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Schizophrenia and Affective Disorders—Cosegregation with a Translocation at Chromosome 1q42 That Directly Disrupts Brain-Expressed Genes: Clinical and P300 Findings in a Family

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A family with a (1;11)(q42;q14.3) translocation significantly linked to a clinical phenotype that includes schizophrenia and affective disorders is described. This translocation generates a LOD score of 3.6 when the disease phenotype is restricted to schizophrenia, of 4.5 when the disease phenotype is restricted to affective disorders, of 7.1 when relatives with recurrent major depression, with bipolar disorder, or with schizophrenia are all classed as affected. This evidence for linkage is among the strongest reported for a psychiatric disorder. Family members showed no distinctive features by which the psychiatric phenotype could be distinguished from unrelated cases of either schizophrenia or affective disorders, and no physical, neurological, or dysmorphic conditions co-occurred with psychiatric symptoms. Translocation carriers and noncarriers had the same mean intelligence quotient. Translocation carriers were similar to subjects with schizophrenia and different from noncarriers and controls, in showing a significant reduction in the amplitude of the P300 event-related potential (ERP). Furthermore, P300 amplitude reduction and latency prolongation were measured in some carriers of the translocation who had no psychiatric symptoms—a pattern found in other families with multiple members with schizophrenia, in which amplitude of and latency of P300 appear to be trait markers of risk. The results of karyotypic, clinical, and ERP investigations of this family suggest that the recently described genes DISC1 and DISC2, which are directly disrupted by the breakpoint on chromosome 1, may have a role in the development of a disease phenotype that includes schizophrenia as well as unipolar and bipolar affective disorders.

Schizophrenia (MIM 181500), bipolar disorder (MIM 125480), and recurrent major depression (i.e., unipolar disorder) are among the most prevalent causes of disability worldwide (Lopez and Murray 1998). Family and twin research has established the importance of inherited factors, and several chromosomal regions likely to harbor susceptibility genes have been identified during 10 years of extensive linkage and association studies (Potash and DePaulo 2000; Riley and McGuffin 2000). At several chromosomal locations—including 13q, 18p, and 22q—linkage has been reported to both schizophrenia and bipolar disorder, raising the possibility that some genetic risk factors contribute to a range of psychotic symptoms and give rise to phenotypes that cross the traditional diagnostic boundaries of schizophrenia and of affective disorders (Wildenauer et al. 1999; Berrettini 2000). However, it is not clear, given the large number of linkage reports for both disorders, that the number of regions with positive results with regard to schizophrenia and bipolar disorder exceeds chance expectation. Whereas most family and twin studies do not support coaggregation of these disorders, some family studies have reported overlap of predisposition to schizophrenia and affective disorders (Maier et al. 1993). We describe the clinical phenotypes found in a large family in which a balanced translocation—(1;11)(q42;q14.3)—that disrupts two novel brain-expressed genes cosegregates with major psychiatric disorders. Clinical diagnoses in family members
Figure 1 Part of the family with a (1;11)(q42;q14.3) translocation. Karyotype analysis has been performed on 87 members of this family, and clinical psychiatric data were obtained from 69 of those family members. Shown are 58 of the family members for whom carrier status is known and whose psychiatric phenotype has been defined through follow-up by direct interview, general-practice contact, or hospital case-note review.

were based on DSM-IV criteria derived from a standard interview and from a case-note review. The phenotype was also investigated in a subgroup of family members, by measurement of intelligence quotient (IQ) and the auditory P300 event-related potential (ERP), which has been shown to be abnormal in patients with schizophrenia and in their unaffected relatives and is a putative trait marker of risk for schizophrenia (Blackwood et al. 1991; Sham et al. 1994; Weisbrod et al. 1999).

This family was first ascertained by Jacobs et al. (1970), who reported the translocation in the propositus, who had adolescent conduct disorder, and in members of four generations of the propositus’s extended family. Follow-up of the family over 20 years revealed an increased incidence of major psychiatric disorders, including schizophrenia and recurrent major depression, among relatives with the translocation and found no cases of these disorders in relatives with a normal karyotype (St. Clair et al. 1990). It was proposed that disruption of one or more genes at or near one of the translocation breakpoints increased the risk of development of psychosis in this family. Over the past 10 years, members of this family have been systematically followed up by direct interview, regular contact with general practitioners, or hospital case-note review. The study has been approved by the local Ethics of Research Committee, and family members have given informed, written consent. Interviews were conducted by experienced psychiatrists (D.H.R.B., W.J.M., and D.St.C.) using the Schedule for Affective Disorders and Schizophrenia L (Endicott and Spitzer 1978); consensus diagnoses blind to carrier status and based on DSM-IV criteria are shown in figure 1. Of the 87 members of the family who were karyotyped, 37 carried the translocation. Of the 50 noncarriers, 18 were married-in relatives. Living relatives were interviewed directly by a psychiatrist, and deceased members were included in the analysis if adequate hospital and general-practice case records were available. A psychiatric diagnosis was reached for 29 carriers, 38 noncarriers, and the 2 founders (who were not karyotyped).

Figure 1 shows the family members for whom psychiatric assessment was possible and for whom karyotype status was available. To preserve the anonymity of family members, 11 individuals with a normal karyotype and without a psychiatric diagnosis all were siblings of carriers) have been omitted from the figure but were included in the linkage analysis.

Nine new cases of major psychiatric disorder have been diagnosed during the follow-up period over the past 10 years. Of note is a relative (IV:17) with bipolar
Table 1

<table>
<thead>
<tr>
<th>PHENOTYPEx</th>
<th>GENE</th>
<th>PENETRANCE</th>
<th>LOD SCORE AT θ = .05</th>
<th>LOD SCORE AT θ = .1</th>
<th>LOD SCORE AT θ = .2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>.004</td>
<td>.2</td>
<td>3.6</td>
<td>3.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Model 2</td>
<td>.03</td>
<td>.3</td>
<td>4.5</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Model 3</td>
<td>.03</td>
<td>.5</td>
<td>7.1</td>
<td>6.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Model 4</td>
<td>.1</td>
<td>.6</td>
<td>1.9</td>
<td>2.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

x Linkage analysis was performed by MLINK, under the assumption of dominant inheritance, for four definitions of the disease phenotype (Terwilliger and Ott 1994); model 1 = 7 cases of schizophrenia (all other diagnoses coded as unknown); model 2 = 11 cases of recurrent major depression and 1 case of bipolar disorder (schizophrenia and other diagnoses coded as unknown); model 3 = schizophrenia, recurrent major depression, and bipolar disorder; model 4 = all diagnoses, including alcoholism, minor depression, anxiety, and adolescent conduct-and-emotional disorder.

b Gene frequencies were compatible with the assumption of a lifetime risk of .006 for schizophrenia or .05 for major affective disorders; the translocation was assumed to be rare in the population, with frequency .00001.
groups, in P300 latency (controls,hoc comparisons of means showed significant differences between
Controls ( ), Patients with schizophrenia ( ).

$F_{1}$ $t$ $x$ $F$ $1$

jects were depression (in three cases), schizophrenia (in
the control mean were recorded in 7 of the 12 relatives
schizophrenia, ; controls
and relatives with a normal karyotype
translocation, ; relatives with a normal karyotype
1
patients with schizophrenia, ; and relatives
with the translocation, ).

With translocation ( $n=12$ )
366.2 (41.8) 6.8 (3.4)

With normal karyotype ( $n=10$ )
338.3 (34.5) 12.1 (3.5)

Patients with schizophrenia ( $n=20$ )
391.3 (47.2) 7.2 (4.0)

Controls ( $n=26$ )
354.8 (26.5) 11.0 (3.1)

Note.—Results were determined by multivariate analysis of vari-
ance. There was a group effect for latency ($F = 5.62$, df = 3, $P = .002$) and for amplitude ($F = 8.62$, df = 3, $P = .0001$). Scheffe post

hoc comparisons of means showed significant differences between
groups, in P300 latency (controls < patients with schizophrenia, $P = .02$; relatives with a normal karyotype < patients with schizo-
phrenia, $P = .007$) and in P300 amplitude (controls > patients with
schizophrenia, $P = .007$; controls > relatives with the translocation,
$P = .01$; relatives with a normal karyotype > patients with schizo-
phrenia, $P = .007$; relatives with a normal karyotype > relatives with
the translocation, $P = .009$).

with schizophrenia, $P = .007$; P300 amplitudes <2 SD below
the control mean were recorded in 7 of the 12 relatives
with the translocation, and the diagnoses for these 7 sub-
jects were depression (in three cases), schizophrenia (in
two cases), and no symptoms (in two cases). Similarly,
for P300 latency, the two translocation carriers with latency
>2 SD above the control mean were a relative with
no psychiatric diagnosis and a relative with schizophrenia.
Significant changes in the amplitude and the latency of
P300 in translocation carriers were therefore not restricted
to subjects with a psychiatric diagnosis. The findings are
consistent with previous findings in other families with
multiple members with schizophrenia, in which the am-
plitude of and the latency of P300 appear to be trait
markers of risk, rather than state markers reflecting the
presence of symptoms (Blackwood et al. 1991; Sham et
al. 1994).

We have described elsewhere two genes, disrupted in
schizophrenia 1 (DISC1 [MIM 605210]) and disrupted in
schizophrenia 2 (DISC2), that are directly disrupted
by the breakpoint on chromosome 1, and a third gene,
translin-associated factor X (TSNAX [MIM 602964]),
that is in very close proximity (Millar et al. 2000). These
and other functionally related genes are strong candi-
dates for a role in the development of psychiatric dis-
orders. There are no genes close to the breakpoint on
11q14.3, making this the less-likely site for genes con-
tributing to psychosis in the family, although we cannot
entirely rule out the possibility that translocation has
long-range positional effects on gene expression.

Single large families with multiple affected members
have important advantages for the study of genetically
complex disorders such as the major psychoses, when
substantial locus heterogeneity is probable. A disadvan-
tage is that findings may be either rare or unique to one
family and, thus, not relevant to the disease itself. There
are, however, independent reports of suggestive linkage,
for both schizophrenia and bipolar disorder, with mark-
ers mapped close to the breakpoint on 1q42. The strong-
est independent support for linkage to the 1q42 break-
point region is from two studies of Finnish families with
schizophrenia. A genomewide scan of 134 affected sib-
ling pairs with schizophrenia revealed a maximum LOD
score of 2.6 with the marker DIS439, which lies <500
kb from the translocation breakpoint (Ekelund et al.
2000). In a second study, of 20 families with schizo-
phrenia that are from an isolated Finnish subpopulation,
Hovatta et al. (1999) reported a maximum LOD score
of 3.7 at 1q32-41, and there is overlap of the regions
showing linkage in these two Finnish populations. Link-
age between the microsatellite DIS103, which maps <1
Mb from the breakpoint, and bipolar disorder has been
reported in two separate studies: Gejman et al. (1993)
found suggestive linkage (LOD score 2.4) with DIS103
in 1 of 19 families with bipolar disorder, and LaBuda
et al. (1996) reported increased allele sharing ($P < .0001$),
under one weighting function, in Old Order Amish families
with bipolar disorder. Detera-Wadleigh et al. (1999),
reported, in a genomewide scan of 22 families
with bipolar disorder, elevated identical-by-descent
sharing (maximum LOD score 2.3) in a 30-cM region
spanning 1q25-q42 and extending to the breakpoint re-
gion; it is noteworthy that, in 15 of these 22 families
with bipolar disorder, at least one individual was diag-
nosed with either schizophrenia or schizoaffective dis-
order. The breakpoint on 1q42 is ~60 cM from the locus
on 1q21-q22, where linkage to schizophrenia has also
been reported (Brzustowicz et al. 2000; Gurling et al.
2001), and this breakpoint appears to be a separate locus
related to schizophrenia.

Some genetic risk factors for psychoses may contribute
to a range of symptoms that cross traditional diagnostic
boundaries, and the locus identified by the breakpoint on
1q42 appears to be implicated in families with either
schizophrenia or bipolar disorder. The range of diagnoses
recorded in the family with the translocation is found in
other extended families with schizophrenia (St. Clair et
al. 1989). Similarly, the observation that, in the family


Table 2
P300 Latency and P300 Amplitude in the Family with the
Translocation, in Patients with Schizophrenia, and in Controls

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEAN (SD) OF P300</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Latency (ms)</td>
</tr>
<tr>
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with the translocation, P300 amplitude and P300 latency are abnormal in individuals with psychoses and in their asymptomatic relatives is similar to the pattern of P300 changes in other families with multiple members with schizophrenia and may provide clues to the biological basis for the varied clinical presentations in these families. For example, reduction of P300 amplitude in patients with schizophrenia and in their relatives has been correlated with reduced regional perfusion, as measured by single-proton-emission computed tomography, in left-frontal regions (Blackwood et al. 1999) and with reduced gray-matter volume of the left-superior temporal gyrus, as measured by positron-emission tomography (O'Donnell et al. 1999). Genetic markers combined with other investigative approaches—including neurophysiology, brain imaging, and neuropsychology—may help to define subtypes of the psychoses.

Acknowledgments

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Electronic-Database Information

The accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for schizophrenia [MIM 181500], bipolar disorder [MIM 125480], DISCI [MIM 605210], and TSNAX [MIM 602964])

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