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Evaluation of Linkage of Markers on Chromosome 6p With Schizophrenia in Taiwanese Families

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Previous studies have indicated possible linkage of schizophrenia with chromosome 6p21-24. In an attempt to replicate these findings, we studied the linkage of schizophrenia with nine markers on chromosome 6p21-24 in 39 Taiwanese schizophrenic nuclear families with at least two affected siblings. Two diagnostic models (narrow: *Diagnostic and Statistical Manual of Mental Disorders*-IV schizophrenia only; and broad: including schizophrenia, schizoaffective, and other nonaffective psychotic disorders) were used to define the disease phenotypes. With the broad and narrow diagnostic models, the marker D6S296 produced maximum two-point lod scores of 1.46 ($\theta = 0.2$) and 1.35 ($\theta = 0.2$), respectively, in the recessive inheritance model. Assuming locus heterogeneity, a multipoint lod score of 0.85 was obtained between markers D6S296 and D6S277 under the narrow/recessive model. Maximum nonparametric lod scores of 1.25 ($p = 0.09$) and 1.36 ($p = 0.08$) were observed, but still not statistically significant, at D6S296 in the narrow and broad diagnostic models, respectively. Both two-point analysis of the dominant model (lod score 0.85) and nonparametric analysis (lod score 1.25) showed a mild peak lod score appeared at marker D6S 285 as well. The results add some support to the suggestive linkage of schizophrenia with markers in the regions of chromosome 6p22 and 6p24 in an ethnically distinct Taiwanese sample. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 96:74–78, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

A genetic component in the etiology of schizophrenia has been emphasized based on family, twin, and adoption studies [Cloninger, 1988; Gottesman and Shields, 1982]. The mode of inheritance is not known, however, because segregation analyses have revealed contradictory results [Kendler and Diehl, 1993; Risch and Baron, 1984; Tsuang et al., 1982]. Linkage analysis using highly polymorphic markers is an important strategy in searching for the location of potential vulnerability gene(s) of schizophrenia.

A number of studies have found reproducible evidence of such linkage [d'Amato et al., 1992; Kendler et al., 1996; Moises et al., 1995; Pulver et al., 1994; Schwab et al., 1995; Straub et al., 1995; Vallada et al., 1995; Wang et al., 1995]. The initial findings of linkage of schizophrenia with chromosome 6p, as reported by Wang et al. [1995], Straub et al. [1995], Schwab et al. [1995], Antonarakis et al. [1995], and Moises et al. [1995], included a wide range of genome markers from 6p24 (F13A1) to 6p21.2 (D6S282). Chromosome 6P markers were further found to have modest linkage with schizophrenia [Maziade et al., 1997; Schizophrenia Linkage Collaborative Group, 1996]. In a meta-analysis of nine linkage studies comprising 11 chromosome 6P markers, from the most proximal (D6S470) to the most distal (D6S291), Turecki et al. [1997] found markers D6S274 and D6S285, which are 2 cM apart on the genome map, had the most strongly significant pooled p-values.

Some other studies [Daniels et al., 1997; Garner et al., 1996; Gurling et al., 1995; Mowry et al., 1995; Riley et al., 1996] could not confirm these findings. Recent reports using whole genome scans [Faraone et al.,

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1998; Kaufmann et al., 1998; Levinson et al., 1998] also showed negative results of linkage of schizophrenia with chromosome 6p markers.

Previous studies suggested that regions of chromosome 6p markers D6S296, D6S285, and D6S291 may be linked with schizophrenia. The samples of these previous studies were of Caucasian populations or of mixed ethnic origins. It is important to investigate whether these findings can be replicated in a distinct ethnic group. Therefore, we recruited the families of Taiwanese schizophrenic probands with at least two affected siblings and sought to confirm these findings.

MATERIALS AND METHODS

Subjects

Schizophrenic probands who had at least two affected sibling(s) were identified from the psychiatric service settings of the Department of Psychiatry, National Taiwan University and the University Affiliated Taoyuan Psychiatric Center. Both hospitals are located in northern Taiwan and serve as referral centers for patients from the northern region of Taiwan. All members of the immediate family including parents and unaffected siblings were also recruited. The data collection was initiated after informed consent was obtained from the identified study subjects and their families. Psychiatric diagnoses were made according to the Psychiatric Diagnostic Assessment Schedule [Hwu et al., 1987, 1991]. The diagnostic interview was performed by the senior author (Hwu). The clinical medical chart records also were used as supplementary data for the final diagnostic ascertainment, according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [American Psychiatric Association, 1994] for definition of psychiatric disorders.

Genotyping

Genomic DNA was isolated from lymphocytes using a modified salting-out method [Lahiri et al., 1993]. Nine highly polymorphic microsatellite markers from the Genethon linkage map [Dib et al., 1996] were used (Table I). Three markers around D6S296 (mean distance of 2.3 cM), and four markers around D6S285 (mean distance of 1.9 cM) were used for the study. Two other markers were also used: D6S291, with a distance of 18.2 cM from D6S285, and D6S461, which is located between D6S285 and D6S291 and is 8.1 cM from D6S285.

These nine microsatellite markers were genotyped by means of polymerase polymorphism chain reaction (PCR) techniques [Saiki et al., 1985]. For all reactions, 20 ng of genomic DNA was used as the template. Fluorescent 5′ labeled primers were used for amplification of these markers. The allele types of these markers were determined by analysis with Genescan™ and Genotyper™ software by comparison of the fragment sizes with an internal standard in an ABI prism 310 Genetic Analyzer (Perkin-Elmer, U.S.A.). Genotypes were read independently by two individuals blind to the clinical status of the subjects.

Statistical Analyses

Two diagnostic (narrow and broad) phenotypes were used to define the disease phenotype. The narrow phenotype included DSM-IV schizophrenia only. The broad phenotype included schizophrenia, schizoaffective disorders, and other nonaffective psychotic disorders. Two-point linkage analysis was performed with the MLINK program of LINKAGE (FASTLINK v 3.0) [Cottingham et al, 1983; Lathrop et al, 1984]. Multipoint lod score analyses and nonparametric linkage analyses were performed on the GENEHUNTER (Version 1.1) program [Kruglyak et al., 1996]. Both parametric and nonparametric linkage analyses were performed. In the parametric analyses the parameters of genetic models used for linkage analyses were as follows. Allelic frequencies were calculated from 69 unrelated individuals in the pedigrees. The disease gene frequencies (%) in the dominant and recessive models were 0.005 and 0.10, respectively. In both the narrow/dominant model and the narrow/recessive model, the penetrance was 0.5 and the probability of phenocopy was 0.005. The penetrance and the probability of phenocopy were 0.7 and 0.01, respectively, in both the broad/dominant and the broad/recessive model.

RESULTS

Thirty-nine schizophrenic families with at least two affected siblings were recruited in this study. Of these, 67 parents available for study; five (7.5%, all females) in five separate families were schizophrenic. Another one (female) had nonaffective psychotic disorder. Eighty-one (68.1%) (51 male, 30 female) of the 119 sib-

TABLE I. Summary of Characteristics and Distances of Microsatellite Markers Used in this Study

Distance in linkage analysis (cM)	Microsatellite markers	Chromosome region	Allele type	Heterzygosity	Size range (bp)
0.00	D6S296	6p24.2-p23	13	0.78	260–300
1.01	D6S277	6p24.2-p23	10	0.79	98–120
4.64	D6S470	6p24.2-p23	7	0.80	120–134
18.49	D6S289	6p23	7	0.79	215–227
19.50	D6S260	6p23	11	0.84	159–179
22.38	D6S274	6p23	9	0.81	170–186
24.11	D6S285	6p22.3-p22.2	6	0.75	207–221
32.24	D6S461	6p22-p21	9	0.72	246–268
42.28	D6S291	6p21.3-p21.2	7	0.70	198–210

lings available (72 male, 47 female) were affected with either schizophrenia or schizoaffective disorder. The mean age of onset of the initial nonspecific clinical symptoms was 21.7 (±7.0) years, while the mean age of onset of definite psychotic symptoms (delusion, hallucination, thought disorder, or bizarre behavior) was 22.5 (±6.8) years. Seventy-seven siblings (65.5%) (48 male, 29 female) were schizophrenic, whereas three (2.5%) (two males, one female) had schizoaffective disorder. Among the siblings of these 39 families, there were three affected triplets and 36 affected pairs.

Table II shows the results of two-point linkage analyses, assuming the existence of heterogeneity, under narrow and broad phenotype models. In the recessive inheritance model, D6S296 had the highest lod score of the nine markers, regardless of whether the broad or narrow definition was used. In the dominant model, the lod scores showed small peaks at D6S285 in both the narrow and broad phenotype analyses.

Table III shows the results of multipoint linkage analysis under the assumption of genetic heterogeneity, as well as the results of nonparametric analysis. In nonparametric analysis there were two high lod score peaks of 1.25 ($p = 0.09$) and 1.26 ($p = 0.09$) at D6S296 and D6S285, respectively, in the narrow disease phenotype model. Under the broad disease phenotype model there were also two high lod score peaks of 1.36 ($p = 0.08$) and 1.14 ($p = 0.12$) at D6S296 and D6S285, respectively. There were small peaks of lod scores of 0.74 ($p = 0.22$) and 0.76 ($p = 0.22$) at D6S291 in both the narrow and broad disease phenotype models.

In the recessive transmission model, the lod scores at D6S296 in the narrow and broad disease phenotype models were 0.84 and 0.80, respectively. A mild peak of lod score (0.78) was also found at D6S291 in the dominant inheritance/broad disease phenotype model.

DISCUSSION

The results of this study, using a distinct ethnic group of Taiwanese families, were compatible with the results reported by some authors with study populations of different ethnic origin [Antonarakis et al, 1995; Moises et al., 1995; Schwab et al., 1995; Straub et al., 1995; Wang et al., 1995].

Although the lod scores revealed in this study were not very high, these results do provide additional support for the linkage of schizophrenia with two or three regions of chromosome 6p (Tables II and III). Two things support this assertion. First, the results obtained by nonparametric analysis are not in conflict with these parametric analyses performed under dominant and recessive models inheritance models. These were observed in the analyses of markers of D6S296, D6S285 (D6S274), and D6S291 (Tables II and III).

Second, there was a gradual change of lod score among nearby markers separated by short distances. The lod scores of D6S296, D6S277, and D6S470 were 1.25, 1.15 and 1.23, respectively, in nonparametric analyses. The lod score of D6S289, which is located far from D6S470, was only 0.49. In parametric analyses, under the recessive model, the lod scores of D6S296 were 1.35 and 1.46 (both at $\theta = 0.2$) in narrow and broad models, respectively. When recessive inheritance was assumed, the lod scores of D6S277 were 0.45 ($= 0.2$) in the narrow model and 0.31 ($\theta = 0.3$) in the broad model. D6S285 and D6S291 also had high lod scores in both the recessive/narrow and recessive/broad models.

Finally, when genetic heterogeneity was assumed, D6S296 had the strongest evidence of linkage with schizophrenia under the recessive model, whereas D6S285 (D6S274) and D6S291 showed the strongest evidence of linkage under the dominant model. These data are compatible with the hypothesis of genetic heterogeneity of schizophrenia [Gottesman and Shields, 1982; Kendler and Diehl, 1993; Tsuang et al., 1982] and suggest the need for further study of this hypothesis.

This study included 39 nuclear families composed of 186 subjects as the study samples. Because of its small size, this statistical power of this study may not have been sufficient to detect linkage. Therefore, we implemented a simulation test to evaluate the power to detect linkage in this sample. Under the assumption of heterogeneity with 40 and 70% of the families linked, the powers to detect a lod score ≥3 in the recessive model were 0.32 and 0.62, respectively. Because of the limited statistical power, our results cannot be considered conclusive; however, they are still of value in providing further suggestive evidence of linkage of schizophrenia with various regions of chromosome 6p. Further studies, using a larger number of study families of a distinct ethnic group, of the linkage of chromosome 6p markers with schizophrenia are encouraged.

TABLE II. Two-Point Linkage Results of Schizophrenia for Markers on Chromosome 6p With the Narrow and Broad Disease Phenotypes for the Taiwanese Pedigrees ($N = 39$)

	Narrow model						Broad model					
	Dominant A- lod score			Recessive A- lod score			Dominant A- lod score			Recessive A- lod score		
Marker	θ	A-lod	α	θ	A-lod	α	θ	A-lod	α	θ	A-lod	α
D6S296	0.3	0.19	1.0	0.2	1.35	1.0	0.3	0.12	0.95	0.2	1.46	1.0
D6S277	0	0	0	0.2	0.45	0.75	0	0	0	0.3	0.31	1.0
D6S470	0.4	0.03	1.0	0	0.49	0.25	0	0	0	0	0.21	0.15
D6S289	0.3	0.14	1.0	0.4	0.03	1.0	0.3	0.09	0.9	0	0	0
D6S260	0.3	0.14	1.0	0.4	0.03	1.0	0.4	0.06	1.0	0	0	0
D6S274	0.2	0.16	0.7	0.4	0.03	1.0	0.3	0.05	0.7	0	0	0
D6S285	0.1	0.85	1.0	0.2	0.32	0.9	0.1	0.72	0.85	0.2	0.32	0.9
D6S461	0	0	0	0	0.06	0.1	0	0	0	0	0	0
D6S291	0.2	0.18	0.65	0.4	0.02	1.0	0.2	0.57	0.95	0.4	0.01	1.0

TABLE III. Lod Scores of Parametric Multipoint Linkage Analyses Under Assumption of Genetic Heterogeneity in Narrow and Broad Disease Phenotypes for the Taiwanese Pedigrees ($N = 39$)

	Narrow model						Broad model					
	Dominant model		Recessive model		Nonparametric analysis		Dominant model		Recessive model		Nonparametric analysis	
	lod score	alpha	lod score	alpha	lod score	*p*-value	lod score	alpha	lod score	alpha	lod score	*p*-value
D6S296	0.23	0.23	0.84	0.27	1.25	0.09	0.10	0.15	0.80	0.24	1.36	0.08
D6S277	0.15	0.19	0.81	0.26	1.12	0.12	0.04	0.10	0.73	0.23	1.17	0.12
D6S470	0.20	0.24	0.61	0.25	1.23	0.10	0.04	0.10	0.30	0.16	1.10	0.13
D6S289	0.07	0.15	−0.00	0.00	0.49	0.30	0.00	0.04	−0.00	0.00	0.38	0.35
D6S260	0.17	0.24	−0.00	0.00	0.76	0.21	0.03	0.10	−0.00	0.00	0.63	0.26
D6S274	0.40	0.36	−0.00	0.00	1.26	0.09	0.11	0.18	−0.00	0.00	1.14	0.12
D6S285	0.51	0.40	−0.00	0.00	1.25	0.09	0.23	0.25	−0.00	0.00	1.14	0.12
D6S461	0.21	0.26	0.00	0.04	0.47	0.31	0.40	0.35	−0.00	0.00	0.38	0.35
D6S291	0.44	0.35	0.00	0.10	0.74	0.22	0.78	0.41	−0.00	0.01	0.76	0.22

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