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RAPID COMMUNICATION

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Suggestive evidence for linkage of schizophrenia to markers on chromosome 13 in Caucasian but not Oriental populations

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Abstract Previously we reported suggestive evidence for linkage of schizophrenia to markers on chromosome 13q14.1–q32. We have now studied an additional independent sample of 44 pedigrees consisting of 34 Taiwanese, 9 English and 1 Welsh family in an attempt to replicate this finding. Narrow and broad models based on Research Diagnostic Criteria or the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised, were used to define the schizophrenia phenotype. Under a dominant genetic model, two-point lod scores obtained for most of the markers were negative except that marker D13S122 gave a total lod score of 1.06 (θ = 0.2, broad model). As combining pedigrees from different ethnic origins may be inappropriate, we combined this replication sample and our original sample, and then divided the total sample into Caucasian (English and Welsh pedigrees) and Oriental (Taiwanese and Japanese pedigrees) groups. The Caucasian pedigrees produced maximized admixture two-point lod scores (A-lod) of 1.41 for the marker D13S119 (θ = 0.2, α = 1.0) and 1.54 for D13S128 (θ = 0, α = 0.3) with nearby markers also producing positive A-lod scores. When five-point model-free linkage analysis was applied to the Caucasian sample, a maximum lod score of 2.58 was obtained around the markers D13S122 and D13S128, which are located on chromosome 13q32. The linkage results for the Oriental group were less positive than the Caucasian group. Our results again suggest that there is a potential susceptibility locus for schizophrenia on chromosome 13q14.1–q32, especially in the Caucasian population.

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Schizophrenia is a serious mental illness that may be caused by abnormal brain development (Jones and Murray 1991). The lifetime morbid risk worldwide ranges from 0.5 to 1% (Gottesman 1991). The aetiology of schizophrenia is unclear, but family, twin and adoption studies have shown that genetic factors account for approximately 70% of the variance in liability (Gottesman 1991). Nevertheless, the mode of inheritance of the disorder remains unclear. Although recent statistical modelling suggests at least three common genes that act multiplicatively on the risk of illness (Risch 1990), the existence of major genes in some families remains a possibility. Linkage studies have identified several "hot-spots" for schizophrenia: chromosome 22 (Pulver et al. 1994a, b; Lasseter et al. 1995; Vallada et al. 1995; Schizophrenia Collaborative Linkage Group 1996), chromosome 3p (Pulver et al. 1995), chromosome 8p (Pulver et al. 1995) and chromosome 6 (Moises et al. 1995; Schwab et al. 1995; Straub et al. 1995; Wang et al. 1995).

Previously we reported suggestive evidence for linkage of schizophrenia to markers on chromosome 13q14.1–q32 (Lin et al. 1995), and recently two other groups have found suggestive evidence for this region (Antonarakis et al. 1996; Kalsi et al. 1996). In order to follow up this provisional finding, an additional independent sample of 44 pedigrees (9 English, 1 Welsh and 34 Taiwanese) were collected. The British small-to-moderate size families were ascertained by referral of patients with schizophrenia who had at least one known, living, first-degree relative affected with the same illness. The Taiwanese nuclear families were recruited by referral of patients with schizophrenia who had at least one known, living sibling affected with the same disease. These studies were approved by the appropriate hospital ethics committees and informed consent was obtained from all study subjects. Diagnoses are based on Research Diagnostic Criteria (RDC); (Spitzer et al. 1978) for the Welsh and English pedigrees and the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R); (American Psychiatric Association 1987) for Taiwanese families. A total of 224 individuals including 93 with

Table 1 Two-point linkage results of admixture *(A-Lod)* and model-free lod *(MFLOD)* scores of schizophrenia for markers on chromosome 13 with the narrow model for replication sample (n = 44), Caucasian group (n = 21) and Oriental group (n = 36)

Marker	Replication sample				Caucasian group				Oriental group			
	A-Lod			MFLOD Lod score	A-Lod			MFLOD Lod score	A-Lod			MFLOD Lod score
	A-lod	θ	α		A-lod	θ	α		A-lod	θ	α	
D13S126	0.58	0	0.45	0.024	0.02	0.3	0.40	0.006	0.79	0	0.55	0.04
HTR2A	0.02	0	0.15	0	0	0	0	0	0	0	0	0.30
D13S119	0.02	0	0.05	0	**1.41**	0.2	1.0	**1.19**	0.14	0	0.20	0
D13S144	0	0	0	0	**1.16**	0	0.35	**1.18**	0	0	0	0
D13S160	0.34	0	0.30	0.72	0.86	0	0.35	0.72	0.11	0	0.15	0.51
D13S121	0.02	0.2	0.20	0.07	0.08	0	0.10	0	0.05	0	0.10	0.24
D13S71	0.01	0.3	0.40	0	0.83	0.2	1.0	0.59	0	0	0	0
D13S122	0.53	0.2	1.0	0.86	**1.19**	0	0.45	**1.08**	0.27	0	0.25	0.48
D13S128	0.03	0.3	0.45	0.22	**1.54**	0	0.30	**1.72**	0.01	0	0.05	0.28
D13S64	0.002	0	0.05	0.17	**1.03**	0.1	0.75	**1.14**	0	0	0	0.18
D13S173	0	0	0	0	0.39	0.3	0.90	0.09	0.12	0	0.15	0

schizophrenia and 17 with other psychiatric disorders were studied. Ten highly polymorphic microsatellite markers and the biallelic HTR2A marker (Warren et al. 1993), which showed positive lod scores from our previous findings, were genotyped using standard polymerase chain reaction (PCR) techniques (Saiki et al. 1985). Genotyping data was first used to construct a genetic map using the program CRI-MAP (Lander and Green 1987). This enabled potential errors appearing as double recombination events in a small genetic distance to be identified and checked. Several rounds of checking and map building were followed until a consistent map was obtained.

Two diagnostic models based on RDC or DSM-III-R were used to define the disease phenotype. A narrow model consisted of RDC or DSM-III-R schizophrenia as affected and a broad model included diagnoses of schizophrenia, schizoaffective disorder and unspecified functional psychosis. Two-point lod score analyses were performed using the program MLINK from the LINKAGE package (Lathrop et al. 1984) and tabulated family by family. As locus heterogeneity was expected, the admixture lod score (A-lod), which assumes that a proportion α of families are linked, was calculated for each marker. Allelic frequencies were calculated from 79 unrelated individuals in the pedigrees. A dominant model was used with a disease gene frequency (q) of 0.008, with penetrance (f_1, f_2) of 0.5 and sporadic risk (f_0) of 0.005 for the narrow model and 0.7 and 0.01 for the broad model. When the narrow model was used, subjects who would have been counted as unaffected under the broad model were designated as phenotype unknown. In this replication sample, two-point total lod scores obtained for most of the markers were negative at a variety of recombination fractions with both diagnostic models except for the marker D13S122, which produced a lod score of 1.06 (θ = 0.2, with the broad model). Because of the uncertainty of the mode of transmission of the disease, the model-free method of linkage analysis, MFLINK (Curtis and Sham 1995), was also applied to our data. Two-point admixture and model-free lod (MFLOD) scores for markers on chromosome 13 with the narrow model for the replication sample are shown in Table 1.

As genes predisposing to a disease may differ between ethnic groups, combining samples from different ethnic origins may be inappropriate. Therefore we divided this replication sample and our original sample into Caucasian (English and Welsh) and Oriental (Taiwanese and Japanese) groups. The 21 Caucasian families used in this group consisted of 171 individuals, including 61 with schizophrenia and 17 with other psychiatric disorders. The 36 Oriental families were composed of 193 individuals, including 85 with schizophrenia and 9 with other psychiatric disorders.

The Caucasian pedigrees gave total two-point lod score of 1.41 and 1.47 for markers D13S119 and D13S128 at θ = 0.2 with the narrow model, respectively. Allowing for heterogeneity, the Caucasian pedigrees produced maximized A-lod scores of 1.41 for marker D13S119 (θ = 0.2, α = 1.0), 1.16 for D13S144 (θ = 0, α = 0.35), 1.19 for D13S122 (θ = 0, α = 0.45), and 1.54 for D13S128 (θ = 0, α = 0.3) with nearby markers also producing positive A-lod scores under the narrow model. A two-point model-free lod score of 1.72 was also obtained for D13S128. When we looked at family-by-family linkage results, the majority of the lod score for D13S128 was contributed by two families (lod score = 1.59 for CAR017, lod score = 1.41 for INS035). The results of two-point admixture and model-free lod scores of schizophrenia for markers on chromosome 13 for the Caucasian sample with the narrow model are shown in Table 1.

When five-point model-free linkage analysis was applied to the Caucasian sample, a lod score of 2.58 (narrow model, as shown in Fig. 1) was obtained around markers D13S122 and D13S128, which are located on chromosome 13q32. A small peak of lod score of 1.09 was also observed near markers HTR2A and D13S119. Twelve-point non-parametric linkage (NPL) analysis using the program GENEHUNTER (Kruglyak et al. 1996) was per-

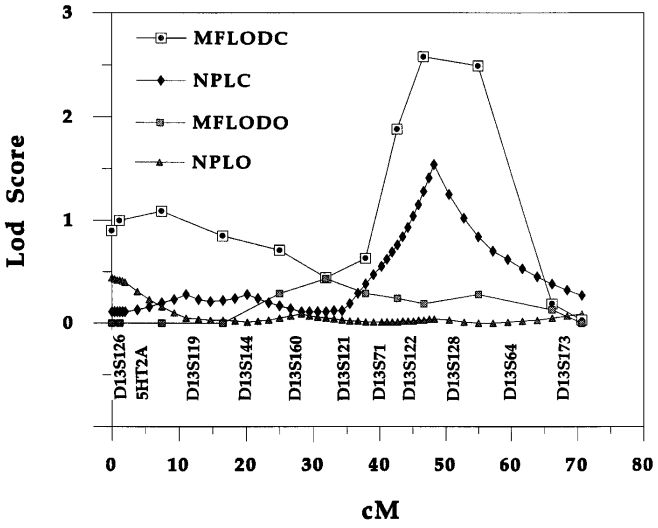

Fig. 1 Multipoint linkage results of schizophrenia for markers on chromosome 13 with narrow model for the Caucasian pedigrees (n = 21) and the Oriental pedigrees (n = 36). *NPL* are 12-point non-parametric linkage analysis using the program GENEHUNTER. *NPLC* indicates lod scores for the Caucasian group and *NPLO* for the Oriental group. *MFLOD* are 5-point model-free lod scores using the program MFLINK coupled with VITESSE. *MFLODC* indicates model-free lod scores for the Caucasian group and *MFLODO* for the Oriental group

formed. For ease of comparison, the NPL statistics and *P* value produced by GENEHUNTER were transformed to lod score equivalents. A maximum NPL lod score of 1.54 was obtained on the same region as the five-point MFLOD results for the Caucasian group (Fig. 1). The inheritance information extracted from the 11 markers used for the multipoint NPL analysis ranges from 0.74 to 0.91. Although the 12-point non-parametric lod scores obtained were less positive than the 5-point MFLOD scores, the pattern of the NPL results is similar to the MFLOD results.

The linkage results for the Oriental group were less positive than for the Caucasian group. Under the assumption of heterogeneity, a maximum two-point lod score of 0.79 for the marker D13S126 (narrow model) was obtained (Table 1). In the Oriental group, a region around markers D13S160 and D13S121 gave a five-point MFLOD score of 0.43 (Fig. 1). Twelve-point NPL results for the Oriental group shown in Fig. 1 do not suggest linkage.

The lod scores obtained from the replication sample are less impressive than our original findings (an approximate multipoint lod score of 2 was the maximum obtained) with both diagnostic models. However, when the combined sample is divided into different ethnic groups, the results from the Caucasian group, which included ten additional families that are not part of our original sample, are consistent with our previous findings. This was not the case for the Oriental group. We may speculate therefore that the susceptibility locus for schizophrenia in Caucasians may be different from that in Orientals.

The lod score we obtained is below the traditional critical value of 3 for linkage; however, it has been pointed out that some true susceptibility loci may never show significant linkage because they confer a very small increased risk and have common alleles (Owen and Craddock 1996). Two other groups have also found suggestive evidence in this region: Antonarakis et al. (1996) obtained a lod score of 2.54 for D13S128 using a dominant model and Kalsi et al (1996) a lod score of 1.09 for D13S144. It remains possible that there is a dominant susceptibility locus for schizophrenia in a proportion of families, especially for subjects of Caucasian ethnicity. An international collaboration and meta-analysis may be required to elucidate this suggestive linkage evidence to markers on the chromosome 13q14.1–q32 region.

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