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Possible linkage of schizophrenia and bipolar affective disorder to chromosome 3q29: a follow-up

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Abstract

The present linkage study is a follow-up within the chromosome 3q29 region in schizophrenia and bipolar affective disorder families, based on our recently published genome scan, resulting in evidence for linkage of both disorders to this region (marker D3S1265: NPL [non parametric lod] score $Z_{all} = 3.74$, $P = 0.003$). Using the same family sample (five pedigrees with schizophrenic index patients and three pedigrees with index bipolar disorder patients $N = 86$; 50 of them were available for genotyping), genotyping of eight additional markers close to D3S1265 was done. Five of those new markers (three centromeric and two telomeric of D3S1265) spanning 4.14 cM (centiMorgan) could be used for statistical analyses ("new markers"). Moreover, marker D3S1265, genotyped within the published genome scan, was used for additional calculations. Linkage analysis was performed using the GENEHUNTER program version 2.1r3. Within newly genotyped markers the highest NPL score Z_{all} observed was 1.93296 with the telomeric SNP (single nucleotide polymorphism) rs1835669, corresponding to $P = 0.032166$. Statistical analysis including D3S1265, located in between the newly genotyped markers, resulted in a peak NPL score $Z_{all} = 4.00179$ with marker D3S1265, that is $P = 0.000128$. Doing subset analyses of the bipolar disorder and schizophrenia families separately with new markers and D3S1265, linkage signals arose substantially from bipolar disorder families, with contribution from schizophrenia families, too. The results of our follow-up study support our previous linkage finding of schizophrenia and bipolar affective disorder to chromosome 3q29.

Keywords: Schizophrenia; Bipolar disorder; Linkage; Chromosome 3q29

1. Introduction

Schizophrenia and bipolar disorder have been considered as nonoverlapping nosologic entities, with distinctive clinical characteristics, unique treatment regimens, and separate etiologies. A review of genetic epidemiology and recent molecular linkage studies, however, reveals a surprising degree of concordance for schizophrenia genetics and bipolar disorder genetics, raising the hypothesis that these two diagnostic categories may share some genetic susceptibility factors. Curiously, despite of the widely accepted view that schizophrenia and bipolar disorder exhibit independent modes of inheritance, some regions that are reported as positive for linkage in relation to schizophrenia overlap with regions of positivity for affective disorder: 18p11.2

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(Berrettini et al., 1994, 1997; Nöthen et al., 1999; Schwab et al., 1998; Stine et al., 1995), 13q32 (Blouin et al., 1998; Detera-Wadleigh et al., 1999; Lin et al., 1997), and 22q11 (Detera-Wadleigh et al., 1999; Gill et al., 1996; Kelsoe et al., 2001; Lachman et al., 1997; Saito et al., 1999).

There are three additional reasons arguing against the concept that schizophrenia and bipolar disorder are distinct illnesses. First, in phenomenology, a bimodal separation of schizophrenic and affective symptoms has not been demonstrated (Kendell and Gourlay, 1970). Second, no clear separation can be demonstrated in terms of treatment response, and the overlap in indications of neuroleptics provides some support for the unitary psychosis concept (Kuhne et al., 1988; Tsuang, 1975). Neuroleptic medication is antipsychotic rather than antischizophrenic, because it can be used in unipolar and bipolar affective as well as in schizophrenic psychosis. Neuroleptics are the treatment of second choice in acute mania (Bowden, 2000; Post et al., 1996). Furthermore there is accumulating evidence for beneficial effect of new atypical neuroleptics in treatment of acute mania and prophylactic treatment for bipolar affective disorder. Some of the atypical neuroleptics are on the market under this indication, too. In addition, antidepressants can be beneficial in schizophrenia (Angst et al., 1970; Johnstone et al., 1988; Klein et al., 1981). Third, family studies have failed to demonstrate a natural point of cleavage on the basis of risk to relatives, and first-degree relatives of schizophrenic patients also have a higher risk for bipolar disorder (Gershon et al., 1988; Henn et al., 1995; Kendler et al., 1985; Maier et al., 1993; Taylor et al., 1993). The same holds true for relatives of bipolar patients (Weissman et al., 1984).

After finding suggestive evidence for linkage with marker D3S1265, mapping to chromosome 3q29, within our recently published genome scan (Bailer et al., 2002), further studies were conducted in order to add further support to our findings. The NPL score Z_{all} for D3S1265 was 3.74 ($P = 0.003$). Within the current analysis, we established fine mapping of the 3q29 region by linkage study, in order to narrow down a possible susceptibility locus for schizophrenia and bipolar affective disorder.

Kelsoe et al., (2001) reported suggestive evidence for linkage of bipolar disorder to 3q27 with marker D3S2398. Meanwhile marker D3S2398 is known not to be located on 3q27, but on 3q29 (6.1 cM centromeric of marker D3S1265, the marker of highest linkage within our genome scan). The present study provides evidence for linkage of both schizophrenia and bipolar affective disorder to 3q29. The dopamine 3 receptor gene (DRD3) is located on the long arm of chromosome 3, but at 3q13.3, far away from the locus identified in this study. Dopamine neurotransmission has long been implicated in the pathogenesis of schizophrenia and, more recently, affective disorder (Dikeos et al., 1997). Concerning bipolar affective disorder, suggestive evidence for linkage was obtained using markers D3S2403 and D3S3038, both located on the short arm of chromosome 3, among families investigated as part of the National Institute of Mental Health Genetics Initiative of Bipolar Disorder (Foroud et al., 1997; Nimgaonkar et al., 1998).

Within the present report, we describe the results of genotyping eight new SNP markers spanning 4.14 cM at the telomere of chromosome 3.

2. Materials and methods

2.1. Families

Within this study, DNA of the same family-sample as in the recently published genome scan (Bailer et al., 2002) was genotyped. Five pedigrees with schizophrenic index patients and three pedigrees with index bipolar disorder patients ($N = 86$; 50 of them were available for genotyping; Fig. 1) were investigated in Vienna. Hospitalized and outpatient individuals with a DSM-III-R (*Diagnostic and Statistical Manual of Mental Disorders*; American Psychiatric Association, 1987) diagnosis of schizophrenia or bipolar disorder were identified as index patients at the Department of Psychiatry at the University of Vienna, Austria. A patient was accepted as schizophrenia index patient if she or he suffered from DSM-III-R schizophrenia and had at least one available sibling with a nonaffective, nonorganic psychosis. A patient was accepted as bipolar index patient if she or he suffered from DSM-III-R bipolar I disorder and had at least one available sibling with an affective, nonorganic or schizoaffective psychosis. The families were ethnically homogenous of Austrian origin. The disease model (affected individuals) of the current analysis included schizophrenia, schizophrenia spectrum disorders (i.e., schizophreniform disorder, delusional disorder, atypical psychosis, schizoaffective disorder), bipolar affective disorder, and recurrent unipolar depression. All participants gave written informed consent. The study was approved by the ethical committee of the Faculty of Medicine at the University of Vienna. Of the genotyped affected, 70% were women; on average, they were 41.59 (S.D. 18.86) years of age at interview. The mean age at onset was 26.33 (S.D. 10.87) years. Age at onset was defined as age at first hospitalization for the disorder. All 27 patients had been hospitalized during the course of their illness.

2.2. Diagnostic procedure

The diagnostic process included: A face-to-face interview with all available living individuals utilizing the Schedule for Affective Disorders and Schizophrenia,