

Susceptibility Locus on Chromosome 1q23-25 for a Schizophrenia Subtype Resembling Deficit Schizophrenia Identified by Latent Class Analysis

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Context: Identifying susceptibility genes for schizophrenia may be complicated by phenotypic heterogeneity, with some evidence suggesting that phenotypic heterogeneity reflects genetic heterogeneity.

Objective: To evaluate the heritability and conduct genetic linkage analyses of empirically derived, clinically homogeneous schizophrenia subtypes.

Design: Latent class and linkage analysis.

Setting: Taiwanese field research centers.

Participants: The latent class analysis included 1236 Han Chinese individuals with *DSM-IV* schizophrenia. These individuals were members of a large affected-sibling-pair sample of schizophrenia (606 ascertained families), original linkage analyses of which detected a maximum logarithm of odds (LOD) of 1.8 ($z=2.88$) on chromosome 10q22.3.

Main Outcome Measures: Multipoint exponential LOD scores by latent class assignment and parametric heterogeneity LOD scores.

Results: Latent class analyses identified 4 classes, with 2 demonstrating familial aggregation. The first (LC2) described a group with severe negative symptoms, disor-

ganization, and pronounced functional impairment, resembling "deficit schizophrenia." The second (LC3) described a group with minimal functional impairment, mild or absent negative symptoms, and low disorganization. Using the negative/deficit subtype, we detected genome-wide significant linkage to 1q23-25 (LOD=3.78, empiric genome-wide $P=.01$). This region was not detected using the *DSM-IV* schizophrenia diagnosis, but has been strongly implicated in schizophrenia pathogenesis by previous linkage and association studies. Variants in the 1q region may specifically increase risk for a negative/deficit schizophrenia subtype. Alternatively, these results may reflect increased familiarity/heritability of the negative class, the presence of multiple 1q schizophrenia risk genes, or a pleiotropic 1q risk locus or loci, with stronger genotype-phenotype correlation with negative/deficit symptoms. Using the second familial latent class, we identified nominally significant linkage to the original 10q peak region.

Conclusion: Genetic analyses of heritable, homogeneous phenotypes may improve the power of linkage and association studies of schizophrenia and thus have relevance to the design and analysis of genome-wide association studies.

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SCHIZOPHRENIA (SZ) IS A DEBILITATING psychiatric illness for which the pathogenesis remains unclear. Although strongly implicating a number of genetic regions and promising candidate genes, genetic analyses have also highlighted the causal complexity of the disorder. Genomic variants and regions showing association or linkage often differ between studies, and statistical evidence is frequently unconvincing. Confirmed functional variants remain elusive. The presence of small-effect risk variants, genetic heterogeneity, incomplete penetrance, and phenocopies renders the phenotype immensely challenging for genetic dissection.

Genetic studies of SZ may also be confounded by clinical heterogeneity. Schizophrenia has no established biological mark-

ers, and diagnoses are based on the presence and duration of symptoms, the prominence of which can vary considerably between patients. Debate has long centered on whether this phenotypic heterogeneity reflects causal heterogeneity. Although the use of operationalized diagnoses has unarguably facilitated substantial progress in SZ research, it also assumes a single causal model for patients with distinct clinical profiles. If this clinical variation reflects the presence of different causal processes, the use of more homogeneous clinical phenotypes may facilitate the identification of genotype-phenotype correlations.¹ Such approaches have yielded promising findings in other complex disorders, including attention-deficit/hyperactivity disorder² and migraine.³

Some evidence suggests that the genetic cause of SZ may differ between pa-

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tients with distinct clinical profiles. Kendler and colleagues⁴ demonstrated significant clinical differences between linked and unlinked families for a candidate region in 8p22-21. Also, in a large association study of the D-amino acid oxidase activator gene (*DAOA*) with SZ, significant association was detected in a subset of subjects ($n=112$) who had experienced major mood episodes but not in the (much larger) subset ($n=597$) who had not, and no association was detected by using the operationalized SZ diagnosis.⁵ However, few studies have used a fully data-driven approach to empirically derive clinical subtypes for genetic analyses of SZ; to our knowledge, there is just one. Fanous and colleagues⁶ recently reported linkage analyses of psychotic subtypes derived by means of latent class analysis (LCA) of 755 psychotic subjects from 270 Irish families. They detected 4 regions that showed suggestive linkage to 1 of the LCA subtypes but little linkage to the traditional clinical diagnosis.

Interestingly, 1 of the LCA subgroups identified in the study by Fanous et al resembled "deficit SZ" (DS), a well-characterized SZ subtype supported by taxometric analysis⁷ and showing good longitudinal stability.⁸ Compared with patients without DS, patients with DS exhibit primary, enduring negative symptoms⁹; poorer social functioning; less depression; less suicidal ideation; and fewer delusions of an exclusively social content while having similar overall severity of all delusions, hallucinations, and formal thought disorder.¹⁰ Family studies suggest utility of the DS subtype in genetic studies, showing significant correlation for deficit vs nondeficit subtypes in sibling pairs concordant for SZ¹¹ and increased family risk of SZ in individuals with DS compared with patients without DS.¹² However, few studies have reported genetic analyses of DS. Bakker and colleagues¹³ reported association of DS with the *PIP5K2A* gene on chromosome 10p12, whereas Fanous and colleagues⁶ identified suggestive linkage of their deficit class to a region in chromosome 20.

To further explore the utility of homogeneous subtypes in identifying SZ risk loci, we conducted genome-wide linkage analyses of empirically derived SZ subtypes in 1236 Taiwanese individuals with SZ.¹⁴ These individuals were members of the largest extant affected-sibling-pair sample for SZ, comprising 606 ascertained families. Initial genome-wide linkage analysis of the *DSM-IV* SZ diagnosis provided support for regions in 10q22.3, 2q14.1, 1p31.1, 15q14, and 4q21.23.¹⁴ However, no region achieved genome-wide significance, with a region in 10q22.3 showing the strongest evidence of linkage ($z=2.88$, logarithm of odds [LOD] = 1.8). We aimed to investigate whether additional regions or increased significance could be detected by means of empirically derived clinical phenotypes.

METHODS

SAMPLE

This data set was accessed via the National Institute of Mental Health Center for Collaborative Genetic Studies on Mental Disorders (distribution 5.0) (<http://zork.wustl.edu/nimh>). The collection of this sample has been previously described.¹⁴ Briefly, affected-sibling-pair families containing at least 2 siblings with SZ were recruited from 6 centers in Taiwan. Each affected sib-

ling underwent a diagnostic screen using supplemental medical records and a semistructured interview, followed by the Mandarin Chinese version of the Diagnostic Interview for Genetic Studies (DIGS).^{15,16} The DIGS interview data were supplemented with information from medical records and a semistructured interview with family members.^{17,18} Best-estimate final diagnoses were assigned by 2 research psychiatrists, with a third diagnostician resolving any disagreements. The sample was genotyped by the Center for Inherited Disease Research for 386 microsatellite markers spaced at 9-cM intervals (average) genome-wide.

LATENT CLASS ANALYSIS

The number and composition of distinct clinical groups were empirically determined by means of LCA, a statistical method for identifying subtypes of related cases from multivariate categorical data.¹⁹ On the basis of clinical experience, we selected 11 symptoms recorded during the DIGS interview that were deemed to capture the important aspects of clinical variation (**Table 1**). The LCA was conducted with Latent Gold software (version 4.5; Statistical Innovations Inc, Belmont, Massachusetts) and included 1236 Han Chinese participants with a *DSM-IV* diagnosis of SZ. Latent cluster models specifying from 1 to 10 latent classes were fitted, allowing up to 5000 iterations of the Expectation Maximization algorithm with a convergence criterion of 1×10^{-6} . To avoid local maxima in parameter estimation, models were refitted multiple times with the use of different starting values. The best-fitting model was selected on the basis of the Bayesian information criterion, as previously recommended.²⁰ The preferred model was that with the lowest Bayesian information criterion, providing optimal balance between fit and parsimony. In addition, we assessed the clinical interpretability of the identified classes and ensured that classes were of nontrivial size. Because many cases contained missing values for at least 1 indicator variable and to use all available data, cases containing missing values were included in the analysis. However, the impact of missing values was reduced by constructing variables from multiple, related DIGS items, providing a degree of redundancy. Latent Gold handles missing indicator values directly in the likelihood function by basing the likelihood contribution of each case on the observed indicators only. That is, parameters are estimated by using all available information for each of the cases.

An important assumption of LCA is that of local independence between observed indicator variables. That is, conditional on latent class membership, the indicator variables are statistically independent (uncorrelated). In cases in which the local independence assumption does not hold, LCA models may be modified to provide adequate fit.²¹ After initial model selection, we used the Latent Gold software to identify indicator variables with significant residual association, indicated by a bivariate residual (BVR) score greater than 3.84 (equivalent to $P < .05$ because the BVR statistic is distributed as χ^2). Residual association was accounted for by incorporating direct effect parameters between significantly correlated variable pairs,²² starting with the highest BVR and proceeding iteratively until all BVRs were less than 3.84.

FAMILIAL AGGREGATION ANALYSES

Before performing genetic analyses of LCA subtypes, we sought evidence of a genetic contribution to latent class group membership, which should produce aggregation of group membership within families. On the basis of all 1236 affected individuals with SZ, the sample contained 758 possible affected relative pairs (ARPs). The proportion of ARPs concordant for membership in

Table 1. Indicator Variables for the Latent Class Analysis and Endorsement Frequencies

Variable (Symptom)	Type	DIGS Item(s)	Proportion of Subjects With Symptom
Schneiderian delusions	Nominal	Control delusions, or having one's thoughts broadcast, inserted, or withdrawn	0.555
Other delusions	Nominal	Persecutory, reference, or bizarre (clearly impossible) delusions	0.808
Schneiderian hallucinations	Nominal	Voices maintaining running commentary, or multiple voices	0.659
Other hallucinations	Nominal	Somatic, tactile, olfactory, visual, or gustatory hallucinations	0.610
Disorganization	Nominal	Bizarre behavior or disorganized speech	0.616
Global symptom severity	Ordinal	Global assessment of symptoms (past month); score 1-100 reflecting level of social and occupational function	
		Severe functional impairment; score ≤ 40	0.399
		Moderate functional impairment; score 41-61	0.460
		Mild or no impairment; score > 61	0.141
Pattern of symptoms	Nominal	4 classes representing common longitudinal profiles of positive and negative symptoms	
		Continuously positive	0.294
		Predominantly negative	0.142
		Positive converting to negative	0.163
		Mixture of positive and negative	0.371
Age at illness onset	Ordinal	Early (< 20 y)	0.373
		Intermediate (20-35 y)	0.564
		Late (> 35 y)	0.063
Suicide attempt(s)	Nominal	History of ≥ 1 suicide attempt	0.275
Affective flattening	Ordinal	Global rating of affective flattening (reduced emotional expression)	
		No symptoms	0.316
		Mild symptoms	0.335
		Moderate to severe symptoms	0.334
Alogia (poverty of speech)	Ordinal	Global rating of alogia (poverty of speech)	
		No symptoms	0.316
		Mild symptoms	0.331
		Moderate to severe symptoms	0.334

Abbreviation: DIGS, Diagnostic Interview for Genetic Studies.

any latent class was compared with the expected value, which was derived by means of the marginal probabilities for each latent class. The expected and observed proportions were treated as binomial variables and compared by means of a normal approximation. Because the sample contained nonindependent relative pairs from families containing 3 or more affected individuals, the analysis was repeated with the use of an average of the number of concordant relative pairs within each family, in which each family was weighted to contribute a single relative pair.

LINKAGE ANALYSIS

On the basis of the posterior probabilities of latent class membership, affected individuals were assigned to their most likely latent class. Genome-wide linkage analyses were conducted for the 2 latent classes exhibiting familial aggregation. For each, individuals endorsing that class were considered affected and multipoint exponential LOD scores²³ were calculated at 1-cM increments by means of the S_{pairs} ²⁴ sharing statistic implemented in the Merlin program.²⁵ Marker positions were determined by means of the sex-averaged Marshfield genetic map,²⁶ as for the original analysis. This was considered the primary linkage analysis.

As a secondary analysis, we also calculated parametric heterogeneity LOD (HLOD) scores in the entire, original data set (606 families). Multipoint HLOD scores were calculated under simple dominant and recessive models, specifying disease allele frequencies of 0.01 and 0.1 and genotype penetrances of (0, 0.5, 0.5) and (0, 0, 0.5) for the dominant and recessive models, respectively, for 0, 1, or 2 copies of the disease allele.^{27,28}

To estimate genome-wide significance levels for our primary analysis, we used an empiric method.²⁹ For each of the

2 latent class groups used in genetic analyses, Merlin²⁵ was used to generate 5000 data replicates under the null hypothesis of no linkage, which were analyzed at 1-cM increments by means of the exponential LOD score.²³ We then derived the empiric distribution of the maximum LOD score at each position (LODmax) by recording, for each replicate, the highest LOD score obtained across the 2 latent class groups. This generated an empiric distribution of the highest score at each position that naturally accounts for both multiple testing and the correlation between statistics. The genome-wide significance level associated with the highest observed score was defined as the frequency of equivalent or higher peaks in the empiric distribution of LODmax. Linkage peaks separated by more than 40 cM were considered independent.^{30,31} Genome-wide significance and suggestive thresholds were defined as scores occurring with a probability of 0.05 and 1 in every LODmax replicate, respectively,³² and nominal $P = .01$ and $P = .05$ thresholds were defined as scores occurring with a probability of 0.01 and 0.05 at any map position.

RESULTS

LATENT CLASS ANALYSIS

The LCA included 1236 individuals with SZ (1175 affected siblings and 61 affected parents), with a mean (SD) age of 36.29 (9.58) years and a mean age at illness onset of 23.05 (6.92) years. Males composed 61.5% of the sample. The affected individuals were contained within 578 families, 561 of which contained 2 or more affected sibling pairs

Table 2. Class Membership and Symptom Endorsement Probabilities for the 4-Cluster Latent Class (LC) Solution

	LC1	LC2	LC3	LC4
γ Estimates ^a	0.4246	0.2897	0.1630	0.1227
ρ Estimates ^b				
Schneiderian delusions present	0.5004	0.4999	0.6602	0.7831
Other delusions present	0.8292	0.7629	0.7882	0.8553
Schneiderian hallucinations present	0.6445	0.5696	0.7470	0.7470
Other hallucinations present	0.6108	0.5977	0.6254	0.6195
Disorganized speech/behavior present	0.5766	0.8238	0.4695	0.4698
Global symptom severity				
Major functional impairment	0.3251	0.6532	0.0268	0.5471
Moderate to serious symptoms	0.5775	0.3314	0.4133	0.4225
Mild or no symptoms	0.0975	0.0154	0.5599	0.0303
Pattern of symptoms				
Continuously positive	0.2442	0.0446	0.5860	0.7480
Predominantly negative	0.1128	0.2585	0.1129	0.0418
Positive converting to negative	0.1832	0.2203	0.0829	0.1014
Mixture of positive and negative	0.4599	0.4766	0.2181	0.1088
Age at onset, y				
<20	0.3571	0.3973	0.4165	0.3126
20-35	0.5748	0.5485	0.5340	0.6028
>35	0.0681	0.0542	0.0495	0.0847
Suicide attempt(s) present	0.2824	0.1993	0.3184	0.3692
Affective flattening				
None	0.1885	0.0029	0.9062	0.7378
Mild	0.5927	0.1454	0.0928	0.2531
Moderate to severe	0.2189	0.8517	0.0010	0.0091
Alogia (poverty of speech)				
None	0.2215	0.0007	0.9345	0.5930
Mild	0.6006	0.0791	0.0651	0.3855
Moderate to severe	0.1779	0.9202	0.0004	0.0215

^aClass membership probabilities.

^bItem response probabilities, conditional on latent class membership.

(28 of the original 606 families had no diagnostic and/or symptom data available and 17 had data for 1 sibling only). Of the 561 multiple-sibling families, 524 families contained 2 affected siblings, 36 contained 3 affected siblings, and 1 family contained 4 affected siblings. Genotype data were available for all individuals included in the LCA.

After fitting a single-class solution, a continuous improvement in fit was observed up to a 4-class solution; the relevant Bayesian information criterion values were 20463.27 (1 class), 19527.27 (2 classes), 19425.43 (3 classes), 19370.09 (4 classes), and 19401.08 (5 classes). To evaluate the robustness of our LCA model, we repeated the primary Latent Gold analysis by using the LCA procedure of SAS. Identical results were obtained, showing that our model was not sensitive to the particular software package used. We also repeated the Latent Gold analysis 20 times, each time randomly selecting 90% of the original sample for inclusion. Each run identified the same 4-class solution, with individuals being classified into the same latent class with 96.8% consistency across the 20 runs.

Assessment of Latent Gold's BVR output for the 4-class solution showed several BVRs greater than 3.84, suggesting a number of pairwise correlations between indicator variables remaining unexplained by the model. To ensure conditional independence of the LCA solution, we used the Latent Gold software to iteratively incorporate direct effects between all variable pairs with a BVR greater than 3.84. The results of the final, 4-class solution are shown in **Table 2** and **Figure 1**.

Visual comparison of the 4 cluster profiles suggests qualitative differences between the identified phenotypic subgroups. A profile analysis of variance statistically validated these differences, rejecting the hypothesis of parallelism of the 4 plots ($F_{57,1628}=85.52, P<.001$). This suggests an underlying phenotypic structure of 4 distinct categories rather than a single continuum of liability, which would produce classes differing primarily in symptom severity.³³ The 4 classes were most differentiated by the levels of disorganization, functional impairment, negative symptoms (alogia and affective flattening), and overall symptom pattern. Negative symptoms best differentiated the 4 groups, with endorsement probabilities differing by approximately 90% between the least and most severely affected groups. All 4 classes exhibited high levels of delusions and hallucinations.

The largest subgroup, LC1 ($\gamma=0.43, n=533$) was not distinguished by marked presence or absence of any particular symptom, rather demonstrating moderate levels of delusions, hallucinations, disorganization, functional impairment, suicidality, and negative symptoms. The pattern of symptoms for this class was most likely to be a mixture of positive and negative symptoms.

The other 3 subgroups were more symptomatically distinctive. The second largest class, LC2 ($\gamma=0.29, n=370$) described a subtype characterized by moderate to severe negative symptoms (flat affect and alogia), prominent disorganization (speech and behavior), and marked to severe functional impairment. This class described a

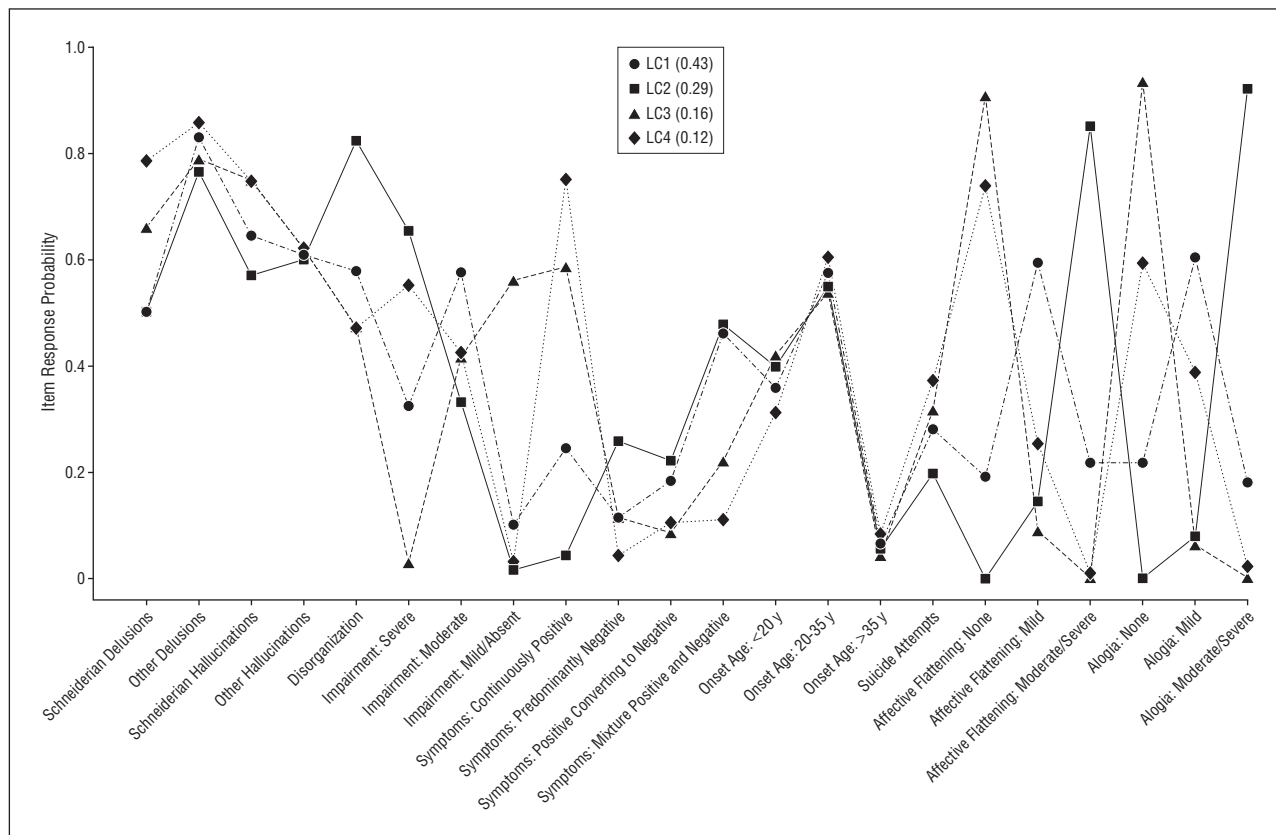


Figure 1. Profile plot for latent classes (LCs) under the 4-class model. Item response probabilities indicate the proportion of individuals in each class exhibiting each symptom. Symptom descriptions are provided in Table 1.

category of severely affected patients with SZ resembling DS. Of the 4 classes, individuals in LC2 were the least likely to experience delusions and hallucinations, although these symptoms were still present in a majority of individuals. Individuals in LC2 were also the least likely to have attempted suicide.

Of the 4 classes, subjects in LC3 ($\gamma=0.16$, $n=213$) were the least severely affected, demonstrating the highest level of global functioning, a virtual absence of negative symptoms, and the lowest levels of disorganization. This group had a pattern of symptoms characterized by predominantly positive symptoms when ill, but relatively few symptoms during remissions.

The fourth and smallest class (LC4; $\gamma=0.12$, $n=120$) displayed prominent delusions and hallucinations, moderate disorganization, and moderate to marked functional impairment. Individuals in this class were most likely to experience continuous, positive symptoms and were also the most likely to have attempted suicide. Negative symptoms were absent or mild for almost all individuals in this group.

FAMILIAL AGGREGATION ANALYSES

To justify linkage analysis of the identified latent classes, it was important to demonstrate familial aggregation of class membership, indicative of an underlying genetic influence. On the basis of the marginal probabilities of LC1, LC2, LC3, and LC4 (0.43, 0.29, 0.16, and 0.12, respectively), the expected number (proportion) of total con-

cordant ARPs was 232 (0.31). The observed number (proportion) was 257 (0.339) ($z=1.97$, $P=.02$), suggesting marginally significant overall familial aggregation. However, this aggregation was nonsignificant when each family was weighted to contribute a single relative pair ($z=1.38$, $P=.08$). Among individual classes, a significant excess of concordant relative pairs was observed for only 2 classes, LC2 and LC3. For these classes, ARP class concordance was elevated on the basis of counts of both total relative pairs (LC2: $z=2.27$, 1-sided $P=.01$; LC3: $z=2$, $P=.02$) and independent pairs per family (counted as $R-1$, where R is the number of affected individuals in the family) (LC2: $z=3.26$, 1-sided $P<.001$; LC3: $z=2.58$, $P=.005$). The excess was nonsignificant for LC1, and LC4 had fewer observed than expected concordant relative pairs. This supports a role of familial factors in the etiology of LC2 and LC3.

LINKAGE ANALYSES

Incorporating correction for testing both LC2 and LC3, empiric genome-wide significant and suggestive linkage thresholds of 3.14 and 1.86 and nominal $P=.01$ and $P=.05$ thresholds of 1.45 and 0.84 were determined. Linkage analyses of LC2 included 257 individuals contained within 64 families, incorporating 67 total or 66 independent sibling pairs. Analyses of LC3 included 93 individuals contained within 23 families, with 25 total and 24 independent sibling pairs. Genome-wide multipoint LOD scores²³ for the LC2 and LC3 subsets are shown in **Figure 2**.

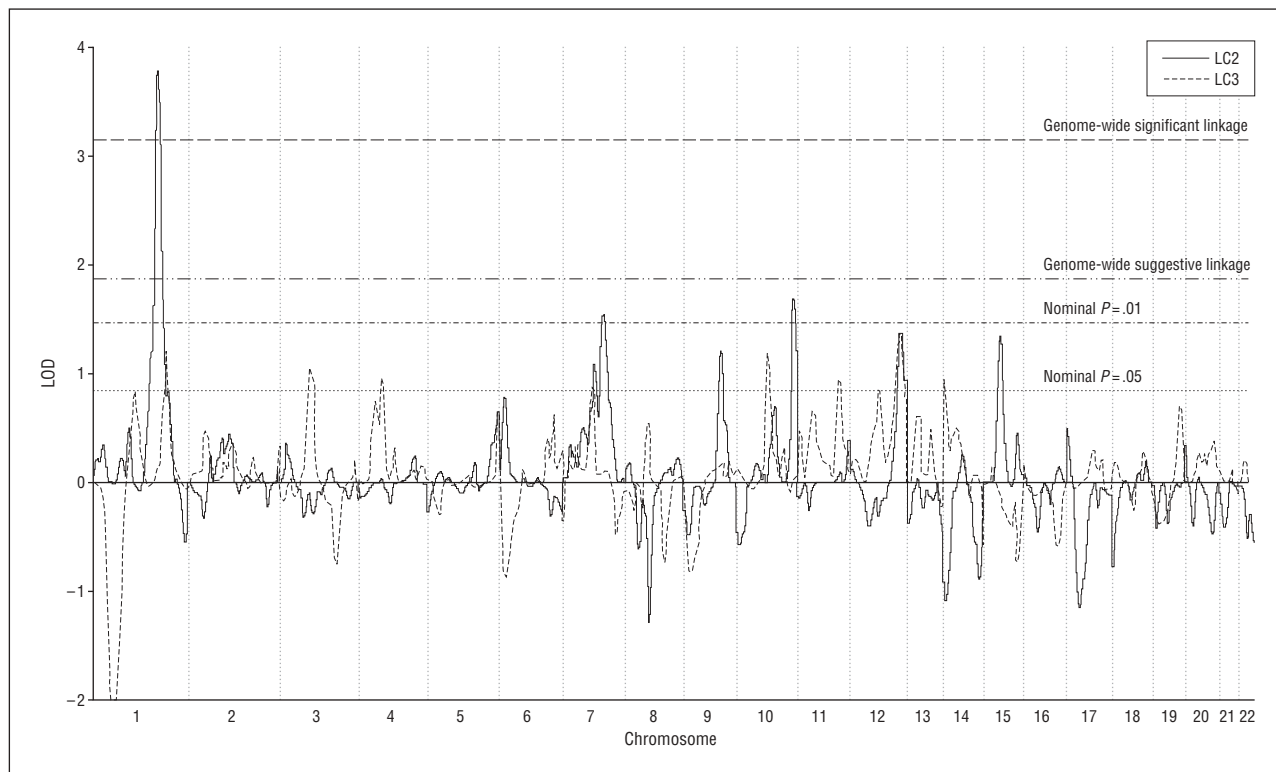


Figure 2. Results of genome-wide nonparametric linkage analysis of the 2 latent classes (LCs) demonstrating familial aggregation. Empiric thresholds for genome-wide significant linkage, genome-wide suggestive linkage, nominal $P = .01$, and nominal $P = .05$ are shown. LOD indicates logarithm of odds.

For LC2, the strongest linkage evidence was observed at 1q23-25, 189 cM from the p-telomere (LOD=3.78). This result easily surpassed the threshold for genome-wide significant linkage, with only 61 peaks of 3.78 or greater occurring in 5000 simulations of LODmax (genome-wide $P = .01$, incorporating correction for testing both LC2 and LC3). The 1-LOD drop (approximating a 95% confidence interval for the location of the peak) delimited a 15-cM region from 183 to 198 cM (approximately 166.6-180.6 megabases, National Center for Biotechnology Information Build 36.2). To explore the potential mode of inheritance of the putative chromosome 1 locus, we calculated multipoint HLOD scores under simple dominant and recessive models (see the “Methods” section for model parameters). These exploratory analyses demonstrated greater linkage evidence under a recessive (peak HLOD=3.539) rather than a dominant (peak HLOD=2.403) model.

Single-point LOD scores greater than 1 were observed for 4 markers in the 1q region: D1S1679 (LOD=1.07), D1S1619 (LOD=2.72), D1S1589 (LOD=1.41), and D1S518 (LOD=1.38), supporting the multipoint results. In the LC2 subset, an additional 2 regions achieved nominal $P \leq .01$ and a total of 6 regions achieved nominal $P \leq .05$ (Table 3).

For LC3, no region achieved genome-wide significant linkage, suggestive linkage, or nominal $P \leq .01$. Ten regions achieved nominal $P \leq .05$ (Table 3). One of these was located on 10q22.1 (peak LOD=1.19, 94 cM from p-ter) and overlapped the maximum linkage peak detected in original analyses of these data using the DSM-IV SZ diagnosis (peak LOD=1.8, $z = 2.88$, 100.9 cM from p-ter).

Parametric analyses of the original (entire) data set detected the strongest linkage evidence on 10q22.1 (HLOD-dominant=2.402), in the same region as the original peak z score. Nine other peaks achieved HLOD scores greater than 1 under either the dominant or recessive model (Table 4). The 1q region detected with the use of LC2 showed little linkage evidence in the entire sample (peak HLOD=0.738; recessive model, 216 cM from p-ter).

COMMENT

This is the second linkage study of SZ to use categorical phenotypes empirically derived from observed symptom profiles. We proposed that, if clinical heterogeneity reflects genetic heterogeneity, homogeneous clinical subtypes may allow the identification of genomic regions that the traditional diagnosis did not.

Our LCA identified a familial SZ subtype with prominent negative symptoms. The characteristics of this class showed striking similarity to a subtype also described by Fanous et al.⁶ In addition to prominent negative symptoms, individuals in both classes demonstrated high levels of social dysfunction and lower-than-average probabilities of delusions, hallucinations, and Schneiderian psychotic symptoms. Although we did not include depressive and manic items in our LCA, independent assessment of their probabilities in our negative subtype (data not shown) showed values lower than the sample median, consistent with Fanous et al.⁶ Individuals in our negative subtype also demonstrated prominent disorganization and low suicidality; how-

Table 3. Linkage Regions Achieving Nominal $P \leq .05$ for the 2 Familial LCs

Chromosome	Class	Map Position, cM	Multipoint LOD	Nearest Marker	Marker Position, cM
1	LC2	189	3.78 ^a	D1S1619	188.32
7	LC2	121	1.53	D7S3061	128.41
9	LC2	119	1.20	D9S930	120.04
10	LC2	159	1.68	D10S217	157.89
12	LC2	152	1.37	D12S2078	149.60
15	LC2	58	1.34	D15S1507	60.17
1	LC3	126	0.86	D1S1588	125.51
1	LC3	215	1.22	D1S1647	215.99
3	LC3	87	1.06	D3S4542	89.91
4	LC3	79	0.97	D4S2367	78.43
7	LC3	92	0.98	D7S2204	90.95
10	LC3	94	1.19	D10S1432	93.92
11	LC3	119	0.94	D11S4464	123.00
12	LC3	83-85	0.87	D12S1052	83.19
12	LC3	145	1.37	D12S2078	149.60
14	LC3	12	0.95	D14S742	12.46

Abbreviations: LCs, latent classes; LOD, logarithm of odds.

^aSatisfies criteria for genome-wide significant linkage, incorporating correction for testing both LC2 and LC3.

Table 4. Regions Showing Evidence of Linkage in Entire Data Set Using Parametric Heterogeneity Logarithm of Odds (HLOD) Scores^a

Chromosome	Map Position, cM	HLOD	Nearest Marker	Marker Position, cM	Model With Strongest Evidence ^b
1	226	1.150	C1S1248	226.16	Dominant
2	129	1.854	D2S410	125.18	Recessive
4	94	1.418	D4S2361	93.48	Dominant
5	163	1.039	D5S820	159.77	Dominant
10	103	2.402	D10S2327	100.92	Dominant
10	144	1.815	D10S1230	142.78	Dominant
11	119	1.165	D11S4464	123.00	Dominant
12	72	1.093	D12S398	68.16	Dominant
15	85	1.248	D15S655	82.84	Recessive
19	75	1.298	D19S246	78.08	Dominant

^aRegions achieving HLOD greater than 1 are shown.

^bDominant and recessive models specified disease allele frequencies of 0.01 and 0.1 and genotype penetrances of (0, 0.5, 0.5) and (0, 0, 0.5), respectively.

ever, these symptoms were not included in the Fanous et al study.

This negative subtype resembles DS. However, an important characteristic of DS is the presence of primary negative symptoms as opposed to those arising secondary to factors such as depression, paranoia, or preoccupation with psychotic symptoms.³⁴ The available data did not allow us to distinguish between primary and secondary negative symptoms in our deficit (LC2) subset. Although LC2 demonstrated several features consistent with DS—including lower levels of depression,³⁵ suicidality, and social/occupational function³⁶ in the presence of similar (lower) overall levels of delusions and hallucinations—it also showed high levels of disorganization (incorporating formal thought disorder), which may influence the severity of negative symptoms. Thus, despite these similarities, our limitation in addressing the primary/secondary distinction precludes us from describing our LC2 subset as classic DS.

Linkage analyses of our negative subtype (LC2) identified a region of genome-wide significant linkage in 1q23-25. Both the original analysis and our secondary parametric heterogeneity analyses failed to detect linkage to

this region, despite the latter's putative allowance for locus heterogeneity. This region has previously shown highly significant linkage to SZ in a Canadian sample^{37,38} and has also shown linkage to SZ in 2 Chinese studies^{39,40} and a European study.⁴¹ Furthermore, this region has been implicated in SZ susceptibility in 2 genome scan meta-analyses of SZ.^{42,43} Our results may suggest that variants in 1q23-25 specifically increase the risk for a negative/deficit subtype of SZ. In this case, although our LC2 subset was modest in size (64 families), its high phenotypic homogeneity may have increased the proportion of 1q-linked families and power to detect linkage. Alternatively, our detection of the 1q region may have resulted less from the specific phenotypic features of the LC2 subset than our use of a familial/heritable SZ subtype. Indeed, Fanous et al⁶ did not identify linkage of their deficit subtype to this 1q region, but rather detected linkage to a region in chromosome 20. However, these differences may reflect the presence of further genetic heterogeneity within negative/deficit subtypes or statistical variation relating to power, given the modest number of deficit sibling pairs included in our study (67 pairs) and the Fanous study (32 pairs).

Involvement of the 1q23-25 region in a negative/deficit SZ subtype may also be specific to the Han Chinese population or have resulted from this sample's ascertainment characteristics. A striking feature of this Taiwanese sample was a low rate of comorbid substance use/abuse, with just 5.2% and 3.7% of affected siblings reporting alcohol or drug abuse/dependence, respectively.⁴⁴ In our negative class, the equivalent rates were 3.1% and 0.8%, which may have further increased phenotypic homogeneity and power to resolve SZ risk loci. Further research is required to clarify the structure, heritability, and relevant risk loci for negative/deficit subtypes of SZ and to determine the generalizability of our findings to other samples and populations.

Several genes in the 1q region have shown statistical association with SZ, although none of the evidence is compelling. Perhaps the best studied is the regulator of G-protein signaling 4 gene (*RGS4*), which is located in 1q23.3 and has shown modest association in multiple studies⁴⁵⁻⁵⁰ and one meta-analysis,⁵¹ although negative results have also been reported.⁵²⁻⁵⁴ Intriguingly, one recent study reported association of an *RGS4* single-nucleotide polymorphism with severity of negative symptoms and neurocognitive performance,⁵⁵ although another study reported negative association of DS with *RGS4* single-nucleotide polymorphisms.¹³ Other genes in the 1q region showing some level of association with SZ include *CAPON*,^{56,57} *CHRN2*,⁵⁸ *Cx50*,⁵⁹ and *UHMK1*.^{60,61} Interestingly, 2 recent, prominent studies detected association of SZ to a large, recurrent microdeletion in 1q21.1.^{62,63} However, the deletion is rare (frequency, <1% in cases) and thus likely accounts for little linkage to the 1q region. Other studies have shown association of SZ with a heterochromatin variant⁶⁴ and a fragile site⁶⁵ in 1q21. Comprehensive research in larger data sets—including genotype-phenotype analyses—may help to identify genetic variants in the 1q region involved in SZ susceptibility.

The other class demonstrating familiarity in this study (LC3) described the least severely affected subgroup, demonstrating high global functioning, low disorganization, and a virtual absence of negative symptoms. Linkage analyses of LC3 detected evidence of linkage (nominal $P \leq .05$) to a region in 10q overlapping the primary linkage peak detected in original analyses of these data.¹⁴ However, any phenotypic interpretation of these results should be undertaken cautiously because of the modest number of concordant sibling pairs included in the linkage analysis of LC3 (25 total pairs).

Our results should be interpreted in light of several considerations. First, the latent class typology we report is dependent on the response variables we selected for the LCA and the statistical method we used for selecting the best-fitting model. It remains to be shown whether these results differ with the use of different response variables, other rating instruments, or different diagnostic systems. The inclusion of additional symptoms may also result in the identification of further latent classes. Second, although the familial aggregation of LC2 and LC3 group membership suggests genetic influences, it could also reflect shared environmental effects. Twin studies could help to clarify the respective contributions of genetic and environmental effects to subtype liability. Third,

the size and position of our linkage peaks may have been influenced by the number of sibling pairs concordant for each LCA subtype, with the number of total concordant sibling pairs for LC2 and LC3 being 67 and 25, respectively. It is possible that the detection of significant linkage with LC2, but not LC3, reflected power differences relating to sample size. However, the position of the 10q peak accords well with those reported in other studies, supporting the validity of its location.

In conclusion, our results suggest that the identification and analysis of homogeneous, heritable clinical subtypes may be an important avenue to progress in SZ genetics research. Reduced genetic heterogeneity in such subtypes may increase power to identify particular risk variants. Although genetic studies have achieved substantial progress by means of the traditional SZ diagnosis, exclusive reliance on *DSM-IV* diagnostic categories of SZ, albeit in ever-increasing samples, may not be sufficient for dissecting its genetic complexity. If the clinical SZ diagnosis comprises multiple, causally divergent subtypes or dimensions, additional value may be extracted from existing and future data sets by conducting empiric analyses of comprehensive phenotype data to identify homogeneous clinical subtypes and dimensions. The analysis of such alternative phenotypes may be an important, complementary approach for clarifying the genetic cause of SZ.

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