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No proof of linkage between schizophrenia-related disorders including schizophrenia and chromosome 2q21 region

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Summary. We examined linkage between schizophrenia and schizophrenia-related disorders and five genetic markers on chromosome 2 in fourteen families ascertained through affected probands in St. Louis and Vienna. The chromosomal region 2q21 was considered a candidate locus for schizophrenia because of a report of a balanced translocation 2;18 (q21;q23) in a schizophrenia family. Linkage analyses were conducted for three disease models: a narrow model including schizophrenia only; an intermediate model including a spectrum of schizophrenia-related disorders; and a broad model including major affective disorders. Multipoint linkage analyses excluded linkage across the region (about 50 c*M*) for the intermediate disease model. The same was generally true for the broad affection status model. None of the two-point and multipoint analyses showed definite linkage of schizophrenia to any marker. The most prominent positive association was between D2S44 and a broad affection status model, giving a two-point lod score of 1.71 at 0.20 recombination fraction.

Key words: Schizophrenia – Linkage – DNA markers – Chromosome 2

Introduction

The cause of schizophrenia is unknown. Family, twin and adoption studies provide strong evidence that genetic factors play a major role in many cases of the disease (Cloninger 1988). The mode of inheritance is unclear, with segregation analyses revealing contradictory findings (Elston et al. 1978; Carter and Chung 1980; O'Rourke et al. 1982; Tsuang et al. 1982; Risch and Baron 1984). The current scientific challenge is to identify major genes contributing to the pathogenesis of schizophrenia. Linkage studies employing polymorphic DNA markers are an important tool that could detect major gene effects involved in the etiology of the disease.

The favored locus approach to detecting genetic linkage has been used successfully in disorders such as familial Alzheimer's disease and retinoblastoma (Friend et al. 1986; St. George-Hyslop et al. 1987). Favored loci can be candidate genes or loci of cytogenetic abnormalities associated with an illness (DeLisi et al. 1988; Bassett 1992). Candidate genes for schizophrenia include dopamine receptors (Moises et al. 1991) and serotonin receptors (Hallmayer et al. 1992a). Regions of reported cytogenetic abnormalities tested for linkage between polymorphic DNA markers and schizophrenia include 5q11–13 (Sherrington et al. 1988; McGuffin et al. 1990; Crowe et al. 1990; Hallmayer et al. 1992b). Previously, we studied chromosome 5q11–13 in a group of St. Louis families collected in St. Louis (included in this study) and reported no proof of linkage between markers and disease (Aschauer et al. 1990).

Other potentially important familial cytogenetic abnormalities associated with schizophrenia or psychotic illness include balanced translocations 1;11 and 6;11 (St. Clair et al. 1990; Holland and Gosden 1990). A translocation of 2;18 (q21;q23) was associated with schizophrenia in a single family (Genest et al. 1976) and we reported preliminary data suggesting linkage between schizophrenia and a chromosome 2 marker (D2S44 [pYNH24]) (Aschauer et al. 1989).

In the current study we have investigated whether or not vulnerability to schizophrenia is linked to chromosome-2 markers located around the centromere (Spurr and White 1991, NIH/CEPH Collaborative Mapping Group 1992). We have constructed a genetic map with these markers, including the marker reported in the preliminary positive results, that spans about 50 centimorgans (c*M*) (NIH/CEPH Collaborative Mapping Group 1992). Three disease models of schizophrenia were tested. The narrowest model included only patients with schizo-

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phrenia. An intermediate model included individuals diagnosed as suffering from schizophrenia, schizoaffective disorders, non-organic and non-affective psychoses and schizotypal personality disorder. The broadest model included individuals in the first two models as well as those suffering from severe affective disorders. Detailed two-point and multipoint linkage analyses do not support the presence of a schizophrenia gene in this region. We discuss the results in relation to prior linkage studies of the role of major genes in schizophrenia.

Methods

Families

Fourteen schizophrenia pedigrees were investigated (see Fig. 1). All participants gave informed consent. Seven pedigrees, sampled in the USA, have been described previously (Aschauer et al. 1990). Seven families were collected in Austria. Hospitalized individuals with a DSM III-R (American Psychiatric Association 1987) diagnosis of schizophrenia were identified at the Washington University Medical Center in St. Louis, Mo, and the Department of Psychiatry at University in Vienna, Austria. A patient was accepted as a proband if she or he suffered from DSM III-R schizophrenia and had at least one available first-degree relative with a non-affective, non-organic psychosis. In our sample, the second affected cases were given a diagnosis of schizophrenia ($n = 10$), schizoaffective disorder ($n = 3$) and atypical psychosis ($n = 1$). We collected all cooperative first-degree relatives above the age of 18 years (nuclear families), and extended the pedigree in 4 of the 14 families through an affected individual or an individual presumed to transmit a severe psychiatric disorder to affected first-degree relatives (FSZ 008, FSZ 009, SCH 020, MZW 001). Families with bilineal cases of psychosis were excluded, although there is little danger that including these families will lead to a false exclusion of linkage (Durner et al. 1992). A total of 143 individuals were included in our analysis. Twenty-six persons were given the diagnosis of schizophrenia. Most of the 25 individuals with an unknown diagnosis (due to insufficient information) were deceased and used to link living members within a family.

Diagnosis

The diagnostic process included a face-to-face interview with all available living individuals utilizing the Diagnostic Interview Schedule (Robins et al. 1981) in St. Louis and the Schedule for Affective Disorders and Schizophrenia, Lifetime version (modified for the study of anxiety disorders) (Fyer et al. 1985) in Vienna. In addition, parts of the International Personality Disorder Questionnaire (Loranger et al. 1987), an unstructured psychiatric interview and a family history evaluation were completed for each subject. Clinical data were obtained from medical records and treating physicians. Using all available data, blind consensus diagnoses were made by at least two independent psychiatrists according to DSM III-R, axis I and II without knowledge of marker status or family relationship.

Laboratory methods

We typed three linked markers from the map of chromosome 2 of O'Connell et al. (1989) [pYNH24(D2S44), pHHH115.2(D2S54) and pYNZ15(D2S43)] and 2 linked markers from the map reported by Donis-Keller et al. (1987) [CRI-L452(D2S41), CRI-L625 (D2S38)], and used the published allele frequencies in calculations. The location of D2S43 (pYNZ15) is 2p12-cen (Spurr and White 1991), and a detailed linkage map locates D2S54 and D2S44 in the 2q14–q21 region (NIH/CEPH Collaborative Mapping Group 1992). pYNH24 reveals a Msp-I polymorphism with more than 30 alleles [polymorphism information content (PIC) 0.81] between 1.0 and 6.0 kilobases (kb); pYNH24 genotypes were coded as a system of five alleles of equal frequency. There was no loss of information by applying this coding approach. By testing influences of reducing the number of alleles on the resulting lod scores, we only found small differences in lod scores. pHHH115.2 is polymorphic for Msp I, showing two alleles (2.4 and 1.7 kb) with frequencies of 0.43 and 0.57 (PIC 0.24). pYNZ15 is polymorphic for Taq I, producing two alleles of 1.8 and 0.9 kb, with frequencies of 0.53 and 0.47 (PIC 0.37). CRI-L452A (Bgl II) showed two alleles (11.5 and 9.0 kb) with frequencies of 0.41 and 0.59 (PIC 0.64). Another polymorphism of this probe (B) was essentially uninformative. CRI-L625A (Msp I) showed three alleles (4.1, 3.9 and 3.7 kb) with frequencies of 0.14, 0.15 and 0.71 (PIC 0.48). Taq-I polymorphisms C and D added no additional information and were not used in our analyses. One hundred and twenty-one individuals were genotyped for pYNH24, 108 for pHHH115.2, 118 for pYNZ15, 117 for CRI-L452A, and 117 for CRI-L625A. Paternity was confirmed using highly polymorphic DNA probes.

Lymphoblastoid cell lines, high molecular weight genomic DNA, and probes were prepared by standard methods. DNA was digested with appropriate restriction enzymes, electrophoretically separated on agarose gels, and transferred to nylon membranes by standard methods. Probes were labeled with ^{32}P α dCTP by the random priming method to a high specific activity (about 10^9 dpm/μg DNA). Hybridization reactions were performed by standard methods (Feinberg and Vogelstein 1983; Neitzel 1986; Sambrook et al. 1989). Genotypes were scored blind to diagnoses and pedigree position by two to four independent raters.

Linkage analysis

Linkage analysis was carried out using the software package LINKAGE (version 5.1). Two-point analysis was performed using the program MLINK and multipoint analysis with the program LINKMAP. Penetrances were estimated with the program ILINK (Lathrop and Lalouel 1984).

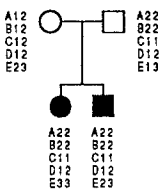
We established a genetic map of chromosome-2 markers and derived the following genetic distance: D2S44 – theta 0.06 – D2S54 – theta 0.07 – D2S43 – theta 0.13 – D2S41 – theta 0.12 – D2S38. Twenty-eight families comprising 288 individuals were used for mapping, including 12 families of the schizophrenia study. Equal recombination fractions were assumed to apply to males and females. The map spans a region of about 50 centimorgans (NIH/CEPH Collaborative Mapping Group 1992).

Our disease models treated the illness as an autosomal dominant trait, because our preliminary results suggested linkage employing this mode of inheritance (Aschauer et al. 1989, 1990). The disease allele (A2) was given a frequency of 0.005. Penetrance for the A1A1 genotype (i.e. sporadic cases) was taken as 0.001. The penetrance for homozygotes was 0.99, penetrance for heterozygotes was set at 0.65, 0.80 and 0.95 for models 1, 2 and 3 respectively (McGuffin et al. 1990). Estimated penetrances for heterozygotes in our families were 0.55, 0.62 and 0.70 for the three models (ILINK). These values were used in additional analyses to test the effect of lower penetrances on lod scores.

Twenty-five individuals had an unknown phenotype in all models. All other individuals were, depending on the model, counted as affected or unaffected. Affected cases included: model 1 (narrowest model), schizophrenia ($n = 26$); model 2 (intermediate model), model 1 plus non-affective and non-organic psychoses

Fig. 1. Pedigrees of 14 schizophrenia families. *Squares* indicate males; *circles*, females; *slash*, deceased. RFLP typing data are shown (A: D2S44, B: D2S54, C: D2S43, D: D2S41, E: D2S38). Alleles of probes are numbered in order of decreasing fragment size (0 = unknown allele). Diagnoses are by DSM III-R (American Psychiatric Association 1987). Diagnostic groups and used symbols are listed

FSZ001



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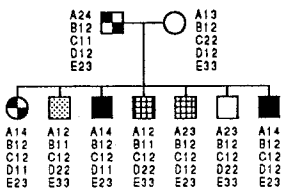

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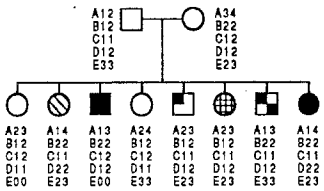

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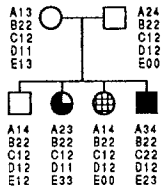

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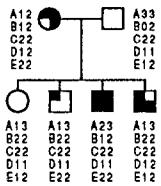

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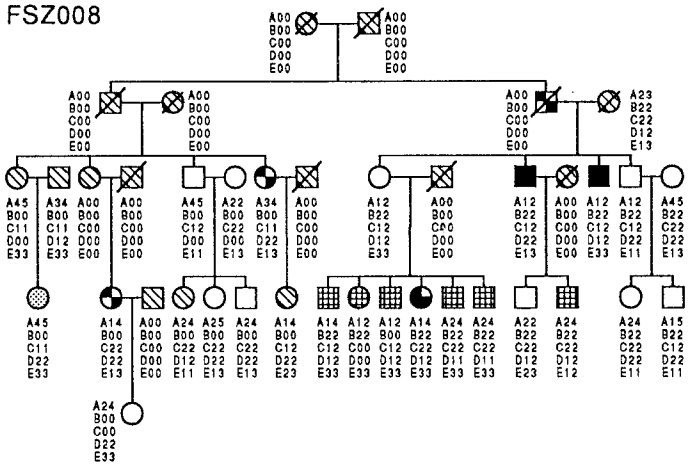

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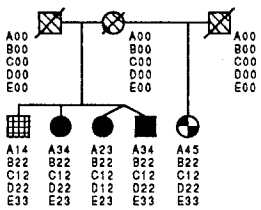

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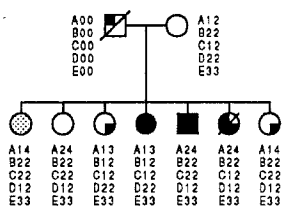

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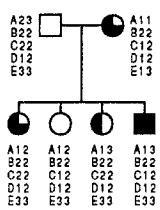

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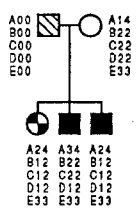

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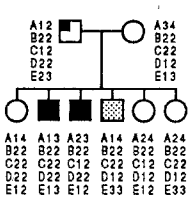

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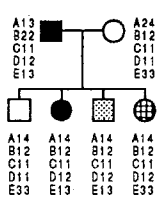

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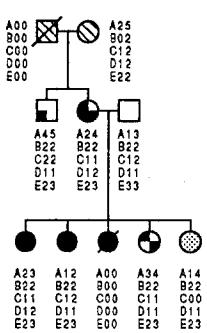
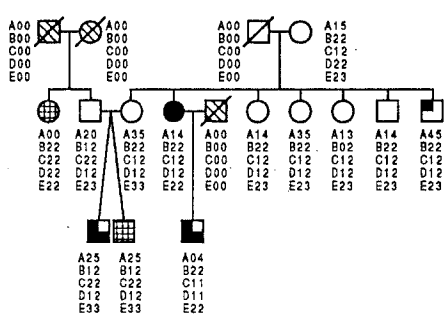


MZW001



- ■ schizophrenia
- ◧ schizoaffective, schizophreniform disorder, atypical psychosis
- ◧ schizotypal personality disorder
- ◪ bipolar disorder
- ◪ major depression, severe unspecified (non-psychotic) chronic mental disorder
- ◩ alcohol dependence
- ◪ adjustment disorder with depressed mood
- ◪ depressive disorder NOS
- ▦ psychoactive substance use, panic, conduct, somatization and obsessive compulsive disorder, organic mental disorder NOS, presenile dementia NOS
- ▩ other diagnoses (axis II)
- □ no diagnosis
- ▨ unknown

Table 1. Lod scores for pairwise linkage analyses of schizophrenia disease models to five chromosome-2 markers

Locus	Probe	Disease model	Penetrance	Recombination fraction					
				0.00	0.05	0.10	0.15	0.20	0.30
D2S44	pYNH24	1	0.650	−0.94	0.29	0.49	0.50	0.44	0.23
		2	0.800	−3.14	−0.30	0.43	0.68	0.67	0.35
		3	0.950	−7.52	−0.20	1.04	1.56	1.71	1.34
D2S54	pHHH115.2	1	0.650	0.05	0.19	0.25	0.25	0.23	0.13
		2	0.800	−0.58	−0.27	−0.11	−0.01	0.04	0.06
		3	0.950	−1.78	0.17	0.45	0.52	0.51	0.35
D2S43	pYNZ15	1	0.650	−1.73	−1.33	−1.02	−0.77	−0.57	−0.28
		2	0.800	−5.43	−2.83	−1.92	−1.33	−0.92	−0.39
		3	0.950	−5.61	−2.46	−1.50	−0.92	−0.53	−0.10
D2S41	CRI-L452A	1	0.650	−1.16	−0.78	−0.50	−0.30	−0.17	−0.03
		2	0.800	−3.61	−1.78	−1.17	−0.77	−0.50	−0.19
		3	0.950	−4.87	−1.41	−0.43	0.05	0.29	0.36
D2S38	CRI-L625A	1	0.650	−1.65	−1.05	−0.71	−0.48	−0.31	−0.12
		2	0.800	−2.70	−1.54	−0.96	−0.58	−0.33	−0.07
		3	0.950	−4.40	−2.04	−0.99	−0.38	−0.03	0.22

[schizoaffective ($n = 6$) and schizophreniform disorder ($n = 1$) and atypical psychosis ($n = 2$)] and schizotypal personality disorder ($n = 1$); model 3 (broad model), model 2 plus major affective disorders [bipolar disorder ($n = 1$), major depression ($n = 8$)] and a severe chronic disorder with features of affective disorder ($n = 1$). Affective disorders were considered in the third model, owing to reports associating a subset of severe affective disorders with liability to schizophrenia (Baron and Gruen 1991; Taylor et al. 1993).

Heterogeneity analysis was carried out using Morton's test of heterogeneity (Ott 1991). This test allows analyses to be performed on two-point data (assumption of homogeneity (H1): recombination fractions at maximum lod scores are equal for all families; assumption of heterogeneity (H2): recombination fraction at maximum lod scores varies between families). Applying the test to our data, we obtained a chi square of 16.45 (13 df, critical value for $p = 0.05$ is 22.36). This result suggests that there is no evidence for heterogeneity in our sample.

Results

Evidence for linkage between three schizophrenia disease models and 5 linked chromosome-2 markers is presented (Table 1) as two-point lod scores at specified recombination fractions. Data are the sum of the lod scores obtained from 14 families. All positive lod scores were non-significant (< 3.0). Linkage between model 1 and all five loci could not be excluded (lod scores between −2.0 and 3.0). Close linkage between model 2 and loci D2S44, D2S43, D2S41 and D2S38 could be excluded. Marker D2S44 showed a two-point lod score of 0.68 at recombination fraction 0.15; the lod scores of the other three markers were negative. D2S54 had lod scores around 0.0 under model 2 due to uninformative families. Close linkage between model 3 and loci D2S44, D2S43, D2S41 and D2S38 was excluded. The most positive lod scores for model 3 were D2S44 1.71 at a recombination fraction of 0.20, D2S54 0.52 at 0.15, D2S41 0.36 at 0.30 and D2S38 0.22 at 0.30. Six families showed positive lod

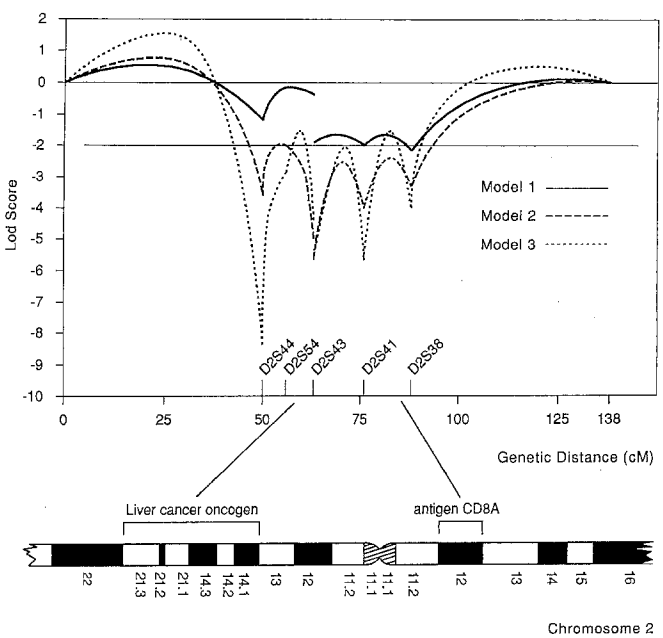


Fig. 2. Multipoint linkage analyses of schizophrenia against a fixed map of chromosome-2 markers. Three different models of affection status were calculated: a narrow schizophrenia model 1, an intermediate model 2 (schizophrenia spectrum) and a broad model 3 including severe affective disorders. Lod score curves are shown as results respectively. Lod scores below −2.0 are considered significant for exclusion of linkage, lod scores between −2.0 and +3.0 are inconclusive. The markers were set according to genetic distances (1 cM = 1% recombination). The relevant part of chromosome 2 is graphically presented at the bottom. Regional assignment of LCO (liver cancer oncogene) and CD8A (antigen CD8A) is shown (Spurr and White 1991), and their relation to our map is indicated, although both are not typed here. They are included in the linkage map of NIH/CEPH Collaborative Mapping Group (1992), together with the markers used in this study, giving us information about the relative position of markers as presented

scores between D2S44 and model 3, eight families were negative (results by families not shown in detail). Results of two-point analyses using the estimated penetrance values of 0.55, 0.62 and 0.70 for model 1, 2 and 3 respectively, showed lod scores without major differences to lod scores shown in Table 1. To demonstrate the main discrepancies found, for D2S44, the most positive lod score for model 3 was reduced to 1.11 at 0.20, and, for D2S38, the lod score was increased to 0.67 at 0.20.

Figure 2 presents the four-point LINKMAP results for schizophrenia models 1, 2 and 3 moved across a fixed map of the five marker loci. For each model, we performed two multipoint analyses with affection status as the test locus: first D2S44 – D2S54 – D2S43 and second D2S43 – D2S41 – D2S38. The curve in Fig. 2 presenting lod scores of the first run in each model stops at D2S43; the lod score curve for the second run is shown starting at D2S43, to avoid overlapping curves. Lod scores below −2.0 are considered significant for exclusion. Linkage between model 1 and the markers could only be excluded around D2S38. Linkage between model 2 and the markers could be excluded across the whole map. Linkage was excluded for model 3 across almost all parts of the map, with the exception of an indefinite result for D2S38. Model 3 showed a lod score of 1.42 outside the map at 0.2 recombination fraction from D2S44. Using the lower penetrance value of 0.70 in this analysis, the lod score decreased to 0.88 at the same map position.

Discussion

The choice of the region of chromosome 2q21 for study was based on a report of an association between a translocation in this region and schizophrenia in a single family (Genest et al. 1976). Few genes of known function or clinical relevance have been mapped to this region. It should be noted, however, that other investigations have recently expressed reservations about associating translocations with schizophrenia in small families (Maziade et al. 1993).

Multipoint analysis excluded linkage between an intermediate schizophrenia disease model (model 2) and a genetic map of RFLP markers in the chromosome 2q21 region across the map (Fig. 2). This model included schizophrenia, schizoaffective and other non-affective and non-organic psychoses and schizotypal personality disorder. For schizophrenia alone (model 1) linkage could not be rejected. The model with the highest positive lod score is a schizophrenia disease model that includes major affective disorders (model 3). Two-point lod scores for linkage of D2S44 with this model were 1.71 (recombination fraction 0.20); multipoint results were similar. These results seem interesting enough to type these and additional families with markers distal to D2S44. Linkage between the remaining markers and model 3 can be excluded in our families. In general, multipoint results should be interpreted with caution, because analysis is dependent upon the accuracy of the underlying map. Differences in the distances between the markers and order of markers will influence lod scores. In our results there is no obvious discrepancy between two-point and multipoint lod scores.

Results of schizophrenia linkage studies, positive or negative, must be interpreted cautiously. First, the correct transmission model is unknown. Second, individual families showed high lod scores with some markers, a result expected if genetic heterogeneity exists. Additionally, one marker locus (D2S44) showed modestly positive lod scores (up to 1.71) for the entire family sample (Table 1). Finally, use of a broad affection status model (including severe affective disorders) increased lod scores outside of the map region (Fig. 2). Use of several linkage tests with different parameters simultaneously in complex diseases can yield an increased probability of false-positive results (Clerget-Darpoux et al. 1990). The inclusion of conditions with a high population prevalence (for example, major depression) increases the probability of considering non-gene carriers as affected. The stepwise increase in lod scores with broadened affection status and the exclusion of linkage between model 3 and several markers underlines the weak association between D2S44 and model 3. Inclusion of individuals identified in the pedigrees of probands afflicted with schizophrenia and suffering from severe affective disorder may be part of a reasonable strategy to detect the genetic contribution of major genes to schizophrenia.

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