993) Reduction of E-cadherin levels and deletion of the alpha-catenin gene in human prostate cancer cells. Cancer Res 53:3585–3590

Ott J (1991) Analysis of human genetic linkage, 2d ed. Johns Hopkins University Press, Baltimore and London

Parker SL, Tong T, Bolden S, Wingo PA (1997) Cancer statistics, 1996. CA Cancer J Clin 46:5–27

Schellenberg GD, Bird TD, Wijsman EM, Moore DK, Boehnke M, Bryant EM, Lampe TH, et al (1988) Absence of linkage of chromosome 21q21 markers to familial Alzheimer's disease. Science 241:1507–1510

Schellenberg GD, Bird TD, Wijsman EM, Orr HT, Anderson L, Nemens E, White JA, et al (1992) Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. Science 258:668–671

Smith JR, Freije D, Carpten JD, Gronberg H, Xu J, Isaacs SD, Brownstein MJ, et al (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 274:1371–1374

St George Hyslop PH, Tanzi RE, Polinsky RJ, Haines JL, Nee L, Watkins PC, Myers RH, et al (1987) The genetic defect causing familial Alzheimer's disease maps on chromosome 21. Science 235:885–890

Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC (1990) Family history and the risk of prostate cancer. Prostate Suppl 17:337–347

Umbas R, Schalken JA, Aalders TW, Carter BS, Karthaus HF, Schaafsma HE, Debruyne FM, et al (1992) Expression of the cellular adhesion molecule E-cadherin is reduced or absent in high-grade prostate cancer. Cancer Res 52:5104–5109

Walker B, Figgs LW, Zahm SH (1995) Differences in cancer incidence, mortality, and survival between African Americans and whites. Environ Health Perspect Suppl 103:275–281

Williams BJ, Jones E, Zhu XL, Steele MR, Stephenson RA, Rohr LR, Brothman AR (1996) Evidence for a tumor suppressor gene distal to BRCA1 in prostate cancer. J Urol 155: 720–725

Zenklusen JC, Thompson JC, Troncoso P, Kagan J, Conti CJ (1994) Loss of heterozygosity in human primary prostate carcinomas: a possible tumor suppressor gene at 7q31.1. Cancer Res 54:6370–6373