Sibling pairs with affective disorders: resemblance of demographic and clinical features


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ABSTRACT

Background. As part of a collaborative linkage study, the authors obtained clinical and demographic data on 160 families in which more than one sibling was affected with a bipolar illness. The aim of the study was to identify clinical characteristics that had a high degree of familiality.

Method. Data on age at onset, gender, frequency of illness-episodes and proportion of manic to depressive episodes were examined to determine intra-pair correlations in affected sibling pairs. Dimension scales were developed measuring frequency and severity of lifetime mania, depression, psychosis and mood-incongruence of psychotic symptoms; degree of familial aggregation for scores on these dimensions was calculated.

Results. Sibling pairs correlated significantly for age at onset ($\rho = 0.293, P < 0.001$); dimension scores for psychosis ($\rho = 0.332, P < 0.001$); and proportion of manic to depressive episodes ($\rho = 0.184, P = 0.002$). These findings remained significant when correcting for multiple testing. Of the other test variables; mania ($\rho = 0.171, P = 0.019$); incongruence dimensions ($\rho = 0.242, P = 0.042$); frequency of manic episodes ($\rho = 0.152, P = 0.033$); and frequency of depressive episodes ($\rho = 0.155, P = 0.028$) were associated with modest correlations but these were not significant after correction. Degree of familial aggregation was not significant for sex ($\kappa = 0.084$) or dimension scores for depression ($\rho = 0.078, P = 0.300$).

Conclusions. Significant but modest familial resemblance has been shown for some specific features of bipolar illness, particularly age at onset and degree of psychosis. Further research may establish the extent to which these findings are mediated by genetic and/or environmental factors.

INTRODUCTION

Although the familial nature of bipolar illness has been well described (Winokur et al. 1969; Perris, 1974; Angst et al. 1980; Andreasen et al. 1987) and the heritability estimated to be high (Kendler et al. 1995) the underlying genetic mechanisms remain unknown. Multiple genes are probably involved in most or all cases (Craddock & Jones, 1999), but it is unlikely that each gene contributes equally to the bipolar phenotype. Rather, each gene probably influences a biological system, which increases the overall likelihood of the bipolar disorder phenotype occurring. Moreover, they may contribute to clinical characteristics of the condition, such as age at onset, episode type and severity, cycling frequency and psychosis. Demonstration of intra-familial resemblance of such clinical characteristics may help to identify familial subtypes suitable for further genetic investigation of bipolar illness.

Previously, within-pair correlations have been shown for age of onset in siblings with bipolar

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illness (Leboyer et al. 1998). In other psychotic disorders, sibling correlations have been found for a variety of clinical measures including age at onset and symptom profiles (Crow & Done, 1986; Burke et al. 1996; Kendler et al. 1997; Cardno et al. 1998), illness outcome (Slater, 1947) and gender (Crow et al. 1989). We have attempted to identify, within the bipolar spectrum, clinical characteristics that have a high degree of familiality and which may be more likely than an operationally defined disorder to be associated with a simple genotype.

Genetic analysis of psychiatric disorders might be improved by the identification of basic phenotypes for which a more homogeneous genetic architecture might exist. The identification of these phenotypes could be achieved by two complementary approaches: (1) the deconstruction into component parts of the categorical phenotype in affected subjects, which is the approach used here; and (2) the identification of vulnerability or latent traits or markers – known as endophenotypes – in non-affected relatives of affected individuals. Such an approach was useful in the detection of genes for haemochromatosis when ferritin levels were measured in the relatives of probands (Borecki et al. 1990). Other clinical measures of disease have similarly been instrumental in gene identification. A gene was identified in melanoma using mean nevus size as a quantitative marker (Blangero et al. 1992) and positional cloning of the adenomatous polyposis coli (APC) gene was facilitated (Kinzler et al. 1991) when assessment of the clinical phenotype of colon cancer was restricted to cases with extreme polyposis.

METHOD

Subjects

During the course of a large genetic linkage study in Ireland and the UK (Gill & Craddock, 1998), families containing two or more siblings suspected of suffering from a bipolar illness were ascertained from community and hospital psychiatric services, private psychiatric hospitals, general practitioners and directly through local and national media (newspaper articles and radio interviews). After description of the study to the subjects, written informed consent was obtained.

Clinical assessments of affected siblings were conducted by trained clinicians and involved: (1) semi-structured interview, using sections of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) diagnostic instrument (Wing et al. 1990); (2) case note review (where affected individuals were in treatment); (3) collateral information (from family and/or treating clinician); and (4) entry of clinical data into the OPCRIT diagnostic system (McGuffin et al. 1991). Information from all sources was used in the preparation of a detailed case summary for blind and independent review by another clinician (M.G. or N.C.) and consensus meetings were held to determine final diagnoses.

Affected individuals were diagnosed according DSM-IV criteria and individuals with the following diagnoses were included: bipolar I (BPI), bipolar II (BPII), bipolar disorder NOS (BPNOS), major depressive disorder (recurrent) (MDD) or schizoaffective bipolar disorder (SABP). Sibships were included in the analysis if at least one member had a diagnosis of BPI. Assessing clinicians were unaware of our intention to investigate the hypotheses postulated here. Inter-rater reliability between clinical field teams working in Ireland and the UK was assessed from 20 randomly selected cases during the study. Mean kappa value for a DSM-IV diagnosis was 0.88 (s.d. = 0.06).

Based on a literature review of bipolar affective disorder using the Pubmed and Psychlit databases a discrete number of clinical characteristics were selected for analysis. These were: age at onset; gender; frequency of illness episodes; proportion of manic to depressive episodes; and, illness dimension scores (mania, depression, psychosis, incongruence). These variables were analysed exclusively; there are no plans to include additional variables in this analysis.

Age at onset was defined as the age at which the individual first met DSM-IV criteria for major depressive episode, hypomania or mania. This definition was based on all available information from a structured clinical interview, collateral history and medical records. Inter-rater reliability between centres for this measure of age at onset was high ($\kappa = 0.90$).

Every confirmed discrete episode of affective illness was documented as ‘manic’, or ‘depressive’ and the frequency of illness episodes...
was calculated from the number of confirmed episodes of affective illness per year between the time of onset and the time of interview. Episodes where the mood state was mixed were included as ‘manic’ episodes. The proportion of manic to depressive episodes was calculated as the number of ‘manic’ episodes divided by the total number of affective episodes.

In addition, dimension scales for quantifying mania, depression, psychosis and incongruence of psychotic symptoms with mood have been developed based on the frequency and severity of the component symptoms of the illness. These scales are rated between 0 and 100, and are operationally described (Craddock et al. 2000).

Statistics

Resemblance for gender between affected siblings was analysed using Cohen’s kappa statistic. Resemblance for the other variables (age at onset; age at first hospitalization; dimension scores for mania, depression, psychosis and incongruence; frequency of episodes; proportion of manic to depressive episodes) was analysed using the Spearman rank correlation (ρ). All tests of statistical significance were two-tailed. For sibships with more than two affected siblings, all possible pairs were included in the analysis, the number of possible pairs in a sibship of size \( s \) (\( s - 1 \))\( /2 \) (Cardno et al. 1998). As the majority of families contained only two affected siblings and the maximum sibship size was four, we predicted that any effect of lack of independence of within-pair correlations in the larger families is likely to be small. To check this however, we calculated the within-pair correlations of all 160 sibships, including one pair chosen from each sibship. Siblings in all families were assigned a sibling number based on order of ascertainment. In the multiply affected families, the pair selected for this analysis was based on a rotational system, which insured no preference for any pairing combination. The results were compared with the results of the full sample.

RESULTS

The mean ages at onset and frequencies of the included diagnoses of sibs are shown in Table 1. The overall mean age at onset was 25-20 years (s.d. = 9.46) and that for BPI was 24.88 years (s.d. = 9.04). There were 362 affected individuals in the sample, of whom 58.3% were female. Of the 160 included families, 119 sibships contained two, 27 contained three, and 14 contained four affected siblings. The sample yielded 264 affected sibling pairs, of which 152 were concordant for the diagnosis of BPI and 250 included at least one individual with this diagnosis. Mean age at interview was 45.1 years (s.d. = 14.1). Mean duration of illness was 19.2 years (s.d. = 11.8).

The level of familial aggregation for clinical variables in the whole sample (264 pairs) is shown in Table 2. There were moderate correlations for age at onset (\( \rho = 0.293, P = 2.2 \times 10^{-6} \)) and for scores on the psychosis dimension (\( \rho = 0.332, P = 0.0003 \)). Weak, but significant, correlations were found for the proportion of manic to depressive episodes, scores on the mania and incongruence dimensions, and frequency of depressive and manic episodes. Correlations, which failed to achieve significance, were found for the depression dimension and frequency of affective episodes (either bipolar or unipolar). Degree of familial aggregation was also not significant for gender (\( \kappa = 0.084 \)). The correlations for age at onset (\( P = 2.0 \times 10^{-6} \)), scores on the psychosis dimension (\( P = 0.0027 \)) and proportion of manic/depressive episodes (\( P = 0.018 \)) remained significant after Bonferroni correction to take account of the number of tests performed.

Analysis of independent sibling pairs (\( N = 160 \)) confirmed the findings from the whole sample of significant correlations within sibling pairs of age at onset and psychosis dimension (see Table 2). Again this remained the case when correcting for multiple testing. The correlation of manic-depressive episodes among independent sibling pairs was weaker and no longer statistically significant (\( \rho = 0.151, P = 0.064 \)).

### Table 1. Age of onset by diagnosis

<table>
<thead>
<tr>
<th>DSM-IV diagnosis</th>
<th>N (%)</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I</td>
<td>281</td>
<td>24.88 (9.04)</td>
</tr>
<tr>
<td>Major depression recurrent</td>
<td>33</td>
<td>27.27 (12.50)</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>24</td>
<td>28.12 (10.45)</td>
</tr>
<tr>
<td>Schizoaffective bipolar</td>
<td>16</td>
<td>25.19 (7.23)</td>
</tr>
<tr>
<td>Bipolar NOS</td>
<td>8</td>
<td>19.37 (6.09)</td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
<td>25.20 (9.43)</td>
</tr>
</tbody>
</table>

NOS, Not otherwise specified.
allele in early onset bipolar disorder, (Holmes et al. 1998) although this finding has not been universally replicated (Kessing & Jorgensen, 1999).

For this investigation age at onset was defined as the age at which individuals first met DSM-IV criteria for manic, hypomanic or major depressive episode. This method has been used in other studies and has been found to be reliable (Egeland et al. 1987; Bellivier et al. 2001). Leboyer et al. (1998) suggested that in collaborative studies reliability for this measure between centres may be poor; from our inter-rater reliability data we have not found this to be the case. Other definitions of age at onset have been used including age at first hospitalization. This has the advantage of being an exact measure (Tsuang, 1967), if all hospital records are available, but would reduce sample size and possibly introduce bias by failing to include less severely affected individuals.

The ascertainment method used here was not independent of family history introducing a potential ascertainment bias, and in particular it has been suggested that such a bias might affect correlation for age of onset. Kendler et al. (1997), in their study of age at onset in schizophrenia, postulated that, where sibships with two or more affected individuals are specifically sought, siblings with ages at onset closer together are more likely to be identified by clinicians. They concluded that a weaker and more accurate correlation is to be expected using a method in which probands are ascertained systematically, which probands are ascertained systematically, independent of family history. However, a study of schizophrenia and schizoaffective disorder that employed a similar methodology to the current study and also ascertained sibships from the UK (Cardno et al. 1998), found within-pair correlations for age at onset similar to those

### DISCUSSION

The within-pair correlations for age at onset and for scores on the psychosis dimension are the most significant findings in the analysis of the sample as a whole, and remain consistent in the independent pairs.

### Age at onset

The correlation for age at onset is modest, but comparable to previous findings in bipolar siblings (r = 0.42) (Leboyer et al. 1998) and in a sample of dizygotic twins with major depression (r = 0.34) (Kendler et al. 1992). Age at onset could be useful for refining the clinical phenotype in bipolar disorder as it has, in the past, helped in delineating disorder subtypes that have led to gene identification. For example, differences in age at onset helped identify single gene forms of Alzheimer disease (Pericak-Vance et al. 1991) and breast cancer (Hall et al. 1991). In addition to familial resemblance for age at onset in bipolar disorder, other clinical and biological differences have been reported in early onset cases (Bellivier et al. 2001). To date, genetic studies of the age at onset phenotype for bipolar disorder have been few; an association has been reported with the apolipoprotein E ε4 (APOE 4) allele in early onset bipolar disorder, (Holmes et al. 1991; Bellivier et al. 1997) although this

| Table 2. Correlations of clinical features within sibling pairs |
|------------------|------------------|
| All pairs (N = 264) | Independent pairs (N = 160) |
| Spearman’s ρ | P | Spearman’s ρ | P |
| Age at onset | 0.293 | 2.2 x 10^-4 | 0.304 | 1.4 x 10^-4 |
| Psychosis dimension | 0.332 | 0.0003 | 0.372 | 0.0007 |
| Mania dimension | 0.171 | 0.019 | 0.210 | 0.027 |
| Depression dimension | 0.078 | 0.300 | 0.118 | 0.236 |
| Incongruence dimension | 0.242 | 0.048 | 0.197 | 0.175 |
| Proportion of manic to depressive episodes | 0.184 | 0.002 | 0.151 | 0.064 |
| Frequency of episodes | 0.107 | 0.129 | 0.199 | 0.028 |
| Manic | 0.152 | 0.033 | 0.115 | 0.204 |
| Depressive | 0.155 | 0.028 | 0.223 | 0.014 |

Analysis of the subgroup of concordant BPI sibling pairs (N = 152) confirmed highly significant intra-pair correlations for age at onset (ρ = 0.379, P = 5.1 x 10^-4) and the psychosis dimension scores (ρ = 0.347, P = 4.1 x 10^-4) but not for the other variables.

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reported in a systematically ascertained sample (Kendler et al. 1987). Several aspects of the methodology employed in this study may limit potential bias. Many of the families included in this study referred themselves; many siblings were attending different clinicians or treatment facilities; and individuals were included who were not receiving treatment. No systematically ascertained data from bipolar samples were available to resolve this issue, which clearly warrants further investigation. The design of this study enabled us to investigate correlation data from a sample the size of which would not be reasonably attainable by systematic ascertainment methods.

Psychosis
The moderate \((r = 0.332)\) but highly significant correlation in dimension scores for psychosis shows familiality, regardless of the diagnostic category, in this group of affected siblings. Thus, it is possible that vulnerability to psychosis, and also to the degree of psychosis, may be inherited within the bipolar spectrum. This, as far as we are aware, is the first study to support a familial basis for a measure of psychosis within a bipolar population. Viewed in the context of evidence that an intermediate phenotype (SABP) occurs in families with schizophrenia and affective disorders (Taylor, 1992) and that both disorders co-occur within the same families (Gershon et al. 1988; Maier et al. 1993), our finding further challenges the Kraepelinian view of psychosis. Molecular studies suggest the possibility of overlapping susceptibility regions for schizophrenia and bipolar disorder (Wildenauer et al. 1999); findings that could be explained by shared functional psychosis genes. Using severity of psychosis as a phenotype may be a powerful way of detecting such loci. For example, Brzustowicz et al. (1997), in a sample of families with schizophrenia, reported significant linkage between severity of psychosis and a marker on chromosome 6p, having failed to detect linkage with the categorical schizophrenia phenotype.

Frequency and type of episodes
There were weak but significant intra-pair correlations for the proportion of manic to depressive episodes in the sample as a whole, although these were not confirmed by the independent sibling pair analysis. No statistically significant correlations were detected for frequency of illness episodes, depressive episodes or manic episodes in the sample. These measures were an attempt to quantify the rate of cycling over the duration of illness in each individual. However, there is likely to be a strong environmental effect, in the form of prophylactic medication that could reduce the potential influence of shared genes on episode frequency. Full information about medication and compliance was unavailable.

The periodic and cyclical nature of bipolar illness is one of its distinguishing hallmarks, with great variability in the frequency with which episodes occur and the duration of each episode. The frequency of affective episodes is a major determinant of morbidity and an important factor in the planning of management of care. DSM-IV defines a ‘Rapid-Cycling Specifier’, which can be applied to BPI and BPII, is seen in approximately 5–15% of persons with bipolar disorder and is associated with a higher incidence of female gender, hypothyroidism and certain neurological conditions e.g. multiple sclerosis. Interestingly, some molecular genetic studies have investigated rapid-cycling bipolar disorder and association with the low activity allele of catechol-o-methyltransferase has been suggested (Kirov et al. 1998), although this association has not been replicated when looking at bipolar disorder as a whole (Kunugi et al. 1997). If this finding is confirmed, it would lend support to the hypothesis that some of the genes contributing to bipolar illness influence frequency and/or periodicity.

Conclusion
The results of our study provide evidence of familiality for some measures of the clinical profile and course of bipolar illness. It is not possible, in a sample such as ours, to establish whether such similarity was due to genetic or environmental factors or both. The within-pair correlations for some of the measures may be too low to be considered as markers of genetic or common environmental factors contributing liability to bipolar illness. However, the findings in relation to psychosis severity and age at onset suggest that these measures may be useful in the...
future as phenotypic measures for molecular genetic studies. However, further investigation of familial aggregation of such measures, including data from twins, is required.

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REFERENCES


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