American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 116B:90–97 (2003)

# Familial Aggregation of Psychotic Symptoms in a Replication Set of 69 Bipolar Disorder Pedigrees

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**We found evidence previously of familial aggregation of psychotic symptoms in 65 bipolar disorder pedigrees. This finding, together with prior evidence from clinical, family, neurobiological, and linkage studies, suggested that psychotic bipolar disorder may delineate a valid subtype. We sought to replicate this finding in 69 new bipolar disorder pedigrees. The presence of psychotic symptoms, defined as hallucinations or delusions, during an affective episode was compared in families of 46 psychotic and 23 non-psychotic bipolar I probands ascertained at Johns Hopkins for the NIMH Bipolar Disorder Genetics Initiative. There were 198 first-degree relatives with major affective disorder including 90 with bipolar I disorder. Significantly more psychotic proband families than non-psychotic proband families (76% vs. 48%) contained at least one affected relative with psychotic symptoms. Psychotic symptoms occurred in 35% of relatives of psychotic probands and in 22% of relatives of non-psychotic probands ($P = 0.10$). Both psychotic affective disorder generally and psychotic bipolar I disorder clustered significantly in families. These results are consistent with our prior report although the magnitude of the predictive effect of a psychotic proband is less in the replication families. Our findings provide modest support for the validity of psychotic bipolar disorder as a subtype of bipolar disorder. This clinically defined subtype may prove more homogeneous than the disorder as a whole at the level of genetic etiology and of neuropathology/pathophysiology. Families with this subtype should be used to search for susceptibility genes common to bipolar disorder and schizophrenia, and for biological markers that may be shared with schizophrenia.** Published 2003 Wiley-Liss, Inc.†

**KEY WORDS: genetics; subtype; heterogeneity; psychosis; family study; bipolar disorder; schizophrenia**

## INTRODUCTION

We reported evidence recently for the familial aggregation of psychotic symptoms, defined as hallucinations or delusions, in bipolar disorder (BPD) pedigrees [Potash et al., 2001]. We found in our earlier report that psychosis in a bipolar I disorder (BPI) proband predicted a 4–5 times increased likelihood of psychosis in affectively ill family members, and that not only psychotic affective disorder generally, but also psychotic BPI, clustered disproportionately in some families.

That study was chiefly motivated by findings of genetic linkage studies of BPD and schizophrenia suggesting four chromosomal regions that could potentially harbor susceptibility genes for both disorders [Berrettini, 2000]. We sought to define a more homogeneous subtype within our BPD pedigrees that might be most reflective of the putative disease loci in these linkage overlap regions. At the clinical level psychotic symptoms represent an important point of overlap between BPD and schizophrenia, as these symptoms are integral to the definition of schizophrenia and also occur in 58% of manias [Goodwin and Jamison, 1990] and 15–19% of depressions [Black and Nasrallah, 1989; Johnson et al., 1991]. Family studies have not found that relatives of

Grant sponsor: National Institute of Mental Health; Grant numbers: U01 MH-46274, K08 MH-02026; Grant sponsor: The Theodore and Veda Stanley Foundation; Grant sponsor: The National Alliance for Research in Schizophrenia and Depression (NARSAD).

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Received 26 February 2002; Accepted 20 May 2002
DOI 10.1002/ajmg.b.10761

BPD probands are at increased risk for schizophrenia or that relatives of schizophrenia probands are at increased risk for BPD. Relatives from both family groups are at increased risk of major depression and schizoaffective disorder [Gershon et al., 1982, 1988; Maier et al., 1993]. Further, in two distinct data sets, family studies have suggested that when psychotic affective disorder probands are considered, their relatives do have increased rates of schizophrenia and, conversely, rates of psychotic affective disorder are increased in relatives of schizophrenia probands [Kendler et al., 1985, 1986, 1993a,b]. A third data set has also suggested shared liability between psychotic affective disorder and schizophrenia [Erlenmeyer-Kimling et al., 1997].

We hypothesized that if psychotic BPD were a genetically meaningful subtype, then familial aggregation of psychotic symptoms would be evident in BPD pedigrees. Though our prior study bore this out, earlier studies had yielded mixed results. Only one prior report had specifically addressed the hypothesis of familiality of psychotic symptoms in BPD pedigrees; the finding was negative in a small sample [Winokur et al., 1985; see Potash et al., 2001 for methodologic discussion of this study]. Another family study grouped BPD and major depression together and found a higher rate of psychotic affective disorder in relatives of probands with psychotic affective disorder than in relatives of non-psychotic probands, though this was not statistically significant [Kendler et al., 1993b]. Two studies had found evidence of familial aggregation of psychotic symptoms in major depression [Leckman et al., 1984; Coryell, 1997], though in only one of these did the finding reach significance [Leckman et al., 1984]. A follow-up study failed to replicate this significant finding [Goldstein et al., 1998].

Because of the lack of consistency between prior studies, we felt it important to determine whether our recent finding of familial aggregation of psychotic symptoms in BPD could be replicated in a new set of families. For the following analyses we used the same methodology to assess 69 new families as we used previously. These families were ascertained at Johns Hopkins as part of the NIMH Bipolar Disorder Genetics Initiative for a linkage study of bipolar I disorder. They are entirely distinct from the 65 families examined in our earlier report.

## MATERIALS AND METHODS

### Subjects

Aspects of family ascertainment have been described in detail previously [NIMH Genetics Initiative Bipolar Group, 1997]. These analyses include interviewed members of all families ascertained at the Johns Hopkins site of the NIMH Genetics Initiative Bipolar Disorder Group and entered into the database. Some probands ($N = 20$) were systematically ascertained from screening of consecutive admissions to Johns Hopkins Hospital. The ascertainment criteria required a proband with bipolar I disorder (BPI) and at least one first degree relative with either BPI or schizoaffective disorder, bipolar type (SA/BP). Either the proband or relative had to have at least two siblings age 18 or older. Families were also enrolled from sources other than the inpatient wards ($N = 49$) if they included at least two subjects with BPI or SA/BP and at least two other subjects with major affective disorder, including bipolar II disorder with recurrent depression (BPII), and unipolar depression, recurrent (UPR). To minimize intrafamilial genetic heterogeneity no families were enrolled if both parents of the proband had BPI or SA/BP. Five families included in the analysis had no BPI or SA/BP first-degree relative, though they did have relatives with BPII or UPR. These families had been ascertained and studied because they had initially appeared to meet the inclusion criterion by family history. Because much useful clinical data had been obtained in these families, we included them in the analysis.

First-degree relatives as well as probands themselves were interviewed by academic psychiatrists specializing in affective disorders using the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994]. After complete description of the study to the subjects, written informed consent was obtained. Collateral information from multiple family informants was obtained, and medical records were added whenever they were available. Affective disorder diagnoses were made independently by two psychiatrists using a best estimate procedure. BPI and SA/BP were diagnosed using the DSM-III-R and BPII and UPR diagnoses were made using the Research Diagnostic Criteria (RDC), with the modification that both diagnoses required that there be at least two episodes of depression.

First-degree relatives with major affective disorder diagnoses including BPI, SA/BP, BPII, and UPR were analyzed in this study. One subject in the data set who had schizoaffective disorder, depressed (SA/D) was also included. No subjects in the data set were diagnosed with schizophrenia. Additional analyses were carried out using only subjects with BPI. The presence of psychotic symptoms, defined as hallucinations or delusions, during mania and during depression was assessed using the DIGS interview that elicits information regarding the most severe manic and the two most severe depressive episodes. The psychosis section of the DIGS was also used, but affirmative answers were only considered positive when the symptoms occurred in the absence of delirium or active substance abuse. A total of 43 probands and 51 first-degree relatives were identified as psychotic based on the interview alone. Family informant data and medical record data were reviewed to increase the sensitivity of detection of psychotic symptoms. This resulted in the identification of an additional three probands and nine relatives as psychotic.

### Statistical Analysis

Pearson's $\chi^2$ and the Student's $t$-test were used to test differences between the psychotic and non-psychotic proband groups on diagnostic, demographic, and clinical variables. Three tests of the hypothesis of familial aggregation of psychotic symptoms were carried out. The first compared the proportion of psychotic probands

having at least one psychotic relative with affective disorder to the proportion of non-psychotic probands with at least one such relative; the $\chi^2$ test was employed for this comparison. A second analysis was done comparing the odds of being psychotic for first-degree affectively ill relatives of psychotic probands to the odds for those relatives of non-psychotic probands. This was implemented using the Generalized Estimating Equation approach [Liang and Zeger, 1986] that uses logistic regression, but has the added advantage of taking into account potential correlation between observations when multiple members of the same family are considered. In these analyses we controlled for gender, age at interview, and duration of illness. A third analysis of familial clustering of psychotic symptoms was carried out by testing the distribution of psychosis among the affectively ill subjects (including probands) across all 69 families. The null hypothesis of no familial aggregation of psychotic symptoms was tested using Tarone's one-sided score test for binomial distributions [Tarone, 1979]. A low and non-significant score indicates the expected random distribution of a variable, in this case psychosis, whereas a high and significant score suggests that the variable clusters more in some families than in others.

These three analyses were repeated using only BPI as the affected phenotype. A further set of all three analyses was carried out on a data set that combined the current data with that from our prior report [Potash et al., 2001]. The analyses of the combined data set were carried out chiefly to increase the sample size for analyses of the BPI only phenotype.

## RESULTS

### Group Characteristics

The subjects included 69 BPI probands and 198 affected first-degree relatives. The diagnoses for the affected relatives were as follows: 90 BPI, 1 SA/BP, 1 SA/D, 60 BPII, and 46 UPR. Among BPI subjects, 99/159 (62.3%) had psychosis, whereas the figure was 2/60 (3.3%) for BPII, and 3/46 (6.5%) for UPR. By definition 2/2 (100%) subjects with SA/BP or SA/D had psychotic symptoms. There were 46 probands with psychotic symptoms and 23 probands with no psychotic symptoms. The psychotic probands had 133 first-degree relatives with affective disorder whereas the non-psychotic probands had 65 such relatives. The two sets of families did not significantly differ in number of first-degree relatives interviewed per family, number of affected first-degree relatives per family, proportion of BPI relatives, proportion of BPII with comorbid panic disorder relatives, or mean age of relatives at the time of interview (Table I). No statistically significant differences were found between affected members of the psychotic and non-psychotic proband families in the following severity indicators: age of onset of affective disorder, duration of longest mood episode, number of hospitalizations, number of episodes of illness per year of illness, rate of attempted suicide, rate of alcoholism or substance abuse.

### Analysis by Family

Among the families of the psychotic probands, 76.1% ($N = 35/46$) contained at least one first-degree relative with psychotic affective disorder (Table I). Among the families of non-psychotic probands, the proportion with psychotic affective disorder in at least one relative was significantly lower, 47.8% ($N = 11/23$) (OR = 3.47, $\chi^2 = 5.51$, $df = 1$, $P < 0.019$). The analysis was also done considering only BPI as affected. Among the psychotic proband families 32/46 (69.6%) contained at least one psychotic BPI first-degree relative compared to 11/23 (47.8%) non-psychotic proband families (OR = 3.09, $\chi^2 = 2.49$, $df = 1$, $P < 0.079$).

### Analysis by Individuals

Among all first-degree relatives with major affective disorder, 30.3% ($N = 60/198$) had a lifetime history of psychotic symptoms during an affective episode. In the families of psychotic probands, 34.6% (46/133) of those with major affective disorder had psychotic symptoms, compared to only 21.5% (14/65) of those in non-psychotic families. Psychosis was a feature of 40/62 (64.5%) BPI relatives in psychotic proband families compared to 13/28 (46.4%) BPI relatives in non-psychotic proband families. The differences found did not reach statistical significance for either of the two designations of affection status (Table II).

### Analysis by Distribution of Family Clusters

When all probands and their first-degree affected relatives were considered, 106/267 subjects (39.7%) had psychosis. Analysis of familial clustering was carried out to determine whether the distribution of psychotic individuals was uniform throughout the 69 families (the null hypothesis) or, conversely, whether these individuals clustered in some families, but not in others. The results indicated marked clustering ($\chi^2 = 142.74$, $df = 1$, $P < 0.0001$) (Table III). A subset of 38 families were found to contain two or more psychotic affected subjects; 35 of these families had a psychotic proband. In 27 of the families the majority of those with affective disorder had psychotic symptoms. Eight families with three or more psychotic affected members were identified; all of these included a psychotic proband. With BPI only considered as affected, there was again evidence for the clustering of psychosis ($\chi^2 = 48.99$, $df = 1$, $P < 0.0001$).

### Combined Data Sets

When the data set from our previous report was merged with the current one, there were 134 BPI proband families containing 400 first-degree relatives with major affective disorder, of whom 150 had BPI. Analysis by family of the combined data set showed that among psychotic proband families, 65/93 (69.9%) had at least one affectively ill relative with psychotic symptoms compared to 16/41 (39.0%) in the non-psychotic proband families (OR = 3.63, $\chi^2 = 11.34$, $P = 0.0008$). When only BPI relatives were considered, there were 55/93 (59.1%) psychotic proband families with at least one

TABLE I. Percentage of Families Containing at Least One First-Degree Ralative with Psychotic Affective Disorder or Psychotic Bipolar I Disorder, by Psychotic status of Proband*

| Family characteristics | Psychotic proband families | Non-psychotic proband families |
|---|---|---|
| Total families in group | 46 | 23 |
| 1st-degree relatives interviewed per family | 4.6 | 4.3 |
| 1st-degree relatives with affective disorder per family | 3.9 | 3.8 |
| 1st-degree relatives with BPI disorder per family | 1.3 | 1.2 |
| Mean age of ralatives at interview (years) | 43.3 | 47.5 |
| Relatives with BPII disorder and comorbid panic disorder | 6 (5) | 6 (9) |
| Families with $\geq 1$ psychotic first-degree affective disorder relative[a] | 35 (76.1) | 11 (47.8) |
| Families with $\geq 1$ psychotic first-degree BPI relative[b] | 32 (69.6) | 11 (47.8) |

*Values are $n$ or $n$ (%) unless indicated.
[a]The difference between the two groups in the proportion of families with $\geq 1$ psychotic affective disorder first-degree relative is significant (OR = 3.47, $\chi^2 = 5.51$, $df = 1$, $P < 0.019$).
[b]The difference between the two groups in the proportion of families with $\geq 1$ psychotic BPI first-degree ralative is not significant (OR = 3.09, $\chi^2 = 2.49$, $df = 1$, $P < 0.079$).

psychotic relative while there were 15/41 (36.6%) such non-psychotic proband families (OR = 2.51, $\chi^2 = 5.80$, $P = 0.016$). The analysis by individual relative showed that when all affectively ill relatives were considered there were 95/279 (34.1%) relatives in psychotic proband families that had psychotic symptoms compared to 20/121 (16.5%) in non-psychotic proband families (OR = 2.51, $Z = 3.19$, $df = 1$, $P = 0.0014$). For the BPI relatives the figures were 77/112 (68.7%) and 18/38 (47.4%) in the psychotic and non-psychotic proband families, respectively (OR = 3.17, $Z = 2.88$, $df = 1$, $P = 0.0039$). The analysis of psychotic symptom clustering was significant for all affective disorder and more highly significant for BPI subjects only (Table IV). When all affectively ill subjects were considered, there were 43 families in which the majority of ill subjects had psychotic symptoms. There were 26 families in which no ill subjects had psychotic symptoms. When only BPI was considered affected, (and excluding 34 families with only one BPI subject) there were 44 families in which all BPI subjects were psychotic, and 14 families with no psychosis among such subjects.

## DISCUSSION

These results are consistent with our prior report although the magnitude of the predictive effect of a psychotic proband is less in the replication families. We replicated the finding from our prior report that psychosis in BPI probands predicted a significantly greater likelihood of psychotic affective disorder in their families. Further, we replicated the finding of significant familial clustering of psychotic symptoms in all affective disorder, and in BPI specifically. Although our earlier study reported that psychosis in probands predicted psychosis in individual affectively ill (and in BPI) relatives, our current data demonstrate a similar effect though not at a statistically significant level.

The consistency of the current findings with our prior report is emphasized in the large combined data set in which every one of the six measures (three methods of analysis times two affection statuses) of familial aggregation of psychotic symptoms is statistically significant. The combined data set suggests that the failure of the psychotic status of probands to significantly predict psychotic BPI families or psychotic BPI individual relatives in either the prior data set or the replication data set was due to insufficient power; both of these comparisons are statistically significant in the larger combined data set. Similarly, the clustering of psychotic symptoms in BPI subjects is strikingly more significant in the combined data set than in either subset alone.

### Methodologic Considerations

Both the comparison between the earlier study and the current one, and the appropriateness of combined data set analyses should be considered in light of the

TABLE II. Odds of Psychotic Symptoms in First-Degree Relatives with Affective Disorder and with Bipolar I Disorder by Psychotic Status of Proband*

| Variable | Parameter estimate | SE | Z | $P$ | OR | 95% CI |
|---|---|---|---|---|---|---|
| Affective disorder | | | | | | |
| Intercept | −0.53 | 0.68 | −0.78 | 0.43 | | |
| Psychotic proband | 0.63 | 0.38 | 1.64 | 0.10 | 1.88 | 0.88–3.98 |
| Age | −0.02 | 0.02 | −1.30 | 0.19 | 0.98 | 0.94–1.01 |
| Gender | −0.43 | 0.31 | −1.41 | 0.16 | 0.65 | 0.36–1.18 |
| Duration of illness | 0.01 | 0.02 | 0.56 | 0.57 | 0.01 | 0.98–1.04 |
| Bipolar I disorder | | | | | | |
| Intercept | 1.94 | 0.96 | 2.03 | 0.042 | | |
| Psychotic proband | 1.02 | 0.53 | 1.92 | 0.055 | 2.78 | 0.98–7.88 |
| Age | −0.06 | 0.03 | −2.04 | 0.042 | 0.94 | 0.89–0.99 |
| Gender | 0.97 | 0.48 | 2.03 | 0.042 | 2.63 | 1.03–6.67 |
| Duration of illness | 0.04 | 0.03 | 1.58 | 0.11 | 1.04 | 0.99–1.10 |

*Controlled for age, gender, and duration of illness analyzed with the generalized estimating equation.

TABLE III. Number of Families with Psychotic Members by Number of Affected Subjects in a Family and Number Within the Cluster Who Had Psychotic Symptoms*

| Cluster size | Number of psychotic subjects in cluster | | | | | | | | | | Number of families |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| All affective disorder[a] | | | | | | | | | | | |
| 2 | 1 | 2 | 1 | — | — | — | — | — | — | — | 4 |
| | (1.5) | (1.9) | (0.6) | | | | | | | | |
| 3[c] | 3 | 7 | 18 | 2 | — | — | — | — | — | — | 30 |
| | (6.6) | (13.0) | (8.6) | (1.9) | | | | | | | |
| 4 | 5 | 8 | 3 | 2 | 0 | — | — | — | — | — | 18 |
| | (2.4) | (6.3) | (6.2) | (2.7) | (0.4) | | | | | | |
| 5 | 2 | 1 | 4 | 1 | 2 | 0 | — | — | — | — | 10 |
| | (0.8) | (2.6) | (3.5) | (2.3) | (0.7) | (0.1) | | | | | |
| 6 | 1 | 0 | 2 | 0 | 1 | 0 | 0 | — | — | — | 4 |
| | (0.2) | (0.8) | (1.3) | (1.1) | (0.5) | (0.1) | (0.0) | | | | |
| 7[c] | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | — | — | 2 |
| | (0.1) | (0.3) | (0.5) | (0.6) | (0.4) | (0.2) | (0.0) | (0.0) | | | |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | 0 |
| | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | | |
| 9[c] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | (0.0) | (0.1) | (0.2) | (0.3) | (0.2) | (0.2) | (0.1) | (0.0) | (0.0) | (0.0) | |
| Number of families | 12 | 19 | 30 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | 69 |
| BPI[b] | | | | | | | | | | | |
| 1 | 1 | 4 | — | — | — | — | — | — | — | — | 5 |
| | (1.9) | (3.1) | | | | | | | | | |
| 2[c] | 11 | 13 | 20 | — | — | — | — | — | — | — | 44 |
| | (6.3) | (20.7) | (17.1) | | | | | | | | |
| 3 | 0 | 6 | 5 | 3 | — | — | — | — | — | — | 14 |
| | (0.8) | (3.7) | (6.1) | (3.4) | | | | | | | |
| 4[c] | 0 | 0 | 3 | 1 | 2 | — | — | — | — | — | 6 |
| | (0.1) | (0.8) | (1.9) | (2.2) | (0.9) | | | | | | |
| Number of families | 12 | 23 | 28 | 4 | 2 | — | — | — | — | — | 69 |

*Values are number observed (expected).
[a]Tarone's one-sided score test for binomial distributions was used to compare these observed values to those expected under the null hypothesis of a random distribution of psychotic symptoms among these affective disorder subjects. The result showed a significant deviation from the expected distribution ($\chi^2 = 142.74$, $df = 1$, $P < 0.0001$).
[b]Tarone's one-sided score test for binomial distribution was used to compare these observed values to those expected under the null hypothesis of a random distribution of psychotic symptoms among these BPI subjects. The result showed a significant deviation from the expected distribution ($\chi^2 = 48.99$, $df = 1$, $P < 0.0001$).
[c]The sums across these rows do not equal the sums of the respective observed rows because of rounding.

methodological continuities and differences between the two studies. Both studies ascertained BPI probands with affectively ill first-degree relatives. In this study, as in the prior one, all interviews were conducted by psychiatrists with expertise in affective disorder. Indeed, this was one major reason for using only the 69 Johns Hopkins families from the NIMH Genetics Initiative study that contains a total of 204 families from four sites. We sought the highest level of validity in the clinical assessment of psychotic symptoms. Whereas the study diagnoses were made at all study sites using the best estimate procedure that requires the agreement of two reviewing psychiatrists, the assessment of psychotic symptoms was made only at the interviewer level, and only at the Johns Hopkins site were the interviews conducted by psychiatrists. Hallucinations and delusions have been found to be highly reliably assessed by psychiatrists [Spitzer et al., 1964; Wing et al., 1967; Luria and McHugh, 1974]. Two other reasons for using only the Johns Hopkins families were for consistency of methodology between the prior study and the current one, and because of access to family informant and medical record data stored at the Johns Hopkins site. There were some methodological differences between the earlier study and the current one.

***Ascertainment.*** The first study required a BPI proband, and two other first-degree relatives with major affective disorder. There was no requirement of another BPI in the family; in fact, the most common diagnosis among relatives was BPII. The replication data set has BPI as the most common diagnosis among relatives because a BPI (or SA/BP) first-degree relative was required for the family to be included in this study. Ascertainment for this study also employed less stringent unilineality criteria than was employed previously.

***Diagnostic instrument.*** The current study had an important strength in this regard relative to the prior one as there were more opportunities to capture a subject's psychotic experiences. Whereas the assessment of hallucinations and delusions was made only for the most severe mania and the most severe depression in the earlier study, which used the Schedule for Affective Disorder and Schizophrenia-Lifetime (SADS-L) [Endicott and Spitzer, 1978], the assessment was made for two depressive episodes rather than one in this study, and a general psychotic symptom screen was

TABLE IV. Comparison of Results From a Prior Study, the Current Study, and the Combined Data Sets for Three Tests of Familial Aggregation of Psychotic Symptoms*

| | *n* | OR[a] | $\chi^2$ | *df* | *P*-value |
|---|---|---|---|---|---|
| By family | | | | | |
| All affective disorder | | | | | |
| Previous | 65 | 4.59 | 6.81 | 1 | 0.009 |
| Current | 69 | 3.47 | 5.51 | 1 | 0.019 |
| Combined | 134 | 3.63 | 11.34 | 1 | 0.0008 |
| Bipolar I disorder | | | | | |
| Previous | 65 | 3.34 | 3.82 | 1 | 0.0505 |
| Current | 69 | 2.49 | 3.09 | 1 | 0.079 |
| Combined | 134 | 2.51 | 5.80 | 1 | 0.016 |
| By individual relative | | | Z | | |
| All affective disorder | | | | | |
| Previous | 202 | 4.22 | 3.01 | 1 | 0.0026 |
| Current | 198 | 1.88 | 1.64 | 1 | 0.10 |
| Combined | 400 | 2.51 | 3.19 | 1 | 0.0014 |
| Bipolar I disorder | | | | | |
| Previous | 60 | 3.56 | 1.83 | 1 | 0.067 |
| Current | 90 | 2.78 | 1.92 | 1 | 0.055 |
| Combined | 150 | 3.17 | 2.88 | 1 | 0.0039 |
| By cluster | | | $\chi^2$ | | |
| All affective disorder | | | | | |
| Previous | 267 | — | 13.17 | 1 | 0.00028 |
| Current | 267 | — | 142.74 | 1 | <0.0001 |
| Combined | 534 | — | 6.28 | 1 | 0.011 |
| Bipolar I disorder | | | | | |
| Previous | 125 | — | 21.36 | 1 | <0.0001 |
| Current | 159 | — | 48.99 | 1 | <0.0001 |
| Combined | 284 | — | 99.37 | 1 | <0.0001 |

*Tests are by family, by individual relative, and by cluster, with each test done by two affection statuses, all affective disorder and bipolar I disorder only.
[a]OR is the odds of psychosis in families or individual relatives of psychotic probands as compared to the odds of psychosis in families or individual relatives of non-psychotic probands.

administered at a later point in the interview. It should be noted, however, that we administered both the SADS-L and the DIGS as semi-structured interviews, probing whenever possible to elicit the maximum amount of psychopathology.

***Diagnostic criteria.*** The current study used DSM-III-R criteria to diagnose BPI and SA/BP whereas the prior study used RDC (both studies used RDC for BPII and UPR). Despite these differences, the two studies found similar rates of psychosis across diagnoses: BPI: 62.3%, 71.2%; BPII: 3.3%, 3.9%; UPR: 6.5%, 6.8% (current rate followed by previous one).

## Limitations

Our findings should further be considered in light of several limitations. One was the largely retrospective nature of our clinical data gathering. Ideally we would assess psychotic symptoms prospectively and observe them rather than gather retrospective descriptions of episodes that may have occurred many years earlier. Second, diagnoses in relatives were made with the knowledge that all probands had BPI. The low rate of psychotic symptoms in UPR could be due to a denominator inflated by diagnostic bias associated with the lack of a control proband family group. Similarly, the low rate of SA/BP (0.5%) could stem from diagnostic bias associated with the lack of a schizophrenia proband family group [Roy et al., 1997]. The surprising complete absence of subjects diagnosed with schizophrenia in the current (and the prior) data set could result from a similar bias. Third, although we found no significant differences in a number of illness severity variables between relatives in psychotic and non-psychotic proband families, we did not comprehensively assess the possibility that psychotic symptoms may be correlated with other indicators of illness severity that may themselves be familial.

## Implications

Our finding that psychotic symptoms aggregate in families stems from a strategy aimed at reducing genetic heterogeneity to facilitate strengthening linkage signals and ultimately identifying BPD susceptibility genes. If there is a gene or genes responsible for our finding, then how best to find it? We have suggested that the chromosomal regions 10p12–13, 13q32, 18p11.2, and 22q11–13, which have been implicated in both BPD and schizophrenia [Berrettini, 2000], should be of particular interest. Linkage analysis could be carried out using families in which multiple members have psychotic BPD. We have recently done such analyses and found that a group of psychotic BPD families show evidence of linkage to chromosome 13q31 and to chromosome 22q12 (Potash et al., unpublished data).

If psychotic affective disorder does share susceptibility genes with schizophrenia then the shared susceptibility might be strictly to psychotic symptoms or it might

be to the co-occurrence of psychotic and affective symptoms. The latter hypothesis would suggest an affective subtype of schizophrenia, as well as a psychotic subtype of BPD. A number of studies have found a high rate of depressive symptomatology in schizophrenia [Siris et al., 1984; Wassink et al., 1999] and this co-occurrence may be familial [DeLisi et al., 1987; Kendler et al., 1997]. One recent report did not find depression to be familial in a schizophrenia sample, but did find familiality of manic symptomatology [Wickham et al., 2001]. Pulver et al. [2000] recently used the presence of at least one first-degree relative with psychotic affective disorder to stratify schizophrenia proband families in a linkage study. The strongest linkage signal in a genome-wide scan on this subset of families was at 22q12 and there was also a nominally significant result for 13q33 [Pulver et al., 2000].

Our results suggest the value of using the putative psychotic BPD subtype in neurobiologic studies as well. A few studies have pursued such a strategy and found evidence for biological and cognitive correlates of psychotic BPD [Guidotti et al., 2000; Gilvarry et al., 2001]. Several neuroimaging studies have yielded particularly intriguing results. A functional imaging study demonstrated elevated D2 dopamine receptor density values in psychotic, but not non-psychotic, BPD, with elevations similar to those seen in schizophrenia patients [Pearlson et al., 1995]. Two structural MRI studies found that subjects with psychotic affective disorder and those with schizophrenia shared the same abnormal volume reduction: in the left hippocampus in one study, and in the left posterior amygdala-hippocampal complex in the other [Hirayasu et al., 1998; Velakoulis et al., 1999]. Other biological markers such as abnormalities in evoked response and oculomotor parameters that have been found to be associated with schizophrenia should be assessed in psychotic BPD as well. If distinguishing neurobiologic features of psychotic BPD were found to be familial, they might provide endophenotypes for linkage analysis in the same way that, for example, the P50 auditory-evoked response has been used in schizophrenia [Freedman et al., 1997].

In summary, we have found some evidence for the familial aggregation of psychotic symptoms in a replication sample of 69 new BPD pedigrees. Our findings provide modest support for the validity of psychotic BPD as a subtype of BPD. This clinically defined subtype may prove more homogeneous than the disorder as a whole at the level of genetic etiology and of neuropathology/pathophysiology; it may thus prove useful in the search for disease mechanisms.

## ACKNOWLEDGMENTS

Supported by contributors to the Affective Disorders Fund, the George Browne Laboratory Fund and the Alexander Wilson Schweizer Fund at Johns Hopkins University. Drs. J. Nurnberger, Jr. (Indiana University), E. Gershon (formerly NIMH Intramural Research Program, now University of Chicago), and T. Reich (Washington University) shared in the development of the multi-site genetic study from which the data presented here derives. The authors thank Dr. G. Pearlson for critical review of the manuscript, B. Schweizer, RN, and N. Rohrer for logistical coordination, J. Thomas, J. Goldstein, and J. Chellis, MS, for database support, and S. Allan, T. Hightower, K. Vishio, and C. Savino for subject recruitment. Many thanks are owed to those in the study families who generously volunteered their time and energy.

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