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Co-morbid anxiety disorders in bipolar disorder and major depression : familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder

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Abstract

Background—Co-morbidity of mood and anxiety disorders is common and often associated with greater illness severity. This study investigates clinical correlates and familiality of four anxiety disorders in a large sample of bipolar disorder (BP) and major depressive disorder (MDD) pedigrees.

Method—The sample comprised 566 BP families with 1416 affected subjects and 675 MDD families with 1726 affected subjects. Clinical characteristics and familiality of panic disorder, social phobia, specific phobia and obsessivecompulsive disorder (OCD] were examined in BP and MDD pedigrees with multivariate modeling using generalized estimating equations.

Results—Co-morbidity between mood and anxiety disorders was associated with several markers of clinical severity, including earlier age of onset, greater number of depressive episodes and higher prevalence of attempted suicide, when compared with mood disorder without co-morbid anxiety. Familial aggregation was found with co-morbid panic and OCD in both BP and MDD pedigrees. Specific phobia showed familial aggregation in both MDD and BP families, although the findings in BP were just short of statistical significance after adjusting for other anxiety co-morbidities. We found no evidence for familiality of social phobia.

Conclusions—Our findings suggest that co-morbidity of MDD and BP with specific anxiety disorders [OCD, panic disorder and specific phobia] is at least partly due to familial factors, which may be of relevance to both phenotypic and genetic studies of co-morbidity.

Keywords

Anxiety disorders; familial; mood disorders; obsessive-compulsive disorder; panic; phobia

Introduction

Mood and anxiety disorders are the most common mental disorders across the lifespan, with epidemiological surveys estimating that over 20 % of the US population will suffer from one

Declaration of Interest
None.

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or more such disorder during their lifetime (Kessler et al. 2005). Although mood and anxiety disorders are classified separately, co-morbidity is common in both clinical (McElroy et al. 2001 ; Zimmerman et al. 2002) and epidemiological samples (Kessler et al. 2003; Merikangas et al. 2007), and is often associated with longer illness duration and greater clinical severity than either disorder alone (Lamers et al. 2011). Prospective studies have found that depressive episodes are more prolonged in patients with anxiety co-morbidity, both at the level of anxiety symptoms or syndromes (Coryell et al. 1992, 2009). Co-occurrence of an anxiety disorder also increases the risk of suicide attempts in people with major depressive disorder (MDD) or bipolar disorder (BP) (Sareen et al. 2005). Moreover, BP with co-morbid anxiety can pose a significant therapeutic quandary since antidepressants, the treatment of choice for most anxiety disorders, may be problematic in patients with BP, particularly those with rapid cycling (Wehr & Goodwin, 1979).

The term `co-mordibity' was first used by Feinstein to refer to the presence of two independent disorders, with the second disorder potentially affecting `the time of detection, prognostic anticipations, therapeutic selections, and post-therapeutic outcome of the index disease' (Feinstein, 1970). The appearance of comorbidity may be due to chance or to ascertainment bias (Berkson's bias). However, the consistent documentation of co-morbid mood and anxiety disorders in community as well as clinical samples suggests that chance or ascertainment bias is unlikely to be primary reasons for the co-occurrence of these syndromes (Kessler et al. 2007). Feinstein's initial conception of `co-morbidity' assumed the presence of distinct disorders ; in psychopathology, however, the term often refers to overlapping symptoms rather than disorderspecific syndromes. Symptom-based overlap between mood and anxiety disorders is extremely common and may represent what has been termed `artefactual co-morbidity' (Maj, 2005). The overlap of anxiety syndromes is likely to be closer to Feinstein's conception of co-morbidity and has the potential to be of greater clinical relevance.

All the major mood and anxiety syndromes have been shown to segregate within families (Sullivan et al. 2000; Hettema et al. 2001). Among the most studied has been the relationship between panic disorder and MDD. Most (Goldstein et al. 1994; Maier et al. 1995), though not all (Crowe et al. 1983; Weissman et al. 1993), family studies have provided evidence consistent with shared familiality, which is consistent with findings from twin studies (Kendler et al. 1995; Mosing et al. 2009). The familial association between major depression and social phobia has been less studied, with only two family studies providing modest evidence for co-aggregation in findings that fall just short of statistical significance (Fyer et al. 1993; Stein et al. 1998). Similarly, twin studies have found only modest evidence for common genetic susceptibility between MDD and social phobia (Kendler et al. 1993, 2011). To our knowledge, no family study has investigated the co-occurrence of simple or specific phobias and MDD, although there is evidence for a modest degree of co-aggregation from twin studies (Kendler et al. 1993). Finally, perhaps because it is one of the least prevalent anxiety disorders, the relationship between obsessivecompulsive disorder (OCD) and MDD has been explored in only a few family studies of OCD, where the evidence for co-segregation has been inconsistent (Nestadt et al. 2001; Carter et al. 2004; Hanna et al. 2011).

Co-morbidity of anxiety syndromes and BP is also common (Merikangas et al. 2007), but far fewer studies have examined the familial relationships between BP and anxiety disorders. In high-risk offspring of BP parents, anxiety syndromes typically precede the onset of mood syndromes (Duffy et al. 2007; Sala et al. 2010), and often persist throughout adulthood (Mantere et al. 2010). In previous studies of the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder Consortium, familial aggregation was described for panic disorder (MacKinnon et al. 2002), specific phobia and OCD (Potash et

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al. 2007), but these analyses did not control for different rates of diagnoses among sites, or for additional co-morbidity amongst the anxiety disorders. To our knowledge, there has been no twin study that has specifically studied the co-morbidity of BP and anxiety disorders.

While previous studies have provided evidence for the co-familiality of certain anxiety and mood disorders, many have been limited by relatively small numbers of co-morbid cases. Moreover, comparison across these studies has been hampered by the use of varying diagnostic criteria and differing analytical methods, which have not always controlled for potential confounds such as additional co-morbid diagnoses. In the present study we extend prior findings by examining two of the largest available family samples of MDD and BP in order to have sufficient power to study the familiality of each individual anxiety disorder. The aim of this study is to determine whether : (1) cases with co-morbid anxiety have clinical correlates of greater severity than cases without co-morbid anxiety ; and whether (2) specific anxiety syndromes show evidence of familial aggregation in mood disorder pedigrees.

Method

Subject ascertainment

In both the BP and MDD family studies, subjects provided written informed consent after hearing a complete description of the study. Subjects were recruited either from in-patient or out-patient clinics, or from a response to advertisement.

The MDD sample was drawn from the Genetics of Recurrent Early-onset Major Depression (GenRED) study, which recruited families with recurrent earlyonset MDD (age of onset ≤30 years in the proband and ≤40 years in the relative) at six sites (Levinson et al. 2003). Exclusion criteria were having a relative with bipolar I disorder (BPI), schizophrenia or schizo-affective disorder. For the present analysis, we selected only subjects with a high-confidence MDD diagnosis in pedigrees with at least two first-degree affected relatives. This led to a total of 1726 affected subjects from 675 families, comprising 867 siblings, 134 children and 50 parents.

The BP sample was drawn from waves 1–4 of the NIMH Genetics Initiative Bipolar Disorder Collaborative project conducted at 10 sites. Ascertainment criteria required a proband with BPI and at least one sibling with either BPI or schizo-affective disorder, bipolar type (SABP). To compare with the MDD sample, the primary analysis included only cases with BPI or bipolar II disorder (BPII). This dataset comprised 566 probands with BPI and at least one additional first-degree relative with BPI and BPII. The analysis included 850 such relatives (651 siblings, 132 parents and 67 offspring). To determine whether familial aggregation was also seen in available family members without BP, a secondary analysis was also performed using all available BPI probands (n=652) and all available first-degree relatives (n=1908) regardless of diagnosis. This latter group, consisting of 1335 subjects with BPI and 167 with BPII, was used for the analysis of clinical correlates.

Diagnostic assessment

Both the MDD and BP studies used the Diagnostic Instrument for Genetic Studies (DIGS) (Nurnberger et al. 1994). Two research clinicians subsequently provided a best-estimate diagnosis incorporating the interview data, as well as information from family informants and medical records. Each best-estimate diagnosis was given a confidence level from one to four; for these analyses we used only the diagnoses with confidence levels of three (`probable') or four (`definite'). The DIGS has been shown to have excellent inter- rater reliability for the major mood diagnoses, with k values greater than 0.7 (Nurnberger et al.

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1994). The GenRED study has also evaluated the inter- rater reliability of panic disorder (k=0.96), social phobia (k=1.0) and OCD (k=0.67) (Levinson et al. 2003).

Diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders (DSM) third edition revised (DSM-III-R) and fourth edition (DSM-IV) criteria, where the presence of a mood disorder is not a hierarchical exclusion to the diagnosis of any of the considered anxiety disorders. The DIGS includes structured questions for the diagnoses of panic disorder (with or without agoraphobia), social phobia, specific phobia and OCD. It does not include structured questions for the diagnoses of generalized anxiety disorder or post-traumatic stress disorder.

Statistical analyses

Initial comparisons of subjects (probands and firstdegree relatives) with mood disorders and co-morbid anxiety disorders versus subjects with `pure' mood disorders were performed using Pearson's two-tailed x^2 test for categorical variables and the Mann–Whitney–Wilcoxon test for continuous variables. Significance levels are presented as nominal two-sided p values.

Familial aggregation was tested using logistic regression and generalized estimating equations to account for within-family correlation between probands and their first-degree relatives (Zeger et al. 1988). The logistic regression analyses were conducted in hierarchical models adjusting for: age at interview and sex [adjusted odds ratio (aOR^1)]; additional anxiety disorder co-morbidity in relatives (aOR^2); and additional anxiety disorder co-morbidity in probands (aOR^3).

Familial aggregation for each co-morbid anxiety disorder was also tested across the MDD and BP samples. To test whether the effect size of the familial aggregation of each co-morbid anxiety disorder differed in the MDD versus the BP sample, we combined both samples and performed the same aggregation analyses with an interaction term derived from a study covariate (the potential effect modifier) and a covariate indicating whether the relative has a proband with the same anxiety co-morbidity or not (the dependent or predictor variable). A full regression model was run including this interaction term and the statistical significance of the interaction regression coefficient was used to test for between-study differences.

Results

Several prominent similarities were present across the MDD and BP datasets. The MDD and BP samples were comparable in their average age at interview (42.6 years V. 42.0 years, p=0.11) and there were no statistically significant differences in the prevalence of panic disorder (p=0.21), specific phobia (p=0.89) or OCD (p=0.09). Social phobia, however, was found to be more common in the MDD sample (13.5% V. 7.8%, p<0.0001). Further demographic and clinical characteristics are shown in Tables 1 and 2 for the MDD and BP samples, where subjects with one of four comorbid anxiety disorders were compared individually with subjects without any of the four disorders.

In the MDD sample there were relatively few demographic differences across the four groups. Subjects with any of the anxiety disorder diagnoses generally completed fewer years of education, though this difference was only statistically significant in cases with co-morbid panic disorder (p<0.0001). Clinical correlates were generally more severe in cases with a co-morbid anxiety disorder, with the exception of comorbid specific phobia. Panic disorder, social phobia and OCD were associated with an earlier age at onset of depression, a greater prevalence of hospitalization, a greater likelihood of treatment with electroconvulsive

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therapy and an increased risk of suicide attempt (Table 1). Compared with the other anxiety disorders, co-morbidity with OCD was notable for an earlier age of first treatment ($p<0.0001$) and for an overall pattern of increased severity.

As shown in Table 2, anxiety disorder co-morbidity in BP had many similar phenotypic patterns. There were reductions in the years of education completed, which was most significant for those with panic co- morbidity ($p<0.0001$). Clinical correlates showed a similar pattern of earlier age of first depression, a substantially higher number of depressive episodes, and an increased risk of suicide attempt across all the anxiety disorders. As in the earlier MDD analysis, comorbidity with OCD was generally associated with greater severity than co-morbidity with the other anxiety disorders. In the BP sample, co-morbid OCD was associated with the earliest age of onset for depressive episodes ($p<0.0001$), the earliest age of treatment ($p=0.0031$) and the highest number of depressive episodes ($p<0.0001$).

Familial aggregation

There were important similarities seen across the MDD and BP samples in the prevalence rates of each anxiety disorder and in the overall excess of each disorder seen in the relatives of probands with the same disorder (see raw numbers in Tables 3 and 4). When all four anxiety disorders were grouped and analysed together in a logistic regression with correction for age, sex and site of ascertainment, the presence of any anxiety disorder in a proband was associated with comparably higher odds of having any anxiety disorder in relatives in both the MDD [OR 1.77, 95 $o/_o$ confidence interval (CI) 1.36–2.30, $p<0.001$] and BP samples (OR 1.71, 95% CI 1.22–2.37, $p=0.002$).

Analyses of specific anxiety disorders showed that panic disorder, specific phobia and OCD, but not social phobia, were familial in the MDD sample (Table 3). Familial aggregation of the three anxiety disorders remained statistically significant after controlling for additional anxiety disorders in relatives (aOR^2) and for additional anxiety disorder comorbidity in both relatives and probands (aOR^3). Similar effect sizes were seen in OCD (aOR^3 2.60, 95 % CI 1.29–5.24, $p=0.008$), specific phobia (aOR^3 2.43, 95 % CI 1.35–4.38, $p=0.003$) and panic disorder (aOR^3 1.98, 95% CI 1.40–2.78, $p<0.001$).

The primary analysis of the BP sample included cases and first-degree relatives with BPI or BPII. Familial aggregation was seen for OCD, panic disorder and specific phobia when controlled for age, sex and site covariates (aOR^1). After controlling for the additional anxiety diagnoses in the proband and relatives, familial aggregation remained significant, albeit with an attenuated effect, in OCD (aOR^3 3.10, 95 % CI 1.31–7.09, $p=0.009$) and panic disorder (aOR^3 1.52, 95 % CI 1.00–2.30, $p=0.047$), but not in specific phobia (aOR^3 1.94, 95 % CI 0.95–3.96, $p=0.069$). As in the MDD sample, we found no evidence for statistically significant familial aggregation of social phobia.

The BP sample also included an additional 1058 first-degree relatives without a BPI or BPII diagnosis. When familial aggregation of the co-morbid anxiety disorders was tested in these relatives similar levels of aggregation were found for OCD (aOR^3 2.51, 95 % CI 1.15–5.49, $p=0.021$) and panic disorder (aOR^3 1.51, 95 % CI 1.08–2.11, $p=0.017$) compared with the BP-only analysis. We again found no evidence of statistically significant familial aggregation of social phobia (aOR^3 1.69, 95% CI 0.84–3.39, $p=0.14$). However, this analysis did find evidence for aggregation of specific phobia (aOR^3 2.12, 95% CI 1.17–3.84, $p=0.013$), which differs from the primary analysis of BP cases although the effect sizes are similar and the confidence levels show significant overlap.

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In further analyses testing differences in ORs between the two samples for each specific anxiety disorder, we found no evidence for statistically significant differences in familial aggregation across the MDD and BP samples.

Discussion

The primary aim of this study was to examine and compare the clinical correlates and familial aggregation of four co-morbid anxiety disorders in MDD and BP pedigrees. Consistent with prior studies, our findings show a strong association of co-morbid anxiety disorders with clinical markers of severity, including earlier age of onset, a greater number of depressive episodes and elevated rates of suicide attempt. In general, indices of clinical morbidity were most associated with co-morbid OCD and panic disorder, and least associated with co-morbid specific phobia. Our results also provide evidence for familial clustering of co-morbid anxiety syndromes when analysed as a group in both MDD and BP samples. In disorder-specific analyses, we found that OCD and panic disorder showed familial aggregation in both MDD and BP pedigrees, while social phobia was not found to be familial in either sample. Specific phobia was familial in MDD pedigrees and showed some evidence of familiality in BP, although findings were just short of statistical significance.

Familial aggregation does not distinguish between genetic or environmental causes; however, the prominent heritability of most psychiatric syndromes suggests that at least part of the familial aggregation seen in this study is likely to be genetic. Several types of segregation can lead to familial aggregation (Klein & Riso, 1994), including co-segregation of the index and co-morbid phenotypes, segregation of a unitary phenotype with co-morbid features, and independent segregation of the two phenotypes. Since the samples used in this study were originally collected for genetic studies, which did not systematically ascertain all affected and unaffected relatives, our study is unable to distinguish among these segregation patterns. The BP sample did include additional first-degree relatives who were unaffected or affected with a non-BP diagnosis. An analysis of this larger sample showed very similar results, suggesting that the majority of the aggregation was driven by the co-morbidity between the anxiety disorders and the BP phenotype specifically.

In both the MDD and BP samples, OCD was found to be the most strongly familial co-morbid anxiety disorder and the most associated with clinical markers of severity. The familial relationship between mood disorders and OCD has been previously studied primarily from the side of OCD family studies. The largest of these studies has supported a familial relationship between OCD and MDD (Bienvenu et al. 2011), though this was not found in prior studies with smaller sample sizes (Carter et al. 2004; Fyer et al. 2005). BP has generally been too rare to be studied in OCD family studies and even the largest of these has not been able to find evidence for a statistically significant familial association, despite BP being found to be twice as prevalent in OCD relatives compared with control relatives (OR 2.40, p=0.08) (Bienvenu et al. 2011). Our current study, with much larger samples, found evidence for familial aggregation of a similar effect size, suggesting that the OCD studies have been underpowered to detect significant familiality for BP. The familial aggregation of panic disorder with MDD or BP has been previously described in several studies (Leckman et al. 1983; Maier et al. 1995; MacKinnon et al. 1997). Our study confirms these findings and provides additional evidence that the segregation of panic disorder in both MDD and BP pedigrees remain statistically significant when controlled for other co-morbid anxiety syndromes. The association effect size was slightly greater in MDD (OR 1.98) than in BP (OR 1.52), but these differences were not statistically significant.

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The familial aggregation of specific phobia appeared to differ between MDD and BP. However, both the prevalence (9.9 % in BP and 9.7 % in MDD) and the evidence for aggregation in the first adjusted regression model (aOR[1]), which controls for age, sex and site differences, showed little differences across both samples (aOR[1] 2.93 in MDD V. 2.38 in BP). While the evidence for aggregation in MDD remained significant after being controlled for additional anxiety diagnoses in the relatives and probands, the findings in BP fell just short of statistical significance. Findings from twin studies suggest that the risk for specific phobias is due to both genetic and individual environmental risk factors, with the latter being the more prominent of the two (Hettema et al. 2006). If the distinct findings across the two samples represent a true difference, it may indicate that phobias are genetically more associated with MDD, and/or that subjects with MDD may potentially have a greater likelihood of experiencing environmental exposures associated with phobias. On the other hand, since the MDD sample is larger than the BP sample, the difference may be due to decreased statistical power in the BP sample, particularly given the overlapping CIs and the lack of statistical significance in the formal comparison between the two ORs.

Although relatives of probands with social phobia had modestly more elevated rates of social phobia compared with relatives of probands without social phobia, we found no evidence for statistically significant familial aggregation in either BP or MDD. In a large epidemiological twin study social phobia was found to be the least heritable of the anxiety disorders, with most of the susceptibility risk coming from individual environmental risk factors (Hettema et al. 2005). Our failure to detect familial aggregation suggests that these and other risk factors do not appear to be shared between first-degree relatives with mood disorders, although our samples are unlikely to be sufficiently powered to exclude a very modest degree of familial aggregation.

In examining the co-morbidity between mood and anxiety disorders, our study has used categorical diagnoses, which can be seen as complementary to dimensional models of co-morbidity that have been proposed by factor analytical and twin modeling studies (Krueger, 1999; Hettema et al. 2006). The familial patterns of mood and anxiety co-morbidity seen in this study provide some support for Krueger's model of `internalizing disorders', where `anxious misery' (in this study represented by mood disorder) and `fear' subfactors (anxiety disorders) are partly correlated and partly distinct. Furthermore, the similar patterns of familiality across our BP and MDD samples suggest that co-morbidity with the internalizing disorders may not distinguish between the two as has been recently proposed (Goldberg et al. 2009).

Familiality between mood and anxiety disorders may be mediated by personality traits such as neuroticism, which are heritable and strongly associated with many internalizing disorders (Bienvenu et al. 2004). Subjects with MDD or BP have been found to have higher levels of neuroticism compared with normal controls (Jylha et al. 2010; Barnett et al. 2011). This could account for some of the familiality seen in this study since neuroticism may partially mediate the development of co-morbid anxiety disorders (Hettema et al. 2006). Unfortunately, we were not able to test this hypothesis since personality measures were not available for most participants.

This study has several strengths. It comprises one of the largest collected samples of MDD and BP pedigrees and has the benefit of a well-characterized and reliable diagnostic instrument used by trained researchers with a clinical background. The large sample size has also allowed us to isolate the effect of specific anxiety disorders rather than having to consider them as a cluster. The MDD and BP samples used identical diagnostic and best-estimate procedures, providing the methodological consistency to compare familiality across the disorders. Diagnoses were made by at least two experienced research psychiatrists or

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psychologists, which provided the clinical expertise necessary to help distinguish among the various anxiety disorders that often overlap in symptoms.

Our results must be viewed in light of several important limitations. The sample consists of familial cases of BP and MDD, which may limit the generalizability of our results to community samples, since familial cases may be more co-morbid (Verhagen et al. 2008). However, the overall co-morbidity prevalence rates in our study are broadly consistent with those from epidemiological samples (Regier et al. 1998; Merikangas et al. 2007). Our findings are also likely to be representative of cases that seek treatment since this population has been found to have high rates of familiality. Large naturalistic treatment studies of both MDD (Nierenberg et al. 2007) and BP (Post et al. 2003), for example, have found that over half of all patients have a family history of mood disorder.

A further limitation is that ascertainment of the sample was opportunistic and focused preferentially on collecting affected relatives. For the purposes of investigating the nature of co-morbidity, a more informative family study would have included probands with `pure' anxiety and would have ascertained all available family members (Wickramaratne & Weissman, 1993). The initial collection of the BP sample included relatives without mood disorders, but the ascertainment was not systematic and focused mostly on affected family members.

The interviews of family members were not conducted blind to the proband diagnosis, which may have biased the assessment. While the use of the DIGS as a diagnostic instrument in a strength of the study in both samples, the DIGS does not include structured questions to diagnose generalized anxiety disorder and post-traumatic stress disorder, and does not provide sufficient information to help distinguish sub-types of anxiety disorders such as generalized versus specific social phobia. Finally, as with most family studies, our diagnoses were based on a retrospective history of mood and anxiety diagnoses, whereas a prospective study would not be affected by the potential for recall bias.

In conclusion, co-morbid anxiety syndromes are common in MDD and BP families. Familial aggregation was seen with panic disorder and OCD in both MDD and BP pedigrees, while familiality of specific phobia was statistically significant only in MDD families. OCD co-morbidity with BP and MDD was found to be most strongly associated with clinical characteristics of illness severity and was found to have the strongest degree of familiality.

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From 1999 to 2003, the principal investigators and co-investigators were : New York State Psychiatric Institute, New York, NY, R01 MH060912 : Myrna M. Weissman, Ph.D. and James K. Knowles, M.D., Ph.D.; University of Pittsburgh, Pittsburgh, PA, R01 MH060866 : George S. Zubenko, M.D., Ph.D. and Wendy N. Zubenko, Ed.D., R.N., C.S.; Johns Hopkins University, Baltimore, R01 MH059552 : J. Raymond DePaulo, M.D., Melvin G. McInnis, M.D. and Dean MacKinnon, M.D.; University of Pennsylvania, Philadelphia, PA, R01 MH61686 : Douglas F. Levinson, M.D. (GenRED coordinator), Madeleine M. Gladis, Ph.D., Kathleen Murphy-Eberenz, Ph.D. and Peter Holmans, Ph.D. (University of Wales College of Medicine); University of Iowa, Iowa City, IW, R01 MH059542 : Raymond R. Crowe, M.D. and William H. Coryell, M.D.; Rush University Medical Center, Chicago, IL, R01 MH059541-05 : William A. Scheftner, M.D. Rush-Presbyterian. Data for the BP samples were collected as part of 10 projects that participated in the NIMH Bipolar Disorder Genetics Initiative.

From 1991 to 1998, the principal investigators and co-investigators were : Indiana University, Indianapolis, IN, U01 MH46282 : John Nurnberger, M.D., Ph.D., Marvin Miller, M.D. and Elizabeth Bowman, M.D.; Washington University, St Louis, MO, U01 MH46280 : Theodore Reich, M.D., Allison Goate, Ph.D. and John Rice, Ph.D.; Johns Hopkins University, Baltimore, MD U01 MH46274 : J. Raymond DePaulo Jr, M.D., Sylvia Simpson, M.D.,

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References

Barnett JH, Huang J, Perlis RH, Young MM, Rosenbaum JF, Nierenberg AA, Sachs G, Nimgaonkar VL, Miklowitz DJ, Smoller JW. Personality and bipolar disorder : dissecting state and trait associations between mood and personality. Psychological Medicine. 2011; 41:1593–1604. [PubMed: 21134316]

Bienvenu OJ, Samuels JF, Costa PT, Reti IM, Eaton WW, Nestadt G. Anxiety and depressive disorders and the five-factor model of personality: a higherand lower-order personality trait investigation in a community sample. Depression and Anxiety. 2004; 20:92–97. [PubMed: 15390211]

Bienvenu OJ, Samuels JF, Wuyek LA, Liang KY, Wang Y, Grados MA, Cullen BA, Riddle MA, Greenberg BD, Rasmussen SA, Fyer AJ, Pinto A, Rauch SL, Pauls DL, McCracken JT, Piacentini J, Murphy DL, Knowles JA, Nestadt G. Is obsessive–compulsive disorder an anxiety disorder, and what, if any, are spectrum conditions ? A family study perspective. Psychological Medicine. 2011 Published online : 13 May 2011. doi:10.1017/s0033291711000742.

Carter AS, Pollock RA, Suvak MK, Pauls DL. Anxiety and major depression comorbidity in a family study of obsessive-compulsive disorder. Depression and Anxiety. 2004; 20:165–174. [PubMed: 15643633]

Coryell W, Endicott J, Winokur G. Anxiety syndromes as epiphenomena of primary major depression : outcome and familial psychopathology. American Journal of Psychiatry. 1992; 149:100–107. [PubMed: 1728156]

Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. American Journal of Psychiatry. 2009; 166:1238–1243. [PubMed: 19797434]

Crowe RR, Noyes R, Pauls DL, Slymen D. A family study of panic disorder. Archives of General Psychiatry. 1983; 40:1065–1069. [PubMed: 6625855]

Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder : a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disorders. 2007; 9:828–838. [PubMed: 18076532]

Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. Journal of Chronic Diseases. 1970; 23:455–468.

Fyer AJ, Lipsitz JD, Mannuzza S, Aronowitz B, Chapman TF. A direct interview family study of obsessive-compulsive disorder. I. Psychological Medicine. 2005; 35:1611–1621. [PubMed: 16219119]

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Fyer AJ, Mannuzza S, Chapman TF, Liebowitz MR, Klein DF. A direct interview family study of social phobia. Archives of General Psychiatry. 1993; 50:286–293. [PubMed: 8466390]

Goldberg DP, Andrews G, Hobbs MJ. Where should bipolar disorder appear in the meta-structure? Psychological Medicine. 2009; 39:2071–2081. [PubMed: 19796430]

Goldstein RB, Weissman MM, Adams PB, Horwath E, Lish JD, Charney D, Woods SW, Sobin C, Wickramaratne PJ. Psychiatric disorders in relatives of probands with panic disorder and/or major depression. Archives of General Psychiatry. 1994; 51:383–394. [PubMed: 8179462]

Hanna GL, Himle JA, Hanna BS, Gold KJ, Gillespie BW. Major depressive disorder in a family study of obsessive-compulsive disorder with pediatric probands. Depression and Anxiety. 2011; 28:501–508. [PubMed: 21538726]

Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. American journal of Psychiatry. 2001; 158:1568–1578. [PubMed: 11578982]

Hettema JM, Neale MC, Myers JM, Prescott CA, Kendler KS. A population-based twin study of the relationship between neuroticism and internalizing disorders. American Journal of Psychiatry. 2006; 163:857–864. [PubMed: 16648327]

Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Archives of General Psychiatry. 2005; 62:182–189. [PubMed: 15699295]

Jylha P, Mantere O, Melartin T, Suominen K, Vuorilehto M, Arvilommi P, Leppamaki S, Valtonen H, Rytsala H, Isometsa E. Differences in neuroticism and extraversion between patients with bipolar I or II and general population subjects or major depressive disorder patients. Journal of Affective Disorders. 2010; 125:42–52. [PubMed: 20171742]

Kendler KS, Aggen SH, Knudsen GP, Roysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. American Journal of Psychiatry. 2011; 168:29–39. [PubMed: 20952461]

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and phobias : the genetic and environmental sources of comorbidity. Psychological Medicine. 1993; 23:361–371. [PubMed: 8332653]

Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. Archives of General Psychiatry. 1995; 52:374–383. [PubMed: 7726718]

Kessler RC, Berglund P, Dernier O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS, National Comorbidity Survey Replication. The epidemiology of major depressive disorder : results from the National Comorbidity Survey Replication (NCS-R). Journal of the American Medical Association. 2003; 289:3095–3105. [PubMed: 12813115]

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2005; 62:593–602. [PubMed: 15939837]

Kessler RC, Merikangas KR, Wang PS. Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the twenty-first century. Annual Review of Clinical Psychology. 2007; 3:137–158.

Klein, D.; Riso, L. Psychiatric disorders : problems of boundaries and comorbidity. In: Costello, CG., editor. In Basic Issues in Psychopathology. Guilford Press; New York: 1994. p. 19-66.

Krueger RF. The structure of common mental disorders. Archives of General Psychiatry. 1999; 56:921–926. [PubMed: 10530634]

Lamers F, van Oppen P, Comijs HC, Smit JH, Spinhoven P, van Balkom AJ, Nolen WA, Zitman FG, Beekman AT, Penninx BW. Comorbidity patterns of anxiety and depressive disorders in a large cohort study : the Netherlands Study of Depression and Anxiety (NESDA). Journal of Clinical Psychiatry. 2011; 72:341–348. [PubMed: 21294994]

Leckman JF, Weissman MM, Merikangas KR, Pauls DL, Prusoff BA. Panic disorder and major depression. Increased risk of depression, alcoholism, panic, and phobic disorders in families of depressed probands with panic disorder. Archives of General Psychiatry. 1983; 40:1055–1060. [PubMed: 6625853]

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Levinson DF, Zubenko GS, Crowe RR, DePaulo RJ, Scheftner WS, Weissman MM, Holmans P, Zubenko WN, Boutelle S, Murphy-Eberenz K, MacKinnon D, McInnis MG, Marta DH, Adams P, Sassoon S, Knowles JA, Thomas J, Chellis J. Genetics of Recurrent Early-onset Depression (GenRED) : design and preliminary clinical characteristics of a repository sample for genetic linkage studies. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2003; 119:118–130.

MacKinnon DF, McMahon FJ, Simpson SG, McInnis MG, DePaulo JR. Panic disorder with familial bipolar disorder. Biological Psychiatry. 1997; 42:90–95. [PubMed: 9209725]

MacKinnon DF, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, Nurnberger J, Reich T, DePaulo JR. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. American Journal of Psychiatry. 2002; 159:30–35. [PubMed: 11772686]

Maier W, Minges J, Lichtermann D. The familial relationship between panic disorder and unipolar depression. Journal of Psychiatric Research. 1995; 29:375–388. [PubMed: 8748062]

Maj M. “Psychiatric comorbidity” : an artefact of current diagnostic systems ? British Journal of Psychiatry. 2005; 186:182–184. [PubMed: 15738496]

Mantere O, Isometsa E, Ketokivi M, Kiviruusu O, Suominen K, Valtonen HM, Arvilommi P, Leppamaki. A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. Bipolar Disorders. 2010; 12:271–284. [PubMed: 20565434]

McElroy SL, Altshuler LL, Suppes T, Keck PE jr, Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. American Journal of Psychiatry. 2001; 158:420–426. [PubMed: 11229983]

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of General Psychiatry. 2007; 64:543–552. [PubMed: 17485606]

Mosing MA, Gordon SD, Medland SE, Statham DJ, Nelson EC, Heath AC, Martin NG, Wray NR. Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia : a twin study. Depression and Anxiety. 2009; 26:1004–1011. [PubMed: 19750555]

Nestadt G, Samuels J, Riddle MA, Liang KY, Bienvenu OJ, Hoehn-Saric R, Grados M, Cullen B. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychological Medicine. 2001; 31:481–487. [PubMed: 11305856]

Nierenberg AA, Trivedi MH, Fava M, Biggs MM, Shores-Wilson K, Wisniewski SR, Balasubramani GK, Rush AJ. Family history of mood disorder and characteristics of major depressive disorder : a STAR*D (sequenced treatment alternatives to relieve depression) study. Journal of Psychiatric Research. 2007; 41:214–221. [PubMed: 16690084]

Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic Interview for Genetic Studies. Rationale, unique features, and training. NIMH Genetics Initiative. Archives of General Psychiatry. 1994; 51:849–859. [PubMed: 7944874]

Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE Jr, McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. Journal of Clinical Psychiatry. 2003; 64:680–690. [PubMed: 12823083]

Potash JB, Toolan J, Steele J, Miller EB, Pearl J, Zandi PP, Schulze TG, Kassem L, Simpson SG, Lopez V, NIMH Genetics Initiative Bipolar Disorder Consortium. MacKinnon DF, McMahon FJ. The bipolar disorderphenome database : a resource for genetic studies. American Journal of Psychiatry. 2007; 164:1229–1237. [PubMed: 17671286]

Regier DA, Rae DS, Narrow WE, Kaelber CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. British Journal of Psychiatry Supplement. 1998; 34:24–28. [PubMed: 9829013]

Sala R, Axelson DA, Castro-Fornieles J, Goldstein TR, Ha W, Liao F, Gill MK, Iyengar S, Strober MA, Goldstein BI, Yen S, Hower H, Hunt J, Ryan ND, Dickstein D, Keller MB, Birmaher B.

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Comorbid anxiety in children and adolescents with bipolar spectrum disorders : prevalence and clinical correlates. Journal of Clinical Psychiatry. 2010; 71:1344–1350. [PubMed: 20868643]

Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJ, ten Have M, Stein MB. Anxiety disorders and risk for suicidal ideation and suicide attempts : a population-based longitudinal study of adults. Archives of General Psychiatry. 2005; 62:1249–1257. [PubMed: 16275812]

Stein MB, Chartier MJ, Hazen AL, Kozak MV, Tancer ME, Lander S, Furer P, Chubaty D, Walker JR. A direct-interview family study of generalized social phobia. American Journal of Psychiatry. 1998; 155:90–97. [PubMed: 9433344]

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and metaanalysis. American Journal of Psychiatry. 2000; 157:1552–1562. [PubMed: 11007705]

Verhagen M, van der Meij A, Franke B, Vollebergh WA, de Graaf R, Buitelaar JK, Janzing JG. Familiality of major depressive disorder and patterns of lifetime comorbidity. The NEMESIS and GenMood studies. A comparison of three samples. European Archives of Psychiatry and Clinical Neuroscience. 2008; 258:505–512. [PubMed: 18575916]

Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. Archives of General Psychiatry. 1979; 36:555–559. [PubMed: 435015]

Weissman MM, Wickramaratne P, Adams PB, Lish JD, Horwath E, Charney D, Woods SW, Leeman E, Frosch E. The relationship between panic disorder and major depression. A new family study. Archives of General Psychiatry. 1993; 50:767–780. [PubMed: 8215801]

Wickramaratne PJ, Weissman MM. Using family studies to understand comorbidity. European Archives of Psychiatry and Clinical Neuroscience. 1993; 243:150–157. [PubMed: 8117758]

Zeger SL, Liang KY, Albert PS. Models for longitudinal data : a generalized estimating equation approach. Biometrics. 1988; 44:1049–1060. [PubMed: 3233245]

Zimmerman M, Chelminski I, McDermut W. Major depressive disorder and axis I diagnostic comorbidity. Journal of Clinical Psychiatry. 2002; 63:187–193. [PubMed: 11926716]

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Table 1

Clinical features of co-morbid anxiety disorders in the major depressive disorder sample

Clinical feature	Cases with co-morbid panic disorder	Cases with co-morbid social phobia	Cases with co-morbid specific phobia	Cases with co-morbid OCD	Cases with no co-morbid anxiety
Subjects, n (% of overall sample)	427 (24.7)	233 (13.5)	168 (9.7)	128 (7.4)	1039 (60.2)
Mean age, years (S.E.)	42.4 (0.6)	41.5 (0.8)	43.1 (1.0)	38.3 (1.1)***	42.8 (13.0)
Female, n (%)	354 (82.9)*	188 (80.7)	153 (91.1)***	96 (75)	809 (77.9)
Married, n (%)	228 (53.4)	120 (51.5)	96 (57.1)	65 (50.8)	556 (53.5)
Mean length of education, years (S.E.)	14.7 (0.1)***	14.6 (0.2)***	14.8 (0.2)	15.3 (0.3)	15.7 (2.9)
Employed, n (%)	348 (81.5)*	196 (84.1)	139 (82.7)	110 (85.9)	900 (86.6)
Mean MDD onset age, years (S.E.)	18.3 (0.4)***	18.4 (0.5)**	19.1 (0.6)	16.0 (0.6)***	19.8 (8.2)
Mean number of MDEs, n (S.E.)	7.3 (0.5)**	7.8 (0.7)	8.2 (1.0)**	8.6 (1.3)	6.4 (10.2)
Mean age at onset of anxiety, years (S.E.)	24.7 (0.6)	14.6 (0.5)	14.7 (0.9)	17.6 (1.0)	–
Alcohol abuse/dependence, n (%)	107 (25.1)	61 (26.2)	39 (23.2)	32 (25.0)	224 (21.6)
Substance abuse/dependence, n (%)	105 (24.6)	69 (29.6)*	38 (22.6)	37 (28.9)	232 (22.3)
Mean age of first treatment, years (S.E.)	24.7 (0.5)	25.3 (0.8)	26.0 (0.9)	20.5 (0.9)***	25.3 (11.0)
Psychiatric hospitalization, n (%)	152 (35.6)***	82 (35.2)**	40 (23.8)	49 (38.3)**	251 (24.2)
History of suicide attempt, n (%)	114 (26.7)**	66 (28.3)**	42 (25)	44 (34.4)***	199 (19.2)
Treatment with ECT, n (%)	32 (7.5)**	12 (5.2)	5 (3.0)	15 (11.7)***	35 (3.4)
Additional anxiety disorder, n (%)					
Panic disorder	–	97 (41.6)	76 (45.2)	61 (47.7)	–
Social phobia	97 (22.7)	–	53 (31.6)	28 (21.9)	–
Specific phobia	76 (17.8)	53 (22.8)	–	16 (12.5)	–
OCD	61 (14.3)	28(12.0)	16 (9.5)	–	–
Mean number of anxiety disorders (S.E.)	2.1 (0.02)	1.8 (0.05)	1.9 (0.06)	1.8 (0.07)	–

MDD, Major depressive disorder; OCD, obsessive-compulsive disorder; S.E., standard error; MDE, major depressive episode; ECT, electroconvulsive therapy.

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$ (comparisons between cases with a specific co-morbid anxiety disorder versus cases without any co-morbid anxiety disorder).

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Table 2

Clinical features of co-morbid anxiety disorders in the bipolar disorder sample

Clinical feature	Cases with co-morbid panic disorder	Cases with co-morbid social phobia	Cases with co-morbid specific phobia	Cases with co-morbid OCD	Cases with no co-morbid anxiety
Subjects, n (% of overall sample)	343 (22.8)	117 (7.8)	144 (9.6)	89 (5.9)	1009 (67.2)
Mean age, years (S.E.)	40.5 (0.61) *	40.6 (1.1)	41.8 (0.9)	36.6 (1.1) ***	42.8 (0.4)
Female, n (%)	264 (77.0) ***	78 (66.7) *	116 (80.6) ***	67 (75.3) ***	561 (55.6)
Married, n (%)	168 (49.0)	52 (44.4)	82 (56.9) *	42 (47.2)	459 (45.5)
Mean length of education, years (S.E.)	13.9 (0.2) ***	13.7 (0.3) **	13.7 (0.3) **	14.3 (0.3)	14.6 (0.1)
Employed, n (%)	236 (68.8)	79 (69.3)	91 (64.5)	60 (69.0)	721 (72.5)
Mean MDD onset age, years (S.E.)	18.6 (0.5) ***	19.0 (1.0) ***	19.5 (0.9) ***	15.9 (0.8) ***	21.8 (0.3)
Mean number of MDEs, n (S.E.)	18.7 (2.0) ***	18.1 (3.8) *	16.0 (2.3) ***	19.7 (3.6) ***	10.3 (0.9)
Mean age at onset of anxiety, years (S.E.)	23.7 (0.6)	12.8 (0.7)	13.2 (0.8)	18.3 (1.2)	–
Alcohol abuse/dependence, n (%)	160 (46.6) **	55 (47.0) *	54 (37.5)	39 (43.8)	372 (36.9)
Substance abuse/dependence, n (%)	52 (15.2) **	13 (11.1)	23 (16.0) *	11 (12.4)	101 (10.1)
Mean age of first treatment, years (S.E.)	22.7 (0.5)	22.4 (0.9)	23.3 (0.8)	20.8 (0.9) **	24.0 (0.3)
Psychiatric hospitalization, n (%)	258 (75.6)	81 (71.1)	91 (65.0)	59 (68.6)	719 (72.3)
History of suicide attempt, n (%)	161 (46.9) ***	48 (41.0) *	70 (48.6) ***	43 (48.3) ***	299 (29.6)
Treatment with ECT, n (%)	40 (11.7)	12 (10.3)	15 (10.4)	11 (12.4)	110 (11.0)
Additional anxiety disorder, n (%)					
Panic disorder	–	56 (47.8)	67 (46.5)	50 (56.2)	–
Social phobia	56 (16.3)	–	36 (25.0)	18 (20.2)	–
Specific phobia	67 (19.5)	36 (30.8)	–	27 (30.3)	–
OCD	50 (14.5)	18 (15.4)	27 (18.8)	–	–
Mean number of anxiety disorders (S.E.)	1.5 (0.04)	1.9 (0.08)	1.9 (0.07)	2.1 (0.09)	–

OCD, Obsessive-compulsive disorder; S.E., standard error; MDD, major depressive disorder; MDE, major depressive episode; ECT, electroconvulsive therapy.

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$ (comparisons between cases with a specific co-morbid anxiety disorder versus cases without any co-morbid anxiety disorder).

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Table 3

Familial aggregation of co-morbid anxiety disorders in the major depressive disorder sample[a]

Relative diagnosis	Diagnosis in relatives		aOR[1][b] (95% CI)	p	aOR[2][c] (95% CI)	p	aOR[3][d] (95% CI)	p
	Proband with anxiety disorder, n (%)	Proband without anxiety disorder, n (%)						
Panic disorder	99/250 (39.6)	179/801 (22.4)	2.32 (1.69–3.19)	<0.001	2.22 (1.60–3.07)	<0.001	1.98 (1.41–2.78)	<0.001
Social phobia	30/137 (21.9)	133/914 (14.6)	1.58 (0.99–2.53)	0.057	1.40 (0.86–2.30)	0.18	1.32 (0.80–2.19)	0.28
Specific phobia	22/104 (21.2)	85/947 (9.0)	2.93 (1.69–5.10)	<0.001	2.42 (1.36–4.33)	0.003	2.43 (1.35–4.38)	0.003
OCD	14/66 (21.2)	76/985 (7.7)	2.88 (1.49–5.56)	0.002	2.64 (1.36–5.15)	0.004	2.60 (1.29–5.24)	0.008

aOR, Adjusted odds ratio; CI, confidence interval; OCD, obsessive-compulsive disorder.

[a] All relatives with recurrent MDD diagnosis.

[b] Adjusted for age at interview, site of ascertainment, and sex.

[c] Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives.

[d] Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives and probands.

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Table 4

Familial aggregation of co-morbid anxiety disorders in the bipolar disorder sample[a]

Relative diagnosis	Diagnosis in relatives		aOR[1][b] (95% CI)	p	aOR[2][c] (95% CI)	p	aOR[3][d] (95% CI)	p
	Proband with anxiety disorder, n (%)	Proband without anxiety disorder, n (%)						
Panic disorder	67/208 (32.2)	119/642 (18.5)	1.95 (1.33–2.86)	0.001	1.70 (1.14–2.54)	0.009	1.52 (1.00–2.30)	0.047
Social phobia	7/67 (10.5)	59/783 (7.5)	1.38 (0.61–3.11)	0.44	1.13 (0.46–2.72)	0.80	1.00 (0.39–2.55)	1.00
Specific phobia	16/76 (21.1)	75/774 (9.7)	2.38 (1.25–4.50)	0.008	1.82 (0.92–3.58)	0.084	1.94 (0.95–3.96)	0.069
OCD	14/64 (21.9)	31/786 (3.9)	6.84 (3.29–14.2)	<0.001	4.62 (2.11–10.12)	<0.001	3.10 (1.31–7.09)	0.009

aOR, Adjusted odds ratio; CI, confidence interval; OCD, obsessive-compulsive disorder; BPI, bipolar I disorder; BPII, bipolar II disorder.

[a] All relatives with BPI or BPII diagnoses.

[b] Adjusted for age at interview, site of ascertainment, and sex.

[c] Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives.

[d] Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives and probands.