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Linkage Evidence of Schizophrenia to Loci Near Neuregulin 1 Gene on Chromosome 8p21 in Taiwanese Families

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Positive linkage of schizophrenia to chromosome 8p22-21 loci had been reported in the Caucasian samples. This study was designed to replicate this finding by using eleven microsatellite markers on chromosome 8p22-21 in 52 Taiwanese schizophrenic families with at least two affected siblings. Two phenotype models (narrow: DSM-IV schizophrenia only; and broad: including schizophrenia, schizoaffective, and other non-affective psychotic disorders) were used to define the disease phenotype. Maximum non-parametric linkage scores (NPL score) of 2.45 ($P = 0.008$) and 1.89 ($P = 0.02$) were obtained for the marker D8S1222 under the broad and narrow models, respectively. Positive linkage was found across about a 4-cM region. The marker D8S1222 was about 400 kbp distal to the exon 1 of glial growth factor 2 (GGF2), an isoform of Neuregulin 1 gene (NRG1), which has been highly suggested to be a candidate gene for schizophrenia. The results provide suggestive linkage evidence of schizophrenia to loci near NRG1 on chromosome 8p21 in an ethnically distinct Taiwanese sample. Further exploration of the candidate gene and nearby chromosome regions is warranted.

KEY WORDS: schizophrenia; linkage; chromosome 8p; Neuregulin 1 gene

INTRODUCTION

Schizophrenia is a serious neuropsychiatric illness affecting about 1% of the general population. Family, twin, and adoption studies have demonstrated that schizophrenia is predominantly genetically determined and has high heritability [McGuffin et al., 1994]. The mode of transmission is still not clear, though a multilocus model is favored in which several genes each having a small effect and acting in epistasis lead to schizophrenia according to the pattern of risk to families [Risch, 1990]. Previous linkage studies have identified a few candidate chromosome regions. However, the individual vulnerability locus has been difficult to determine definitively. Because so many aspects of the statistical analysis of linkage to complex traits like schizophrenia are uncertain, it is difficult in any single study to exclude the possibility of a false positive. Replication is therefore critical for evaluating putative linkage findings [Lander and Kruglyak, 1995].

The 8p22-21 region was first identified as possible genetic linkage to schizophrenia in 57 American families, with a maximum admixture log of odds ratio (LOD) score of 2.35 at D8S136, under a dominant model, and 2.20 under a recessive model [Pulver et al., 1995]. This finding was followed-up within the same family sample, with denser markers, and resulted in a LOD score of 3.64 ($P = 0.0001$) at D8S1771 [Blouin et al., 1998]. Another study obtained maximal heterogeneity LODs (HLODs) of 2.52 at D8S1715 in 265 Irish families [Kendler et al., 1996]. A collaborative study that involved a sample of 403–567 pedigrees from 14 research groups yielded HLODs of 3.06 at D8S261 ($P = 0.00018$) for the combined sample [Levinson et al., 1996]. Another study in 21 Canadian families has provided support for linkage to this region, with a LOD score of 3.49 at D8S136 [Brzustowicz et al., 1999]. A genome-wide linkage analysis using British and Icelandic samples revealed HLODs of 3.6 at D8S503 ($P = 0.0001$) [Gurling et al., 2001]. Recently, another genome-wide scan of an Icelandic sample also revealed a multipoint LOD score of 3.48 at D8S278, and further fine-mapping of the 8p locus identified neuregulin 1 gene (*NRG1*) as a positional candidate gene by haplotype association study [Stefansson et al., 2002]. Other studies of 8p22-21 have either offered less significant statistical support [Kaufmann et al., 1998; Shaw et al., 1998] or have been negative [Kunugi et al., 1996; DeLisi et al., 2000].

The studies showing significant or suggestive linkage to chromosome 8p22-21 were all applied to Caucasian samples. It is important to investigate whether the linkage findings can be replicated in another distinct ethnic group. Therefore, we recruited the families of Taiwanese schizophrenic probands with at least one affected sibling and sought to replicate these findings.

MATERIALS AND METHODS

Subjects

Schizophrenic probands who had at least two affected siblings were identified from the Department of Psychiatry,

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National Taiwan University Hospital and the University-affiliated Taoyuan Psychiatric Center. Data collection was initiated after informed consents were obtained from the identified study subjects and their families. All of the family members were personally interviewed by the research psychiatrists using the Psychiatrist Diagnostic Assessment (PDA) [Hwu and Yang, 1987; Hwu, 1999]. The final diagnostic assessment was formulated by integrating the PDA data and clinical information of medical chart records. The final diagnosis was done following DSM-IV criteria for schizophrenia, schizoaffective disorder, and other non-affective psychoses.

The probands, fulfilling the criteria of schizophrenia and schizoaffective disorder, who had at least one sibling with schizophrenia, schizoaffective disorder, or non-affective psychotic disorder were recruited. Fifty-two schizophrenic nuclear families with at least two affected siblings were recruited in this study (Table I). One of the affected sibling subjects was married and had one affected son. A total of 242 subjects were recruited for this genotype study, of which 109 members (45.0%) were diagnosed with schizophrenia, four members (1.7%) with schizoaffective disorder, and four (1.7%) with other non-affective psychotic disorders. Forty-nine of these 52 families had the affected siblings all with the diagnosis of schizophrenia, which belonged to the narrow definition of phenotype for statistical analysis. Among these 49 families, 4 families each had 3 affected siblings (representing 8 independent pairs of affected siblings) and 45 families each had an affected pair of siblings. In this sample, thus, there were a total of 53 independent pairs of affected siblings for linkage analysis under the narrow model of schizophrenia. For analysis under the broad model of phenotype definition, there were 6 families with 3 affected siblings each (i.e., 12 independent pairs of affected siblings) and 46 families with two affected siblings each, which comprised a total of 58 independent pairs of siblings.

Of these 86 parents (39 fathers, 47 mothers) available for study, 4 (4.7%) subjects (all are mothers) in 4 separate families had schizophrenia, and 3 (3.5%) subjects (2 fathers, 1 mother) had other non-affective psychotic disorders. One hundred nine (70.8%; 67 males, 42 females) of the 154 siblings (95 males, 59 females) were affected by either schizophrenia (104; 65 males, 39 females), schizoaffective disorder (4; 2 males, 2 females), or other non-affective psychoses (one female case). The affected subjects were 60% male and were 32 (±0.8) years of age. The mean age at onset was 21.6 (±6.1) years. The unaffected subjects were 52.8% male and 49.1 (±1.8) years of age.

Genotyping

Eleven microsatellite markers located in the chromosome 8p23-21 region were genotyped. The detail information of these markers is shown in Table II. These markers were distributed across a 52.67-centimorgan (cM) region. The intermarker distance was determined mainly from the Marshfield map (http://research.marshfieldclinic.org). The marker D8S1222 is not in the Marshfield map. Its location was determined to be between the marker D8S1820 and D8S1810 according to the Genome Database. The intermarker distance among the three markers was determined by CRI-MAP version 2.4 [Lander and Green, 1987].

DNA was extracted from whole blood using a modified salting-out method [Lahiri et al., 1992]. The microsatellite markers were amplified using standard polymerase chain reaction (PCR) conditions and 10 ng of genomic DNA with fluorescent 5′-end labeling of the primers. The allele types of these markers were determined by comparing the fragment sizes with an internal standard in an ABI-310 Genetic Analyzer (Perkin-Elmer, Foster City, CA). Genotypes were read independently by two individuals blind to the clinical status of the study subjects.

Statistical Analyses

Although the traditional parametric linkage analysis has proven to be a powerful tool in mapping genes for simple disease [Cottingham et al., 1993; O'Connel and Weeks, 1995; Kainulainen et al., 1999] such as Cystic Fibrosis, the power declines dramatically under wrong assumption of mode of inheritance [Abreu et al., 1999; Durner et al., 1999]. Unfortunately, the mode of inheritance for schizophrenia is unclear; in this study, we chose to report the results from non-parametric statistical analyses that base on the probability of allele sharing by using the affected sibpairs. The allele sharing methods are carried out on the basis of marker inheritance.

TABLE I. Family Member Relationships, Gender, and Disease Categories of the Study Subjects in 52 Families

	Disease category									
	Schizophrenia		Schizoaffective disorder		Other non-affective psychotic disorder		Non-psychotic disorder and normals		Total subjects	
Relation	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Siblings[a,b]										
Proband	32	20	—	—	—	—	—	—	32	20
Affected sibling with any psychotic disorder	33	19	2	2	0	1	—	—	35	22
Non-affected sibling	—	—	—	—	—	—	28	17	28	17
Parents[c]										
Father	0	—	0	—	2	—	37	—	39	—
Mother	—	4	—	0	—	1	—	42	—	47
Others										
Couple	—	0	—	0	—	0	—	1	0	1
Son	1	—	0	—	0	—	0		1	0
Total subjects	66	43	2	2	2	2	67	60	136	107

[a]Four families with three affected siblings having DSM-IV schizophrenia; six families with three affected siblings having DSM-IV schizophrenia and/or schizoaffective disorder, or non-affective psychotic disorder.
[b]Number of families with different numbers of siblings (affected and non-affected) recruited in this study: 2 siblings, 11 families; 3 siblings, 34 families; 4 siblings, 5 families; and 5 siblings, 2 families.
[c]One parent available only: 18 families; 2 parents available: 34 families.

TABLE II. Characteristics and Distances of Microsatellite Markers Used in This Study (8p23.2-8p21.1)

Microsatellite markers	Distance from the p-terminal (cM)	Chromosome region	Allele type	Heterozygosity	Size range (bp)
D8s1742	7.67	8p23.2-8p22	14	79.8	128–160
D8s1819	9.96	8p23.2-8p22	12	72.5	208–232
D8s351	15.38	8p23.2-8p22	13	54.0	108–132
D8s550	21.33	8p23.2-8p22	9	75.6	258–286
D8s1106	26.43	8p23.2-8p22	6	65.3	132–148
D8s1731	31.73	8p23.2-8p22	16	82.0	218–250
D8s1786	45.41	8p23.1-8p21.3	10	78.9	212–230
D8s1771	50.05	8p23.1-8p21.3	10	73.3	214–238
D8s1820	56.04	8p23.1-8p21.3	8	21.8	100–114
D8s1222	58.15	8p22-8p21.2	11	82.0	124–148
D8s1810	60.34	8p21.3-8p21.1	6	58.0	192–202

Connection to disease is established on affected individuals only. Therefore, there is no need to assume the mode of inheritance. Two phenotypes were included in the analysis. The narrow phenotype met DSM-IV criteria for schizophrenia only, whereas the broad model met DSM-IV criteria for schizophrenia, schizoaffective disorder, and other non-affective psychotic disorders.

Two-point non-parametric linkage analysis was performed using the SIBPAL program of the SAGE 3.1 package [Bierut et al., 2000]. The multipoint non-parametric linkage analyses were calculated using GENEHUNTER (version 2.1) program [Kruglyak et al., 1996]. Allelic frequencies were calculated from 86 unrelated individuals in these study pedigrees.

RESULTS

Table III shows the results of a two-point non-parametric linkage analysis using the narrow and the broad phenotype models. In this table, estimated proportion of alleles sharing identical by descent (IBD) and *P*-values are listed. In the broad phenotype model, at the markers D8S1771 and D8S1222, the estimated proportion of allele sharing IBD was about 0.57 ($P = 0.03$) and 0.61 ($P = 0.003$), respectively, which were positive evidences. In the narrow phenotype model, the same two markers ($P = 0.01$) were identified; the estimated proportion of allele sharing IBD was 0.59.

The results of multipoint non-parametric analysis are shown in Figure 1. The NPL curve for the narrow model (dashed line) is similar to the one derived for the broad model (solid line). Using the broad phenotype model, there was a peak NPL score of 2.45 ($P = 0.008$) at marker D8S1222, suggesting that it was at the site of a susceptibility locus. The flanking markers D8S1820 and D8S1810 also showed positive results, with NPL scores of 1.97 ($P = 0.02$) and 2.00 ($P = 0.02$), respectively. Additionally, using the narrow phenotype model, the peak NPL score was also found for the marker D8S1222 (NPL score = 1.89, $P = 0.02$), and for the flanking markers D8S1820 and D8S1810, the NPL scores of 1.76 ($P = 0.03$) and 1.79 ($P = 0.03$), respectively, were notably high. On the other hand, the marker D8S1771, having been positively identified in the two-point analysis, did not reveal positive linkage evidence in the multipoint analysis, using either the broad model (NPL score = 1.24, $P = 0.11$) or the narrow one (NPL score = 1.19, $P = 0.11$). The positive linkage was associated with a region of about 4 cM (i.e., from D8S1820 to D8S1810). Figure 2 shows the information contents of these markers. For all the markers used in the multipoint analysis, the information content exceeded 60%.

DISCUSSION

In our study, the maximum NPL score of 2.45 ($P = 0.008$) and 1.89 ($P = 0.02$) at the marker D8S1222 was revealed using the broad and narrow phenotype models, respectively. The flanking markers D8S1820 and D8S1810 also had positive scores. In support of this multipoint analysis result, the two-point

TABLE III. Two-Point Linkage Results Identifying Markers of Genetic Vulnerability to Schizophrenia on Chromosome 8p23-21 Using Narrow and Broad Disease Phenotype Models for Analysis of the Taiwanese Family Pedigrees (N = 52)

	Narrow model		Broad model	
Marker	Allele sharing proportion	*P*-value	Allele sharing proportion	*P*-value
D8s1742	0.52	0.36	0.51	0.36
D8s1819	0.48	0.73	0.49	0.64
D8s351	0.50	0.47	0.52	0.29
D8s550	0.46	0.86	0.47	0.82
D8s1106	0.50	0.50	0.53	0.23
D8s1731	0.49	0.56	0.50	0.47
D8s1786	0.47	0.79	0.45	0.90
D8s1771	0.59	0.01	0.57	0.03
D8s1820	0.50	0.54	0.49	0.60
D8s1222	0.59	0.01	0.61	0.003
D8s1810	0.52	0.31	0.50	0.48

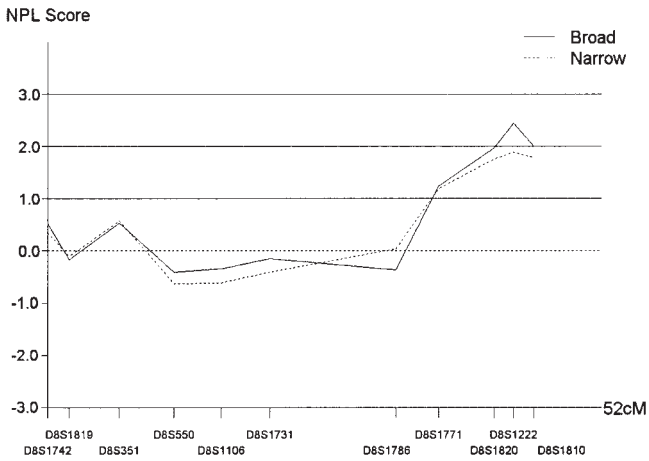

Fig. 1. NPL score of 11 loci in the chromosome 8p23-21 region for both narrow and broad disease phenotypes for the 52 Taiwanese pedigrees.

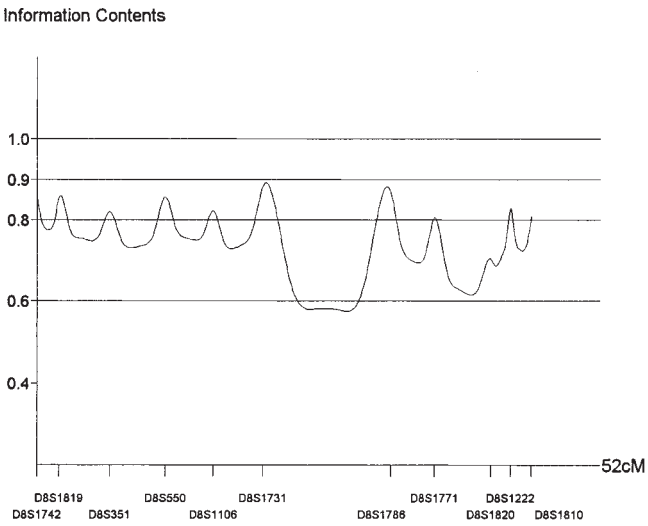

Fig. 2. Information contents of the 11 markers located in the chromosome 8p23-21 region.

analysis revealed the largest estimated proportion of allele sharing identical by descent at the marker D8S1222 under the broad model ($P = 0.003$). The chromosome regions with suggestive linkage evidence extended from D8S1820 to D8S1810 across about a 4-cM interval. This study replicated the evidence of linkage to chromosome 8p22-21 in an ethnically distinct sample.

The previous positive linkage evidence to 8p was the demonstration of a susceptibility gene region of about $5 \sim 10$ cM, centered on the marker D8S136 (43.96 cM from the p-terminal) [Pulver et al., 1995; Kendler et al., 1996; Levinson et al., 1996; Blouin et al., 1998; Brzustowicz et al., 1999]. The genome-wide study in British and Icelandic families reported peak LOD scores of more than 20 cM distal to this region, although the positive evidence of linkage extended over a wide range including the above region [Gurling et al., 2001]. Our study found that this linkage region ($56.04 \sim 60.34$ cM from the p-terminal) was in fact $10 \sim 20$ cM centromeric to most previously reported locus locations on chromosome 8p. Our finding was consistent with the recently reported genome-wide linkage study in Icelandic families [Stefansson et al., 2002], which also reported positive linkage within the same region. The marker D8S1222 with the peak NPL score in our study is only 2.7 cM from the marker D8S278 with the peak LOD score in that study [Stefansson et al., 2002].

Our study found that NPL scores were higher under the broad phenotype definition. The finding was consistent with that of Kendler et al. [1996], who reported diminished support for linkage under a narrow diagnostic classification, and that of Stefansson et al. [2002], who reported a similarly located linkage region using the phenotype definition we used in our broad model. Several of the prior reports of linkage on 8p considered only a narrow definition of affection [Pulver et al., 1995; Levinson et al., 1996; Blouin et al., 1998]. One study [Gurling et al., 2001] obtained higher HLOD scores under the narrow (core) phenotype definition than under the broad (spectrum) one. A recent genome-wide linkage disequilibrium mapping of severe bipolar disorder in a population isolate observed linkage disequilibrium on several chromosomes; the most striking linkage disequilibrium was located in proximal 8p, in a region with previously shown linkage to schizophrenia [Ophoff et al., 2002]. Though still inconclusive, the results of our study and other recent ones imply that the 8p locus could be associated with the broader phenotype of schizophrenia.

The most promising positional candidate gene is NRG1. The positive chromosome region we found is near the NRG1 locus. The marker D8S1222 is only about 400 kbp from the exon 1 of glial growth factor 2 (GGF2), an isoform of NRG1, whereas the marker D8S1810 is located in the intron 1 of GGF2, according to the STS map of the NCBI Genbank Map Viewer (http://www.ncbi.nlm.nih.gov) and the submitted NRG1 complete genome sequence in Genbank (accession number TPA BK000383). NRG1 isoforms are expressed in many tissues, including the central nervous system (CNS), and these isoforms clearly have a developmental role, as indicated by knockout mice displaying severe developmental anomalies in the heart and the nervous system [Liu et al., 1998; Gerlai et al., 2000]. NRG1 isoforms influence gliogenesis and neuronal migration during development of the brain and in the adult nervous system [Fernandez et al., 2000].

NRG1, as a strong candidate gene for schizophrenia, comes from several lines of genetic, animal model, and neurobiological evidence. The genetic evidence includes previous suggestive linkage evidences to this region and a highly significant association of overlapping haplotypes that contain only NRG1 within the overlap [Stefansson et al., 2002]. Our study provides further genetic evidence in a different population. Mice hypomorphic for two mutations in NRG1 [Erickson et al., 1997; Gerlai et al., 2000; Stefansson et al., 2002] and for one mutation in a receptor (ErbB4) for NRG1 [Gassmann et al., 1995] display hyperactive behavior that is consistent in part with mouse models for schizophrenia, and this is reversed in part with clozapine in a NRG1 mutant line [Stefansson et al., 2002]. Prepulse inhibition (PPI), a psychometric measure of sensory gating impaired in some schizophrenic patients [Braff and Geyer, 1990], was also impaired in the NRG1 hypomorphic mice [Stefansson et al., 2002]. The number of N-methyl-D-aspartate (NMDA) receptors in the NRG1 hypomorphs is reduced, which is in keeping with observations made on brains from schizophrenia patients [Stefansson et al., 2002]. NRG1 appears to signal for glutamate receptor subunit expression, localization [Garcia et al., 2000; Huang et al., 2000], and phosphorylation [Lau and Huganir, 1995] facilitating subsequent glutamate transmission. It was pointed out that the NRG1 and its receptor ErbB4 might regulate synaptic plasticity by recruiting tyrosine kinases that regulate NMDA receptor function [Garcia et al., 2000]. Abnormalities in synaptic plasticity may lead to the abnormalities in thought processes and cognition seen in schizophrenia.

Several brain-expressed genes in this region, including the genes for prepronociceptin (PNOC), neuronal nicotinic cholinergic receptor alpha polypepeide 2 (CHRNA2), and arylamine N-acetyltransferase 1 (NAT1), are the other potential positional candidate genes. A case–control association study using a novel highly polymorphic dinucleotide repeat near the PNOC gene, two dinucleotide repeats at the CHRNA2 locus, and a restriction fragment length polymorphism (RFLP) at the 3'UTR of the NAT1 gene found no differences between patients and controls [Blaveri et al., 2001]. However, this result does not exclude the involvement of other polymorphisms of these candidate genes.

In summary, the present study provides additional positive evidence for linkage of schizophrenia to loci near the NRG1 gene on chromosome 8p21 and replicates the previous linkage findings in an ethnically distinct sample. However, this study is the first step to replicate the positive linkage evidences on 8p22-21 in Taiwanese family samples. The intermarker distance is larger than expected. We are carrying on a study using more dense markers, which disperse evenly around the marker D8S1222, in a larger sample to further confirm these findings. These findings may serve as a guide to positional cloning of candidate genes in this chromosome region.

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