Letters to the Editor

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No Evidence of Linkage for Chromosome 1q42.2-43 in Prostate Cancer

To the Editor:

On the basis of a genomewide search involving 47 French and German families with multiple cases of prostate cancer, Berthon et al. (1998) reported linkage to chromosomal region 1q42.2-43 (multipoint nonparametric Z score of 3.1, $P = .001$ at marker D1S2785). This finding is interesting because, although D1S2785 is considerably distal to the region 1q24-25—identified by Smith et al. (1996) as containing the putative hereditary prostate cancer locus HPC1—it is only 14 cM away from the marker D1S235, which also produced an elevated Z score in the scan by Smith et al. In an attempt to confirm the finding by Berthon et al., we have evaluated linkage to three markers in the 1q42.2-43 region in 97 unrelated families 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, and/or two or more individuals affected at 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, 69.2 years in Asian American families). The overall number of genotyped affected individuals and the overall mean age at diagnosis are similar to those found for the families reported by Berthon et al. (1998). A total of 382 samples were genotyped for the three markers. Genotyping was performed by the NHLBI (National Heart, Lung, and Blood Institute) Mammalian Genotyping Service at the Marshfield Medical Foundation (Yuan et al. 1997), by use of an ABI 377 sequencer to read fluorescently labeled primers for PCR products. We retyped individuals with ambiguous or missing genotypes and also retyped one or more relatives of each such individual to insure interlaboratory comparability. All samples were typed without knowledge of disease status.

Parametric LOD scores, nonparametric Z scores, and one-tailed P values were obtained with the software GENEHUNTER (Kruglyak et al. 1996). For the parametric analyses, we assumed an autosomal dominant mode of inheritance of a disease-susceptibility allele with frequency .003 and with penetrances as estimated in the segregation analysis by Carter et al. (1992). For the multipoint analyses, the three markers were assumed to be in the order shown in table 1. We estimated allele frequencies for the three markers in family founders, using the software FASTLINK (Cottingham et al. 1993; Schaffer et al. 1994).

Table 1 shows the three markers analyzed and their estimated positions in relation to D1S2785, the marker most strongly linked in the data of Berthon et al. (1998). Table 1 also shows multipoint LOD scores and nonparametric Z scores among the 48 families with mean age at diagnoses <67 years, among the 49 remaining families, and among all families. The negative values of the LOD scores and Z scores and the nonsignificant P values provide no support for linkage. The three markers each had negative two-point Z scores, and either negative or very small positive heterogeneity LOD scores. Berthon et al. found stronger evidence for linkage when analysis was restricted to the nine families in their data for which the age at diagnosis of all affected members in the last generation was <60 years. In contrast, we found negative scores similar to those in table 1 when we analyzed the 14 families in the present data who satisfied this criterion.

Thus, the present data do not support the possibility of a prostate cancer–susceptibility gene in the 1q42.2-43 region. Although the reasons for this lack of confirmation are unclear, several possible explanations come to mind. First, the spikes in this region seen by both Smith et al. and Berthon et al. could be due to chance, since the evidence supporting linkage is somewhat weak. The P value of .001 for the Z score of 3.1 for marker D1S2785, reported by Berthon et al., does not reflect the multiple testing involved in their genome scan. As

Table 1

Multipoint *Z* Values and NPL *Z* Values in 97 Families with Prostate Cancer, for Three Markers in Chromosomal Region 1q42.2–43

Marker	Distance[a] (cM)	Mean Age at Onset <67 Years (48 Families)		Mean Age at Onset >67 Years (49 Families)		All 97 Families	
		Multipoint *Z*	NPL*Z* (*P*)	Multipoint *Z*	NPL *Z* (*P*)	Multipoint *Z*	NPL *Z* (*P*)
D1S235	10.6	−11.46	−1.05 (.85)	−8.82	.40 (.31)	−10.18	.08 (.46)
D1S2785	0	…	…	…	…	…	…
D1S547	2.3	−16.42	−1.52 (.94)	−12.83	−1.01 (.84)	−14.69	−1.04 (.85)
D1S1609	9.3	−18.98	−1.92 (.98)	−10.78	−.36 (.63)	−14.69	−.97 (.83)

[a] From D1S2785, the marker most strongly linked in the data of Berthon et al. (1998).

noted by Lander and Kruglyak (1995), a nominal *P* value of .001, such as that reported by Berthon et al., can be expected to occur by chance once in every genome scan. To keep the chance of encountering a false positive ≤5%, one must impose a threshold of nonparametric Z score >4.1, LOD score >3.6, which corresponds to a significance level of $P = 2 \times 10^{-5}$.

A second possible explanation for the lack of confirmation is differences in ancestry and ethnicity in the two sets of families. Although most of the families in the present analysis were white and of European ancestry, their genetic heritage differs from that of the French and German families analyzed by Berthon et al.

Prostate cancer may be diagnosed at a more advanced stage in France and Germany than in the United States, because of international differences in the prevalence of screening with prostate-specific antigen (PSA). However, such differences are unlikely to explain the discrepant results, because most of the prostate cancers in the present U.S. series were diagnosed before PSA screening became prevalent. Moreover, there is no evidence that PSA screening is less likely to detect inherited cancer than sporadic cancer.

The lack of confirmation for this locus mirrors the difficulties in confirmation of the HPC1 locus. Some data have shown only weak confirmation (Hsieh et al. 1997; Cooney et al. 1997), whereas other data do not support linkage (McIndoe et al. 1997; Eeles 1998). This ambiguity may reflect considerable heterogeneity in hereditary prostate cancer, with any one locus accounting for only a small fraction of such disease. It also may reflect an inability to identify sporadics and to model them correctly.

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