Splitting Schizophrenia: Periodic Catatonia–Susceptibility Locus on Chromosome 15q15

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The nature of subtypes in schizophrenia and the meaning of heterogeneity in schizophrenia have been considered a principal controversy in psychiatric research. We addressed these issues in periodic catatonia, a clinical entity derived from Leonhard's classification of schizophrenias, in a genomewide linkage scan. Periodic catatonia is characterized by qualitative psychomotor disturbances during acute psychotic outbursts and by long-term outcome. On the basis of our previous findings of a lifetime morbidity risk of 26.9% of periodic catatonia in first-degree relatives, we conducted a genome scan in 12 multiplex pedigrees with 135 individuals, using 356 markers with an average spacing of 11 cM. In nonparametric multipoint linkage analyses (by GENEHUNTER-PLUS), significant evidence for linkage was obtained on chromosome 15q15 ($P = 2.6 \times 10^{-5}$; nonparametric LOD score [LOD*] 3.57). A further locus on chromosome 22q13 with suggestive evidence for linkage ($P = 1.8 \times 10^{-3}$; LOD* 1.85) was detected, which indicated genetic heterogeneity. Parametric linkage analysis under an autosomal dominant model (affecteds-only analysis) provided independent confirmation of nonparametric linkage results, with maximum LOD scores 2.75 (recombination fraction [θ] .04; two-point analysis) and 2.89 ($\theta = .029$; four-point analysis), at the chromosome 15q candidate region. Splitting the complex group of schizophrenias on the basis of clinical observation and genetic analysis, we identified periodic catatonia as a valid nosological entity. Our findings provide evidence that periodic catatonia is associated with a major disease locus, which maps to chromosome 15q15.

Introduction

Schizophrenia afflicts >1% of the population and is one of the most devastating and cost-intensive disorders in medicine (Knapp 1997). The hereditary impact in schizophrenia is impressive, as pointed out in numerous family, twin, and adoption studies (Gottesman 1991; Kendler and Diehl 1993), although linkage studies have had considerable difficulties in identifying susceptibility loci (Levinson et al. 1998; Williams et al. 1999). During the past few years, replications of suggestive positive findings have been reported for several loci, and significant evidence for a major susceptibility locus at 1q21-q22 has been reported, probably as a result of better genomewide search strategies as well as greater statistical power owing to larger studies (Karayiorgou and Gogos 1997; Brzustowicz et al. 2000). Another important development with the potential to mediate the results of linkage studies involves the definition of the phenotype used to assess whether family members are affected (Leboyer et al. 1998). In this regard, there is a growing consensus that phenotype definitions for genetic studies in schizophrenia will profit from the use of symptoms that are closer to their etiology than are the end-stage clinical symptoms that, according to either the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) (American Psychiatric Association 1991) or *International Classification of Diseases* (*ICD*), define schizophrenia (Tsuang and Faraone 1995; Leonhard 1999). Thus, restriction to discrete phenotypes offers a valuable opportunity to classify nosological entities with distinct underlying genetic bases.

Periodic catatonia (MIM 181500), a clinical subtype of unsystematic schizophrenias, exhibits subtle derangements of facial expression and gestures, so-called psychomotor disturbances (Leonhard 1999). Two psychotic poles—psychomotor excitement and inhibition—give way to grimacing or masklike facies, iterations, and posture stereotypes, as well as to distorted stiff movements, or parakinesis, which contrasts with akinetic negativism. In most cases, acute psychotic episodes are accompanied by hallucinations and delusions, but, in remission, there remains a distinct mild-to-severe cat-

Received June 12, 2000; accepted for publication August 17, 2000; electronically published September 19, 2000.

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0002-9297/2000/6705-0018$02.00

atonic residual state with psychomotor weakness of facial expression and diminished incentive. In periodic catatonia, we earlier predicted a major-gene effect because of a morbidity risk of 26.9% in first-degree relatives of the index cases and, thus, found this phenotype particularly appropriate for further molecular-genetic evaluation (Stöber et al. 1995; Beckmann et al. 1996). In a genomewide linkage study, periodic catatonia crystallized now as a distinct inherited phenotype within the group of schizophrenias, with evidence for a major susceptibility locus on chromosome 15q15, in most of the pedigrees analyzed, and a further potential locus on chromosome 22q13, which points to genetic heterogeneity in periodic catatonia.

Methods

Ascertainment of Pedigrees

We identified the pedigrees analyzed here through a previous family study of 139 probands with chronic catatonic schizophrenia according to DSM (American Psychiatric Association 1991; Beckmann et al. 1996). In the family study, we reached an interrater reliability of Cohen's $\kappa = .93$, and the diagnostic stability during catamnesis was 97%. Additional families segregating for periodic catatonia were ascertained at the Department of Psychiatry and Psychotherapy, University of Würzburg, during 1997. The department serves the city of Würzburg (130,000 inhabitants) and the surrounding, mostly rural area, with a mean of 1,150 admissions per year (years 1995–99), in the full spectrum of psychiatric disorders. All families were seen by one of us (G.S.). To perform consistent diagnostic evaluation within the families segregating periodic catatonia, the clinical assessment was performed by a single experienced investigator. Extensive clinical semistructured examinations were conducted on the basis of Leonhard's operationalized psychopathological descriptions, and information was collected from different sources (personal history, medical records, and/or family informants). Subjects were considered affected if Leonhard's strict criteria for periodic catatonia were fulfilled (Leonhard 1999). The diagnosis was confirmed only if all the symptoms found in Leonhard's psychopathological descriptions were found in the subject. Many relatives were visited several times during the course of 3 years, thus permitting detection of new episodes of illness and improving diagnostic accuracy. Unaffected partners were interviewed, and their family history was obtained, to detect possible bilinear transmission of the disorder. All individuals actively participated in the study after giving their informed consent. Approval of the study was obtained by the Ethics Committee at the University of Würzburg and by the data-protection officials of the Bavarian State Ministry of Culture and Science.

Evaluation by Simulation

Twelve pedigrees were included in a genomewide linkage analysis to detect susceptibility loci for periodic catatonia (pedigree data will be made available on request). To evaluate the potential informativeness of ascertained families, we performed power calculations, using the program SLINK (Ott 1989). Expected LOD scores were determined with affecteds-only analysis at various recombination fractions, under a weak autosomal dominant model, and a disease-allele frequency of .001. DNA specimens were available for 135 individuals (61 males and 74 females), including 57 subjects affected with periodic catatonia. Mean age at assessment was 51.1 years ($\pm$ 17.1 SD; range 18–88), with no significant gender differences. Those individuals affected with periodic catatonia (24 males and 33 females) had a mean age at study of 45.9 years ($\pm$15.4 SD) and an age at onset of 29.4 years ($\pm$12.3 SD), with no evidence of significant gender differences.

Genotyping

Microsatellite markers were selected from the human genetic map (Dib et al. 1996). Three hundred fifty-six microsatellite markers were chosen for regular spacing throughout the genome, including markers at the most telomeric positions. The markers had a mean sex-averaged spacing of ~11 cM and an average heterozygosity of .78 (range .51–.92). X-chromosomal markers were not tested because periodic catatonia obviously does not have characteristics of X-linked inheritance (Franzek et al. 1995). Marker amplification was performed in microtiter plates on Tetrad PCR machines (MJ Research), and PCR pools were separated on ABI 377 automatic sequencers (Applied Biosystems), as described elsewhere (Saar et al. 1997). Genotyping was done by operators blind to phenotype. Allele calling was checked by operational procedures and was subject to an automated Mendelian check using the UNKNOWN program from the LINKAGE program package. Allele sizes were standardized to those of known CEPH control individuals. For a total of 47.655 genotypes, the effective typing ratio was 96.5%.

Linkage Analysis

Nonparametric, model-free multipoint linkage analyses were performed with the GENEHUNTER-PLUS (GH-PLUS) modification of the GENEHUNTER package (Kruglyak et al. 1996). GH-PLUS allows pedigree analysis of complex inherited traits, and it estimates the statistical significance of shared alleles identical-by-de-

scent between all affected members of the pedigree. The GH-PLUS modification (Kong and Cox 1997) permits exact calculation of likelihood ratios on the basis of an exponential allele-sharing model—that is, Z_{lr} values. *P* values can be approximated by applying normal approximation. The nonparametric LOD scores (LOD*), based on the allele sharing, can be used within the same inferential framework as is used for traditional LOD scores (Kong and Cox 1997). Maximum two-point homogeneity LOD scores (Z_{max}) were calculated using the MLINK program of the FASTLINK software package (Lathrop et al. 1985), version 5.1, and tests of heterogeneity were performed using the HOMOG program (Ott 1991), version 3.35. For computation of parametric multipoint likelihoods, we performed four-point LOD-score analyses, using the program VITESSE (O'Connell and Weeks 1995), with three adjacent pairs of screening-set markers and the disease locus. Intermarker distances were derived from the Généthon map. We performed analyses with affected individuals only (setting those not affected to unknown), under an autosomal dominant model (penetrance vector 0.0, 1.0, 1.0) and a disease-allele frequency of .001; phenocopy rate was set at .0 (Terwilliger and Ott 1994). All statistical analyses were run under the assumption of uniformly distributed marker-allele frequencies.

Results

Twelve pedigrees (comprising DNA specimens of 135 individuals, including 57 affecteds) segregating for periodic catatonia were studied in a genomewide linkage scan. Evaluation studies supposed an expected Z_{max} of 5.7 in the family panel, under an autosomal dominant affecteds-only model (average expected Z_{max} values are based on 1,000 replicates). In the presence of genetic homogeneity, the power was 98.5% to detect LOD scores ⩾2.0 and 94.5% to detect those ⩾3.0 (five marker alleles, uniformly distributed; recombination fraction [θ] ⩽.05).

Table 1

Multipoint Nonparametric Linkage Analysis in the Sample with Periodic Catatonia, for Loci with *P* <.025 (by GH-PLUS)

Chromosome	Coordinate (cM)	GH-PLUS		
		Z_{lr}	LOD*	*P*
6	184.6	2.17	1.02	.015
11	131.0	2.22	1.07	.013
13	65.2	2.43	1.28	.0075
15	35.3	4.05	3.57	.000026
16	33.0	1.96	.83	.025
20	16.6	2.07	.93	.02
22	58.2	2.92	1.85	.0018

On the basis of multipoint nonparametric linkage analyses (by GH-PLUS), the most significant allele sharing between individuals in the pedigrees who are affected with periodic catatonia is on chromosome 15q15, at position 35.3 cM (Généthon human linkage map), with a Z_{lr} score of 4.05 ($P = 2.6 \times 10^{-5}$) and a LOD* of 3.57 (fig. 1 and table 1). At chromosome 22q13, linkage was obtained by GH-PLUS, with a Z_{lr} score of 2.92 ($P = 1.8 \times 10^{-3}$) and a LOD* score of 1.85 at position 58.2 cM. On the basis of Lander and Kruglyak's (1995) rigorous criteria for linkage, the linkage to chromosome 15q is significant, whereas that to chromosome 22q is suggestive. Inspection of the linkage results, by family, revealed that different pedigrees were contributing to the findings at chromosomes 15q and

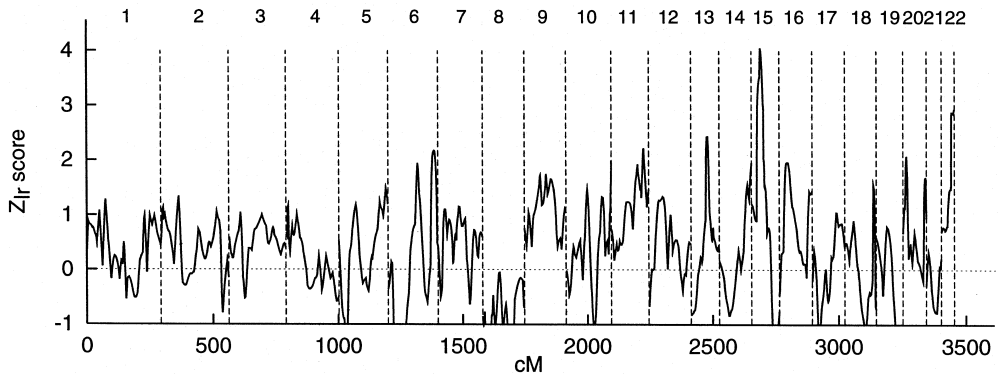

Figure 1 Genomewide linkage scan for periodic catatonia–susceptibility loci. The multipoint nonparametric Z_{lr} scores (GH-PLUS) are computed for the whole panel of 12 families. The *X*-axis represents the genetic location on the 22 autosomes; chromosomes are arranged, by number, from pter to qter, on a linear scale (in cM); and the *Y*-axis represents the nonparametric Z_{lr} score. Evidence for linkage was obtained at chromosome 15q15 with $Z_{lr} = 4.05$ ($P = 2.6 \times 10^{-5}$). A second susceptibility locus is on chromosome 22q13 ($Z_{lr} = 2.92$; $P = 1.8 \times 10^{-3}$).

22q. Additionally, chromosomes 6, 11, 13, and 20 showed minor peaks of Z_{lr} scores >2.0 and/or LOD* scores >1.0, with $P < .025$ (table 1), but these loci fell short of conventional standards for linkage.

At loci with Z_{lr} scores >2.5, two-point parametric Z_{max} analyses were performed under an autosomal dominant model with affecteds-only analysis (table 2). Two-point analyses produced a Z_{max} of 2.75 at marker D15S1012, under the assumption of linkage homogeneity. Assuming linkage heterogeneity, we obtained a Z_{max} of 2.75 with an estimated 100% of families linked. In the second candidate region, the homogeneity Z_{max} was 1.04 at D22S1169 and the heterogeneity Z_{max} was 1.57, with an estimated 38% of families linked. Analysis by pedigree showed that different families contributed to the linkage at chromosomes 15q and 22q, which indicates genetic heterogeneity in periodic catatonia. Subsequently, for the candidate regions, four-point LOD-score analyses were computed separately for the two exceptionally large pedigrees. Both are four-generation families, each having seven living affected individuals. Affecteds-only analysis using an autosomal dominant model yielded a multipoint Z_{max} of 2.89 (θ = .029) at D15S1042, and a Z_{max} of 2.59 (θ = .0) at D22S1169 (VITESSE).

Discussion

In a genomewide linkage study of the schizophrenic phenotype periodic catatonia (Leonhard 1999), we were able to localize a major-gene locus for periodic catatonia and thereby confirm that it is a valid diagnostic entity in the group of schizophrenias. In periodic catatonia, the nuclear syndrome consists of distinct hyperkinetic and/or akinetic disturbances of psychomotor behavior. This involves distorted expressive and reactive movements, as well as subtle derangements of facial expression, with grimacing facial movements, stereotyped and iterative gestures, bizarre parakinesis, and stiff and clumsy motor activity, along with rigid posture stereotypies, negativism, or hyperkinetic restlessness with distorted parakinetic movements (Leonhard 1999). These qualitative psychomotor symptoms are present in both the acute psychotic episode and the residual state. Lifetime prevalence of periodic catatonia is estimated to be .001 in the general population, and the phenotype affects both genders, with equal risk and without age-at-onset differences (Stöber et al. 1995). Kahlbaum's gross catatonic motor signs, which define DSM and ICD catatonic schizophrenia, are considered a nonspecific symptom cluster, compared with the meticulously elaborated analysis of disturbed reactive and expressive movements in periodic catatonia (Pfuhlmann and Stöber 1997).

We focused on the phenotype periodic catatonia because of the clinical impression of homogenous symptomatology and dominant mode of transmission within pedigrees (Stöber et al. 1995; Leonhard 1999) and because it seems possible that current psychiatric diagnostic criteria obscure major-gene effects by classifying genetically diverse subtypes together (Levinson et al. 1998). Besides his pioneering differentiation of unipolar and bipolar affective psychoses, which has now become an integral part of medical textbooks, Leonhard (1999) proposed a differentiated classification of schizophrenic psychoses into three main groups: cycloid psychoses, unsystematic schizophrenias, and systematic schizophrenias. Periodic catatonia is one form of the unsystematic schizophrenias (i.e., affective paraphrenia, cataphasia, and periodic catatonia), each of which exhibits high familial aggregation of homogenous psychoses. Regarding Leonhard's diagnostic system, we obtained a high level of diagnostic agreement—Cohen's κ = .82–.91—in mixed populations of patients with schizophrenia, indicating that the subtypes can be distinguished reliably (Franzek et al. 1992, 1996; Pfuhlmann et al. 1997). In addition, we reached sufficient interrater-reliability on catatonic schizophrenia subtypes (periodic catatonia vs. systematic catatonias), representing Cohen's κ = .93, and considerable stability of diagnoses with κ = .93 (Beckmann et al. 1996). To maintain high diagnostic standards, the families involved in the present genome scan were seen by a single clinical investigator who has >10 years supervised experience in the field of differentiated psychopathology, including experience with interrater-reliability tests (Franzek et al. 1996; Pfuhlmann et al. 1997). Application of different diagnostic systems or best-estimate procedures with diagnostic hierarchy are suitable for phenotypes that are

Table 2

Two-Point Parametric Analysis of Pedigrees Segregating Periodic Catatonia, under an Autosomal Dominant Model, at Loci with Z_{lr} Scores >2.5

			Two-Point Parametric Analysis				
			Homogeneity		Heterogeneity		
Marker	Chromosome Location	Coordinate (cM)	Z_{max}	θ	Z_{max}	θ	α
D15S1012	15q15	35.3	2.75	.04	2.75	.04	1.00
D22S1169	22q13	58.2	1.04	.22	1.57	.04	.38

difficult to define, such as schizophrenia (Leckman et al. 1982; Andreasen and Carpenter 1993). In the present study, however, we had to discriminate between affected and unaffected individuals in large multigenerational pedigrees segregating periodic catatonia. Thus, according to Leonhard's diagnostic guidelines, thorough clinical examination and diagnostic evaluation by a single experienced investigator seemed most appropriate (Vogel and Motulsky 1997). Diagnostic assignment was made prior to genotyping, genotyping was done blind to phenotype, and statistical analyses were processed, with nonparametric and parametric methods (dominant model), in a given phenotype; this may reduce the false-positive rate by decreasing the number of disease and inheritance models. Nevertheless, some caveats should be considered when we interpret our findings. Although the small sample size may be among the limitations, it appears to be compensated by the sample's ethnic and geographic homogeneity and the appropriate power of 94.5% to detect LOD scores ≥ 3.0. The statistical analyses were based on (1) nonparametric, model-free methods that allow accurate analysis in a small number of extended pedigrees with arbitrary mixture of family structures and (2) parametric methods that demand specification of an inheritance model. We used an autosomal dominant affecteds-only model for two-point and multipoint linkage analysis, although certain parameters, such as penetrance, may not be accurate.

Nonparametric, model-free linkage analysis was performed with the GH-PLUS package, which allows *P*-value estimation on the basis of likelihood-ratio tests in a one-parameter, allele-sharing model (Kruglyak et al. 1996; Kong and Cox 1997). For complex traits, the latter test statistic seems to offer a more appropriate evaluation of statistical significance. On the basis of previous criteria for linkage (Lander and Kruglyak 1995), the nonparametric Z_{lr} score of 4.05, with $P = 2.6 \times 10^{-5}$ and a LOD* of 3.57, on chromosome 15q15, reached significant evidence for linkage. This corresponds to a genomewide significance level of <.05—that is, the chance that a LOD score of this magnitude will be achieved at some location that does not contain a disease gene in the course of a genome scan is <.05—and thus satisfies the criterion for global significance. Furthermore, we found on chromosome 22q13 susceptibility for a second chromosomal locus for periodic catatonia, which met the criterion for suggestive evidence for linkage, with $P < .002$. Statistically, scores of that magnitude may occur one time at random per genome scan.

The parametric two-point analyses under an autosomal dominant affecteds-only model provided independent confirmation of nonparametric linkage results: the dominant model gave Z_{max} of 2.75 on chromosome 15q, under both linkage homogeneity and heterogeneity. Under the assumption of linkage heterogeneity, a Z_{max} of 1.57 was obtained on chromosome 22q. Further analysis of the two largest pedigrees with seven affected individuals each gave four-point LOD scores (VITESSE) of 2.59 ($\theta = .00$) at the chromosome 22q region and 2.89 ($\theta = .029$) at the chromosome 15q candidate region. To achieve a robust genetic model, we analyzed the data by using a dominant inheritance model with affecteds-only analysis (arbitrarily setting disease-allele frequency at .001 and allowing no phenocopies). Multipoint analyses using VITESSE (O'Connell and Weeks 1995) are a conservative procedure that does not take into account those probands who were scored as unaffected and who may carry dubious linkage information. Therefore, the informational content of the pedigrees is reduced, in favor of reliability. This approach results in a loss of power to detect linkage, and, thus, the two largest families fall short of the threshold LOD score of 3 that is usually required for declaring linkage in monogenic diseases. Nevertheless, since the genome scan is completed, these are the only genomic regions that, under this restrictive model, are produced for both families.

Parametric linkage results are in concordance with the assumption of monogenic inheritance in periodic catatonia in an autosomal dominant mode of transmission, as indicated by previous family studies that demonstrated, for first-degree relatives, a cumulative morbidity risk of ~27% (Stöber et al. 1995; Beckmann et al. 1996; Leonhard 1999). On the basis of the nonparametric and parametric linkage analyses we claim for putative disease loci in periodic catatonia, a schizophrenic phenotype derived from Leonhard's classification of schizophrenia. One locus resides on chromosome 15q15 and supports the assumption of a single-gene model in this distinct schizophrenic phenotype. A further susceptibility locus, which is supported mainly by data on a single large family, is located on chromosome 22q13, which indicates genetic heterogeneity. On chromosome 15q15, the candidate segment overlaps with a putative schizophrenia locus defined by a neurophysiological deficit of the P50 auditory-evoked–response inhibition in patients with schizophrenia and in unaffected relatives (Freedman et al. 1997). The most positive linkage of the composite inhibitory phenotype involves a chromosomal region of ~45 cM, including the α-7 nicotinic acetylcholine receptor gene (CHRNA7). Except the early findings by Coon et al. (1994), most genomewide linkage scans, however, found no evidence for a schizophrenia-gene locus on chromosome 15q (Craddock and Lendon 1999). Renewed interest in chromosome 15q12-15 resulted in either exclusion of linkage or weak evidence for a gene locus associated with schizophrenia, in that region (Kaufmann et al. 1998; Leonard et al. 1998; Neves-Pereira et al. 1998;

Curtis et al. 1999). Moreover, replication studies pointed to an association between chromosome 22q markers and the P50-gating deficit (Myles-Worsley et al. 1999). Thus far, we have not been able to assess the P50 measures in our families. Pulver et al. (1994) reported on potential linkage between markers at 22q12-13 and schizophrenia; thus, the long arm of chromosome 22 is a prime candidate region for susceptibility to schizophrenia. These results, however, are inconsistent, being confined neither to a single locus nor to a specific method of analysis (Schwab and Wildenauer 1999). In our study, linkage to chromosome 22q was based mainly on one large family with seven affected individuals, and thus evidence for linkage is weaker than that at chromosome 15. However, this locus was by far the best fit, in the entire genome, for this family, which suggests that this linkage is a true finding. Additionally, positive nonparametric-linkage and LOD* scores of $P < .01$ were detected at various regions throughout the genome, which may represent spurious linkages or weak true-minor loci.

Findings regarding the phenotype of periodic catatonia have inspired a century of debate on the nature of phenotypes in psychiatry and whether schizophrenic psychoses breed true. With regard to the clinical symptoms that define ICD and DSM schizophrenia, modern research gives preference to extensive variability in long-term and intrafamilial symptomatic presentation (Peralta et al. 1992; Maier et al. 1993; Oulis et al. 1999). In view of differentiated psychopathology, fixed symptom constellations and hierarchical symptom patterns form characteristic syndromes, and distinct disorders, such as periodic catatonia, show homogenous intrafamilial transmission (Leonhard 1999). Our results provide support for such a view but will require independent replication and additional research into these phenotypes.

In conclusion, our results suggest that phenotypic observations are a useful approach to identify genetically meaningful subgroups of schizophrenic psychoses. A major disease locus, which maps to chromosome 15q15, was identified in periodic catatonia. On the basis of these findings, we propose that periodic catatonia can be differentiated clinically and genetically within the complex group of schizophrenia.

Acknowledgments

We are greatly indebted to all families for their cooperation and to all probands for their generous and active participation in this study. This work was supported by the Deutsche Forschungsgemeinschaft (support to H.B. and G.S.). K.P.L. is supported by the Hermann and Lilly Schilling Stiftung. The Gene Mapping Center is supported by a grant-in-aid from the German Ministry of Research, German Human Genome Project (to A.R. and T.F.W.).

Electronic-Database Information

The accession number and URLs for data in this article are as follows:

Généthon, http://www.genethon.fr

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for schizophrenia and periodic catatonia [MIM 181500])

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