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ORIGINAL ARTICLE

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Genomewide linkage analysis of familial prostate cancer in the Japanese population

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Abstract Prostate cancer (PC) is one of the most common causes of cancer mortality in Western countries, and familial aggregation of PC is well known. Multiple PC susceptibility loci have been reported in Western countries, but attempts to confirm the loci in independent data sets have proven to be inconsistent. We performed a genomewide linkage analysis with 53 affected sib pairs to identify genetic loci related to PC in a Japanese population. Two linkage analyses, GENEHUNTER-PLUS and SIBPAL, were applied and detected nominal statistical significance of linkage to PC at chromosome 1p and 8p, which were reported as being loci for PC in Caucasians. The best evidence of linkage was detected near *D8S550* on 8p23 (maximum $Z_{lr} = 2.25$, $P = 0.037$), and the second-best evidence of linkage was observed near *D1S2667* on 1p36 (maximum $Z_{lr} = 2.24$, $P = 0.034$). This is the first genetic mapping of PC in Japanese, and the results suggest that susceptibilities to PC lie close to *D8S550* on 8p23 and *D1S2667* on 1p36.

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Introduction

Prostate cancer (PC) [MIM 176807] is the most frequent malignant tumor among men over the age of 50 years and the second cause of cancer mortality in the United States (Parker et al. 1997). Substantial differences in the prevalence of PC are observed among populations, with African Americans having the highest prevalence of the disease and with Asians having the lowest prevalence (Parkin et al. 1997). In Japan, the age-adjusted incidence rate of PC calculated using the world population is low at 12.9 per 100,000 (Research Group for Population-based Cancer Registration in Japan 2003). However, it has increased over the past 10 years, probably due to a trend to Westernized lifestyle and diet and the increased use of serum prostate-specific antigen (PSA) testing (Nakata et al. 2000).

Epidemiological data suggest that a strong familial component is involved in the etiology of at least a subset of PC patients. A large number of studies have reported that first-degree relatives (fathers, sons, and brothers) of an affected individual are two-to-three times more likely to develop PC compared with cases in the general population (Steinberg et al. 1990; Whittemore et al. 1995). The independent segregation analyses, which found that both early age of onset and the presence of multiple affected family members were strong predictions of risk in relatives (Carter et al. 1992; Grönberg et al. 1997; Schaid et al. 1998; Valeri et al. 2003), most likely support an autosomal dominant model of inheritance.

We have been collecting PC pedigrees in Japan. According to our previous report, the members of familial PC were significantly younger at the time of diagnosis compared with the mean onset age of sporadic cases (Ohtake et al. 1998). This indicates a substantial genetic background in our familial cases should exist despite the low frequency of PC among Japanese.

Numerous gene-mapping studies have indicated evidence of linkage to regions that possibly contain disease-susceptibility loci for PC. The first region detected in 91 nuclear families of northern European origin was on chromosome 1q24–25 (HPC1 [MIM 601518]) (Smith et al. 1996). Subsequently, several other susceptibility loci have been identified by linkage analyses in nuclear families, including PCAP [MIM 602759] at 1q42–43 (Berthon et al. 1998), HPCX [MIM 300147] at Xq27–28 (Xu et al. 1998), CAPB [MIM 603688] at 1p36 (Gibbs et al. 1999), and HPC20 at 20q13 (Berry et al. 2000). In addition, loci at 4q24–25, 8p22–23 (Smith et al. 1996), 16p13 (Suarez et al. 2000), and 19q12 (Witte et al. 2000) were reported. The first PC-susceptibility gene, *ELAC2* [MIM 605367], was identified at the HPC2 locus on 17p11 from extended families of the Utah Population Database (Tavtigian et al. 2001). At the HPC1 locus, mutations in *RNASEL* [MIM 180435] have been associated with hereditary and sporadic PCs (Carpten et al. 2002). The locus of particular interest at 8p was first identified by the studies of frequent loss of heterozygosity (LOH) in PC cells (Bova et al. 1993; MacGrogan et al. 1994; Suzuki et al. 1995). Recently, germline mutations and sequence variants of the macrophage scavenger receptor 1 gene (*MSR1* [MIM 153622]) of chromosome 8p22 have been reported to be associated with PC risk (Xu et al. 2002). Replication studies for the linkage regions presented conflicting results within and between studies, indicating a complex nature of PC. PC is likely to be a genetically heterogeneous disorder, with several genetic and environmental factors contributing to the development of disease.

Thus far, gene-mapping studies of PC were performed among non-Asian populations, and it is important to survey loci to PC in the Asian population because loci specific to the Asian population might play important roles in the etiology in the distinct population. In the present study, we conducted a genomewide linkage analysis in 44 nuclear Japanese families affected with PC.

Materials and methods

Disease criteria and pedigrees

The present study included 92 PC patients in 44 Japanese nuclear families with family history of PC in first-degree relatives, and the number of affected sib pairs was 53. The family structure was as follows: 41 affected pairs, two affected trios, and one affected quartet. The families with three or more affected members and the distinguished families containing complications of brain cancer are displayed in Fig. 1. All PC patients were diagnosed by histological examinations at Gunma University Hospital and its affiliated hospitals. Age at diagnosis ranged from 55 to 88 years, with a mean age of 69.5. Clinical stages were A in two, B in 41, C in 25, D in 22, and unknown in two according to Jewett's staging system (Jewett et al. 1975). Gleason score (Gleason 1992) was assigned to PC for pathological assessment of aggressiveness, and the score range was from 2 to 10. Higher scores indicate that the tumor cells were less differentiated and appeared to be solid. Gleason scores were lower than 7 in 26, equal or higher than 7 in 65, and unknown in one. The Ethical Committee of Gunma University and University of Tokyo approved this study, and all patients gave written informed consent.

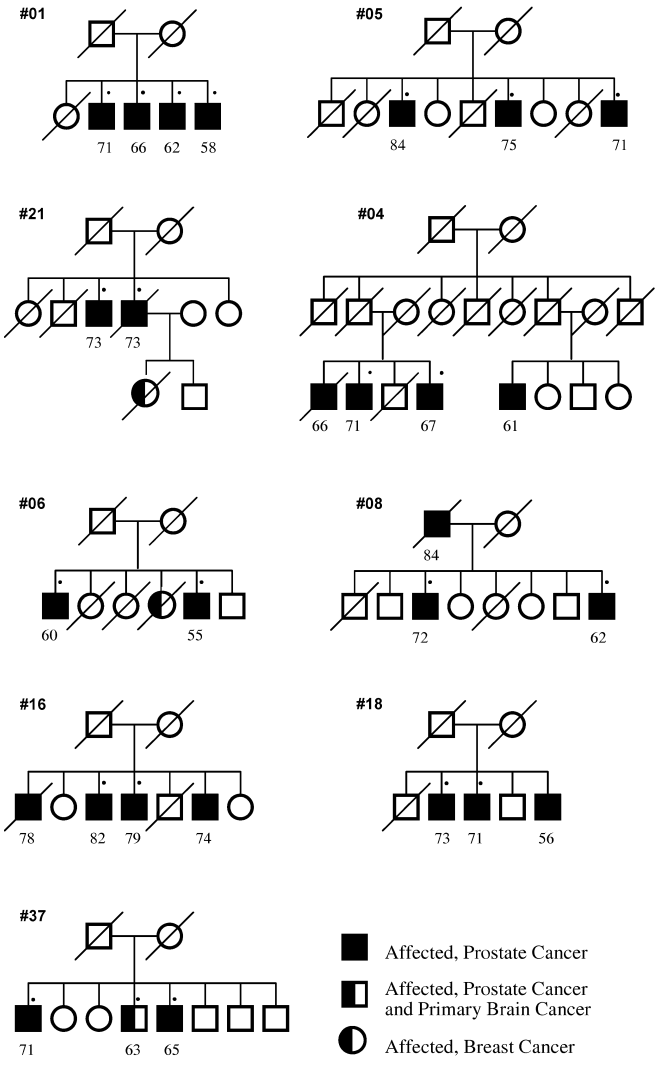

Fig. 1 Representative pedigrees with three or more affected prostate cancer (PC) patients. Representative pedigrees out of 44 families were shown with pedigree number. *Fully filled boxes* represent men affected with PC. *Half-filled boxes* represent men with PC and primary brain cancer simultaneously. *Half-filled circles* indicate women affected with breast cancer. *Open boxes and circles* represent unaffected men and women, respectively. A *filled superscripted circle* indicates that a DNA sample from individual was available and their genotype is known. The *numbers under the boxes* represent the age at diagnosis of PC

Microsatellite genotyping

Genomic DNA was isolated from whole blood cells using a GENOMIX kit (Talent srl. Treisete, Italy). Multiplex fluorescent genotyping was performed using ABI PRISM linkage mapping set version 2.5 (Applied Biosystems). Because several markers were not polymorphic in Japanese (Ikari et al. 2001), a set of 47 markers obtained from online information (GDB: http://gdb.org/) was added to the original set to fill in gaps (Onda et al. 2001). An extra sequence was attached to the 5' end of reverse primer to promote nontemplated addition of adenine so that accurate genotyping could be achieved (Brownstein et al. 1996). Genomescan was performed with a total of 405 microsatellite markers having average heterozygosity of 0.76 (minimum: 0.60) and average interval of 8.8 cM (maximum: 20.7 cM). Marker positions (in Kosambi centimorgans) were obtained from Marshfield Medical Research Foundation (Broman

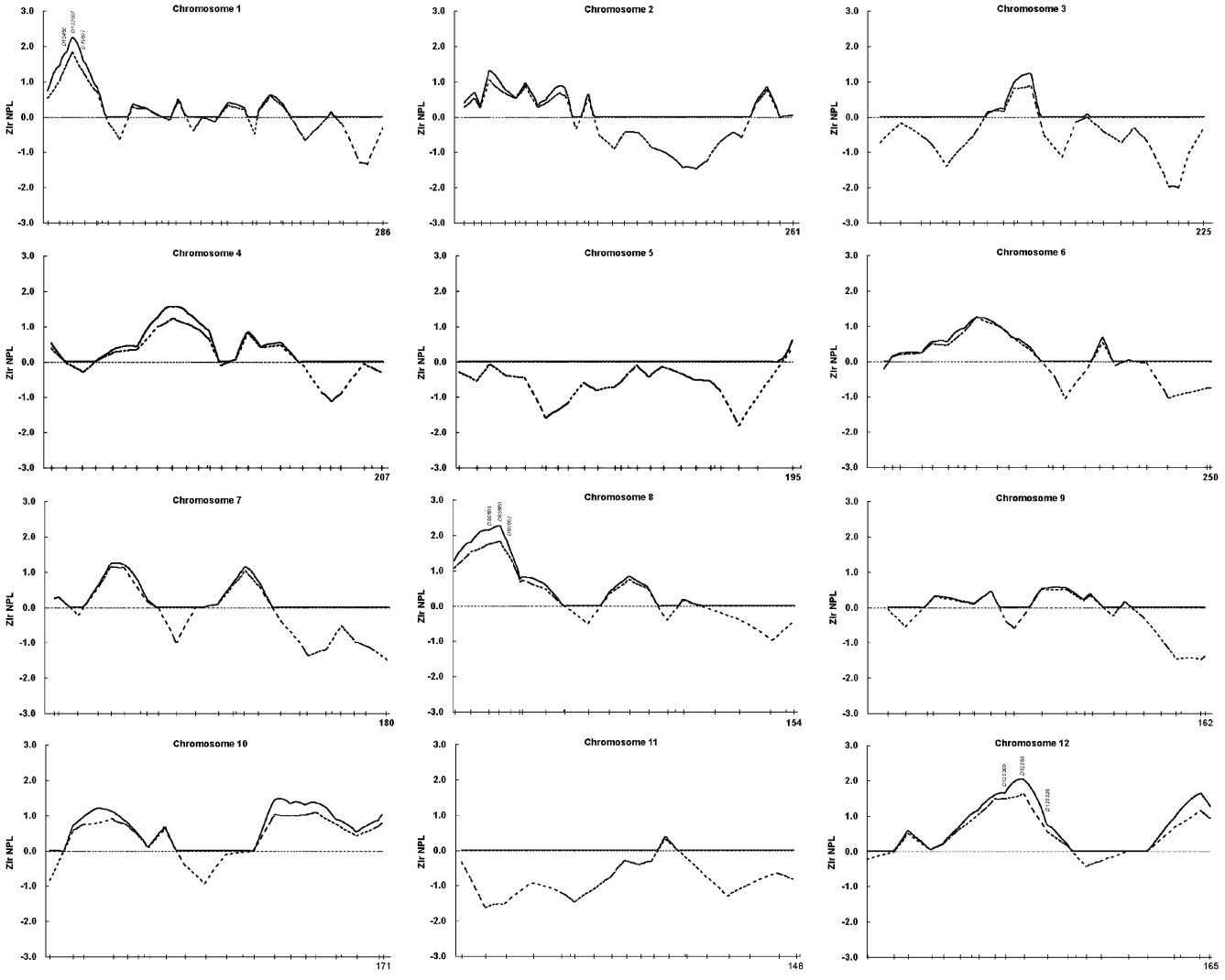

Fig. 2 Genomewide linkage analysis of prostrate cancer (PC) with 53 affected sib pairs. Z_{lr} score (*solid lines*) and NPL score (*dotted lines*) for 405 markers genotyped on 92 patients with PC who were from 53 multiplex sibships. The *check marks* show the position of the markers. The total length of each analyzed chromosome (in cM) is shown in the *lower right corner*

et al. 1998). For chromosome 1p and 8p that demonstrated significant linkage using the framework marker set, microsatellite markers were added for fine mapping that covers < 5 cM in the two regions (*D1S434, D1S2644, D8S503, D8S552,* and *D8S1827*).

Affected sib-pair linkage analysis

Because the mode of inheritance for PC is still uncertain, at least in our pedigrees, we applied two different nonparametric linkage methods, GENEHUNTER-PLUS (version 1.3)/GENEHUNTER (version 2.1) (Kong and Cox 1997, Kruglyak et al. 1996) for multipoint analysis and SIBPAL program from SAGE package (version 3.1) (Elston et al. 1997) for single-point analysis. Multipoint analysis of the data from the genomewide scan was performed with weighting each family equally by GENEHUNTER-PLUS, a modified version of GENEHUNTER. GENEHUNTER-PLUS assumes a linear model for risk to obtain greater accuracy of the variance than the original program. Results are reported with Z_{lr} score and traditional NPL score. GENEHUNTER (version 2.1) was utilized to estimate the mean proportion of alleles shared IBD (identical by descent) and to calculate information contents. The SIBPAL program estimated the mean ratio (π) of alleles shared IBD among affected sib pairs at each microsatellite marker. The obtained π was tested against the null hypothesis of no linkage ($\pi = 0.5$). The statistic has a standard normal distribution under the null hypothesis, and because the alternative hypothesis of linkage is given when IBD sharing is over 50%, the test is one sided. Accordingly, accurate *P* values can be obtained by use of a one-sided *t* test, as implemented in the SIBPAL program. Allele frequencies of microsatellite markers were calculated with 64 unrelated Japanese subjects.

Results

A total of 44 families comprising 53 affected sib pairs was subjected to the genomewide linkage study. Multipoint Z_{lr} scores and NPL scores for all chromosomes (except the Y chromosome) were displayed in Fig. 2. Two chromosomal regions gave nominal statistical evidence for linkage (Z_{lr} score > 2.2). The region with the best evidence of linkage was found on chromosome 8p23 with maximum Z_{lr} score of 2.25 near marker *D8S550*, and the second peak was observed on chromosome 1p36 with maximum Z_{lr} score of 2.24 near marker *D1S2667*. In addition to these

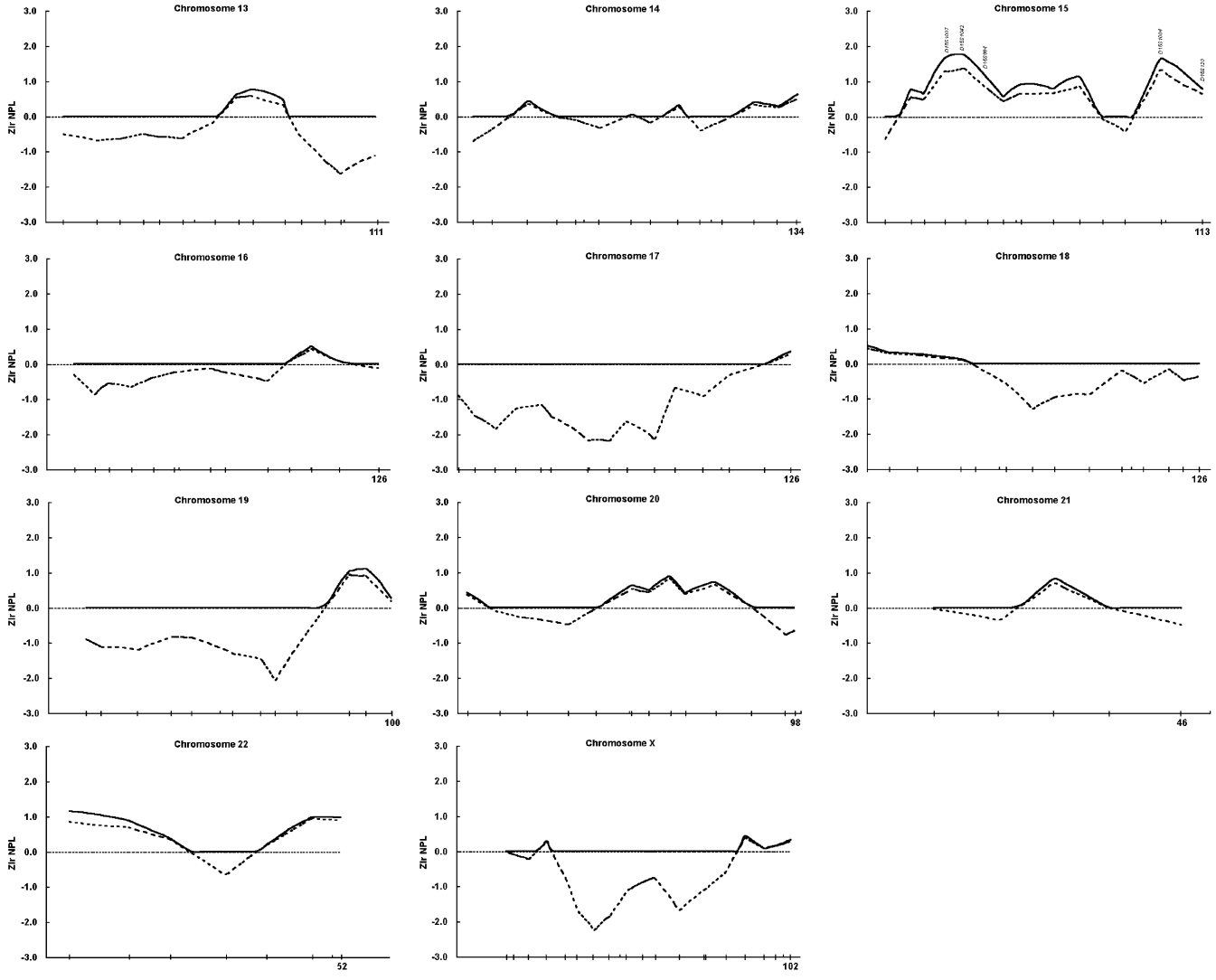

Fig. 2 (Continued)

regions, significant linkage was observed on chromosome 12q13 with maximum Z_{lr} score of 2.01 near marker *D12S83*, 15q13 with maximum Z_{lr} score of 1.75 near marker *D15S1042*, and 15q26 with maximum Z_{lr} score of 1.62 near marker *D15S1004*. The best IBD sharing of 65.5% ($Z_0 = 0.096$, $Z_1 = 0.500$, $Z_2 = 0.404$) was observed at *D1S2667* on 1p36, and the second-best IBD sharing of 63.5% ($Z_0 = 0.135$, $Z_1 = 0.500$, $Z_2 = 0.365$) was found at *D8S550* on 8p23. The alternative linkage test with SIBPAL that gives accurate *P* value showed positive evidence of linkage with *D1S2667* ($P = 0.0069$) and *D12S83* ($P = 0.0058$), and weak evidence of linkage with *D8S550* ($P = 0.0423$), *D8S503* ($P = 0.0345$), and *D15S1004* ($P = 0.0105$) (Table 1).

Discussion

The linkage results of the genomewide scan with 44 multiplex Japanese PC families revealed that two loci of

Table 1 Multipoint and single-point results for regions on chromosomes 1p, 8p, 12q, and 15q that show nominal linkage

Locus	Marker	Position from pter (cM)	GENEHUNTER/ GENEHUNTER-PLUS					SIBPAL
			IBD sharing	Z_{lr}	NPL	MLOD	*P* value	*P* value
1p36	*D1S2667*	24.68	0.653	2.24	1.82	1.09	0.034	0.0069
8p23	*D8S503*	20.61	0.625	2.13	1.73	0.98	0.041	0.0345
	D8S550	21.33	0.635	2.25	1.80	1.10	0.037	0.0423
	D8S552	26.43	0.576	1.49	1.30	0.48	0.097	0.3568
12q13	*D12S83*	75.17	0.631	2.01	1.60	0.88	0.055	0.0058
15q13	*D15S1042*	32.58	0.615	1.75	1.36	0.66	0.088	0.0648
15q26	*D15S1004*	98.44	0.598	1.62	1.31	0.57	0.096	0.0105

chromosomes 8p23 and 1p36 confer susceptibility to PC. Thus far, numerous linkage studies have been reported for PC; however, all are results for non-Asian populations. It is well recognized that ethnicity is a risk factor for PC, i.e., the highest incidence is observed in the African American population, and the lowest frequency is observed in the Asian population. Thereby, linkage analysis in a distinct population might provide new implications in the etiology of PC. Because the relative power and accuracy of linkage tests varies with the methods used, we applied two different programs, SIBPAL from the SAGE package and GENEHUNTER-PLUS. SIBPAL calculates the excess allele sharing comparing with null hypothesis under no linkage by *t* statistics. Thereby, accurate *P* values can be obtained. GENEHUNTER-PLUS is a likelihood method calculating LOD-type score, which is generally a more powerful linkage analysis than the probability test.

We obtained two loci with nominal evidence of linkage for PC on chromosome 1p36 and 8p23. The peak Z_{lr} scores at 8p23 and 1p36 were 2.25 near *D8S550* and 2.24 near *D1S2667*, respectively (Fig. 2). In our data set, significant evidence of linkage to published loci such as HPC1, HPC2, PCAP, HPC20, and HPCX, and loci at 4q24–25, 16p12, and 19q13, were not observed (Z_{lr} score = 0–0.61). The two linkage regions, 8p23 and 1p36, were both reported as being the PC-susceptibility loci by several different data sets (Smith et al. 1996; Gibbs et al. 1999; Gibbs et al. 2000; Suarez et al. 2000; Witte et al. 2000; Badzioch et al. 2000; Goddard et al. 2001; Xu et al. 2001a; Xu et al. 2001b). The short arm of chromosome 8, specifically 8p22–23, was first identified by the studies of frequent LOH in PC cells, suggesting the existence of tumor suppressor genes associated with progression of PC (Bova et al. 1993; MacGrogan et al. 1994; Suzuki et al. 1995).

The macrophage scavenger receptor 1 gene (*MSR1*) and the farnesyldiphosphate farnesyltransferase 1 gene (*FDFT1*) locate in this region. Several germline mutations, mostly rare nonsynonymous substitutions of *MSR1*, have been reported to be associated with risk for PC (Xu et al. 2002). *MSR1* is localized 7 cM centromeric from *D8S550* that showed the peak linkage in Japanese. *D8S552* is the closest marker to *MSR1*, and a maximum Z_{lr} score of 1.49 was observed with the marker. *FDFT1* is associated with the cholesterol biosynthetic pathway and the gene product catalyzes conversion of trans-farnesyldiphosphate to squalene. Typical PC has commonly a characteristic of androgen sensitivity, and androgens modulate the expression and activity of enzymes involved in lipogenesis (Swinnen et al. 1997). Thereby, *FDFT1* holds a possibility that associates with PC risk. Chromosome 1p36 was highlighted because the loci appear to be responsible for inherited disease in a defined subset of families with PC that share a family history of primary brain cancers or breast cancers (Gibbs et al. 1999; Suarez et al. 2000; Witte et al. 2000; Badzioch et al. 2000; Xu et al. 2001a). Although it has not been reported as a region of frequent LOH in PC, it has been frequently cited as a region of LOH in a variety of types of brain tumors and central nervous system (CNS) tumors (Bello et al. 1995; Kaghad et al. 1997). In our family set, one PC patient had primary brain cancer simultaneously (#37) and two PC families had family members with breast cancer (#06 and #21) (Fig. 1). We excluded these three families to re-perform the linkage; however, no major reduction or increase of evidence of linkage was observed.

Although Z_{lr} score cannot be directly compared with LOD score, the observed evidence of linkage would not reach to the genomewide screen criteria of "suggestive linkage," as proposed by Lander and Kruglyak (1995). Given the moderate number of sib pairs in the current study, mainly due to the low frequency of PC in Japanese, the confirmative linkage results could not be attained. However, it should be noted that the large-scale linkage analysis also failed to detect even "suggestive linkage" (Suarez et al. 2000, Xu et al. 2001b). Because the linkage results of PC were hardly replicated, there should be a tremendous influence of heterogeneity in the susceptibility of PC. Therefore, large-scale studies of well-distinguished subjects are warranted to confirm the evidence of linkage for PC.

In summary, we performed the genomewide linkage analysis with 44 PC families in the Japanese population and mapped two chromosomal loci, 8p23 and 1p36, for PC.

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