The Heritability of Bipolar Affective Disorder and the Genetic Relationship to Unipolar Depression

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Background: Twin studies of bipolar affective disorder (BPD) have either been small or have not used explicit diagnostic criteria. There has been little use of genetic model fitting and no analyses to explore the etiological overlap with unipolar depression (UPD).

Methods: Sixty-seven twin pairs, 30 monozygotic and 37 dizygotic, in which the proband had BPD were ascertained, and lifetime diagnoses were made using DSM-IV criteria. Univariate models were applied to estimate the contribution of additive genetic and environmental effects. Bipolar data were then combined with those from 68 monozygotic and 109 dizygotic pairs in which the proband had UPD. Two models were explored: a classic 2-threshold approach, in which BPD and UPD occupy the same continuum of liability but differ in severity, and a correlated liability model of mania and depression.

Results: Heritability of BPD was estimated at 85% (95% confidence interval [CI], 0.73-0.93) using narrow concordance and 89% (95% CI, 0.61-1.0) using broad concordance, with no shared environmental effects detected. A 2-threshold model was an unsatisfactory fit. Fitting a correlated liability model revealed a genetic correlation of 0.65 (95% CI, 0.58-0.75) between mania and depression and a correlation of 0.59 (95% CI, 0.15-0.84) for nonfamilial environment. Approximately 71% of the genetic variance for mania was not shared with depression.

Conclusions: As defined by the DSM-IV, BPD is highly heritable. There are substantial genetic and nonshared environmental correlations between mania and depression, but most of the genetic variance in liability to mania is specific to the manic syndrome.

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heritability was also suggested by the analysis of the Swedish twin register data, but the very small number of twin pairs inevitably meant that confidence intervals on estimates of heritability were wide.

A third problem is the relationship between UPD and BPD. Family genetic studies have been influential in gaining widespread acceptance of the proposal, originally put forward by Leonhard,12 that major affective disorders can be divided into these 2 broad types. However, the consistent finding that there is an excess of both UPD and BPD among the relatives of probands with BPD suggests at least some degree of genetic overlap.1,2 The extent of this presumed overlap has not yet been quantified. This presents problems for gene-finding studies, which, to date, have largely concentrated on BPD in families with multiple affected individuals.1 The difficulty then arises as to how to classify the relatives in such families who are affected by UPD, and many researchers have dealt with this by analyzing their data under 2 or more diagnostic models, for example, a narrow model, in which only subjects with BPD are classified as affected, and a broad model, in which relatives with UPD or BPD are classified as affected.

In this study, we estimate the heritability of operationally defined BPD and carry out model fitting to assess the extent to which the same or different genes contribute to UPD and BPD using data from the Maudsley Hospital Twin Register in London, England. This sample is the largest clinically ascertained series of twins with affective disorders that has been studied to date.

METHODS

SUBJECTS

Probands were ascertained from the Maudsley Twin Register. The register contains all patients of multiple births since 1948 who attended any facility of the Maudsley and Bethlem Royal hospitals for clinical reasons unrelated to being a twin and who had a same-sex co-twin surviving at least until the age of 15 years. The twins included in the present study were ascertained via probands who had an initial hospital diagnosis of affective disorder, psychosis (mania and depressive psychosis), or both. The same ascertainment procedures were used in both series, except that the ascertainment period was 1948-1985 for the affective disorder series and 1948-1992 for the psychosis series. As reported in a previous study,13 our initial focus on the affective disorder series was on UPD, so the 34 twin pairs in that study who were found to have had 1 or more episodes of mania were removed from the analysis. In the psychosis study reported by Cardno et al,14 there were 38 pairs in which the proband had 1 or more episodes of mania or hypomania. Twenty-five pairs were included in both studies. Therefore, combining the 2 data sets gives a total of 67 pairs, 30 monozygotic and 37 dizygotic, ascertained via probands and/or co-twins with BPD. One of the monozygotic pairs contained a double co-twin and was counted twice (ie, there were 29 independent monozygotic pairs). The assignment of zygosity was based on blood types and/or questionnaires, as previously described.8,13 There were 68 monozygotic and 109 dizygotic pairs ascertained via probands with UPD.13

DIAGNOSTIC ASSESSMENT

Diagnoses were based on all available clinical information concerning each twin, including a research interview. As previously described,8,13 research interviews14,15 were conducted with 73% of probands and 60% of co-twins from the psychosis series and 40% of probands and 40% of co-twins from the affective disorder series. In addition, information was gathered from case notes, case summaries, and relatives and primary care physicians. Diagnostic information was assessed by researchers blind to zygosity and the identity of the twins. Main lifetime diagnoses of DSM-III-R disorders were made using the OPCRIT checklist and its associated computer diagnostic program17 for the subjects in the psychosis series. Interrater agreement for affective disorders of all types averaged 91% (κ=0.68). For the 34 pairs in the affective disorder series, nonblind ratings on a modified OPCRIT checklist were made by one of us (P.M.) and checked against ratings blind to zygosity and co-twin information made by another author (M.A.). Agreement for all types of DSM-IV affective disorder was 97% (κ=0.90). Any diagnostic differences in the 25 overlapping pairs were resolved by consensus, and DSM-III-R diagnoses were translated to DSM-IV diagnoses. To allow adequate numbers for statistical analysis, bipolar I and bipolar II disorders were lumped together.

GENETIC ANALYSIS

The 30 monozygotic and 37 dizygotic proband–co-twin pairs were used to calculate probandwise concordance rates. The population lifetime morbid risk for BPD (mania and depression or mania alone) was 0.32%, which was estimated using Camberwell case register data (Camberwell is the old borough of London where Maudsley Hospital is located), as previously described.8 Similarly, Camberwell data provide a sex-averaged lifetime risk estimate for DSM-IV UPD of approximately 6%.13

UNIVARIATE MODEL FITTING

The data on the 67 BPD proband–co-twin pairs were first analyzed under a liability-threshold model with a single threshold using the Mx program.14 Two sets of biometrical model fitting were then conducted. In the first, concordance was defined narrowly; only pairs in which the co-twin had a diagnosis of BPD were classified as affected. Second, a broader diagnostic perspective was taken, and pairs in which the co-twin had either UPD or BPD were classified as concordant. For both the broad and the narrow definitions of concordance, 4 models were fitted: a model containing additive genetic (A), common environmental (C), and specific environmental (E) variance; an additive genetic and specific environmental variance model (AE); a common environmental and specific environmental variance model (CE); and an individual specific environmental model (E). Models were compared using χ² difference for nested models, and the Akaike information criterion (AIC), which is equal to χ² minus twice the df was used as an aid to selecting the best-fitting model on the grounds of parsimony and goodness of fit.

MODELLING THE RELATIONSHIP BETWEEN UPD AND BPD

Two approaches were adopted, both of which are extensions of the simple single-threshold model.

Multiple Thresholds

Reich et al10 have pointed out that when a disorder exists in 2 forms that show familial overlap and when 1 form is comparatively common, the broad form, and the other is less common, the narrow form, the relationship between the 2 can be explored using a 2-threshold model. If the 2 forms are on the same continuum of liability, with the narrow form occurring
beyond a more extreme threshold then the broad form, an isocorrelational model should fit. That is, the correlations within the first disorder, r_{11}, and within the second disorder, r_{22}, should be equal to the cross-correlations r_{12} and r_{13}. If, on the other hand, the 2 disorders are independent (ie, show a familial overlap that is no different from chance), then the cross-disorder correlations r_{12} and r_{13} will not differ significantly from 0. The isocorrelational and the independent model can be compared with the general model in which all 4 correlations are estimated and, again, models can be compared using χ² analysis and the best-fitting model selected with the aid of the AIC. These analyses were performed using the FORTRAN program TWIN2.²⁰

Correlated Liability

In contrast to the multiple-threshold approach, which retains the DSM-IV hierarchy whereby each subject has a single Axis I diagnosis, the correlated liability approach allows individuals to be classified as having mania, depression, or both. Again the correlation between mania and depression is partitioned into additive genetic (A), common environmental (C), and specific environmental (E) sources in a Cholesky de-composition (Figure). For all 3 sources of variation, there are common factors affecting both disorders and specific factors influencing the second disorder only. The effect of a common additive genetic factor, A_c, on the first disorder is represented by the path coefficient ac. The effect on the second disorder is represented by a_c’. The effect of specific additive genetic factors, A_s, on the second disorder is represented by the path coefficient a_s. In addition to the relative magnitudes of the A, C, and E effects, the correlation between the 2 liabilities can be estimated for each of the components of variance (r_a, r_c, and r_e) indicating the extent to which genetic and environmental effects are shared between the 2 disorders. Correlated liability models were fitted using the Mx program,¹⁵ with a goodness of fit assessed by likelihood ratio χ² analysis. Again, nested models were compared by χ² difference and AIC.

As we have described elsewhere,²¹ a complication of fitting this type of model is that when ascertainment is probandwise, pairs in which neither twin is affected are omitted from observation. This introduces a potential bias that can be adjusted for by dividing the likelihood of the data by the proportion of the population remaining after ascertainment. Additionally, 3 ascertainment parameters (b, c, and d) were modeled to account for unequal ascertainment probability across disorders. The scalar b represents adjustment of the probability of ascertaining probands with mania only, c of ascertaining probands with depression only, and d of ascertaining probands with both disorders. With the given data set, only 2 of these can be estimated; therefore, we fixed b to 1, and c and d were estimated.

RESULTS

The probandwise concordance in the 67 pairs ascertained via probands with BPD is presented in Table 1 for comparison, we also provide concordances for pairs ascertained via probands with UPD, as previously reported.¹² Among the twins ascertained via probands with BPD, monozygotic concordance was significantly higher than dizygotic concordance, whether concordance was defined broadly (co-twin had either UPD or BPD) (χ² = 15.69; P < .001) or narrowly (co-twin had BPD) (χ² = 11.99; P < .001; Fisher exact test P < .001).

The results of univariate model fitting are presented in Table 2. For both definitions of concordance, the data were best explained by an AE model with a heritability of 0.89 (95% confidence interval [CI], 0.61-1.00, with the upper estimate at a bound) for the broad diagnosis and a heritability of 0.85 (95% CI, 0.73-0.93) for the narrow diagnosis. The CE and E models could be rejected.

TWO-THRESHOLD MODEL

Because we found no evidence of shared environmental effects, either in our univariate analysis of the bipolar sample or in our previous analysis of twins ascertained via probands with UPD,¹² we fit a simplified 2-threshold model in which the only source of correlation was additive genetic effects, such that the within- and across-disorder tetrachoric correlations for monozygotic pairs were twice that for dizygotic pairs.

The isocorrelational model was a poor fit (χ² = 14.79; P = .04), and the independent model was a very poor fit, (χ² = 5517.2; P < .001). The data are best explained by the general model in which the within- and across-disorder correlations are unconstrained (χ² = 1.76; P = .78). We can conclude that BPD and UPD are not genetically independent, but a straightforward 2-threshold model, in which BPD is a more severe form of the disorder on the same continuum of liability as UPD, can be rejected.

CORRELATED LIABILITY

Fitting a correlated liability model requires that we relax the usual hierarchical diagnostic rules and classify the subjects as having mania, depression, or both. Twenty-one of 98 monozygotic probands and 25 of 146 dizygotic probands had both depression and mania corresponding to within-proband across-disorder correlations in liability of 0.64 (95% CI, 0.52-0.74) and 0.63 (95% CI, 0.53-0.72), respectively. The within-pair concordances and correlations in liability within and across disorders are presented in Table 3. These were then used in fitting the correlated liability models, the results of which are summarized in Table 4. Adding the ascertainment parameters c and d improved the fit of the ACE model substantially, and there was not a significant worsening.
of fit when the family environment, C, was constrained to be 0, suggesting again that additive genetic factors are sufficient to explain the familiality and covariance of mania and depression.

We next tested the effects of fixing the ascertainment parameters. The results indicate that the c parameter is significantly different from 1, whereas d is not. This suggests that probands with only depression are less likely to be ascertained than those who have both depression and mania.

We also fitted models not presented in Table 4

| Table 1. Probandwise Concordance for Unipolar (UPD) and Bipolar (BPD) Affective Disorder (AD) |
|---------------------------------------------|-------------|----------------|
| Co-Twin Diagnosis | Monozygot | Dizygotic |
| Proband Diagnosis | N | UPD, % | BPD, % | Total AD, % | N | UPD, % | BPD, % | Total AD, % |
| BPD | 30 | 26.7 | 40 | 66.7 | 37 | 13.5 | 5.4 | 18.9 |
| UPD | 68 | 44.1 | 1.5 | 45.6 | 109 | 20.2 | 0.0 | 20.2 |

| Table 2. Univariate Model Fitting on Twins Ascertained via Bipolar Probands* |
|---------------------------------------------|-------------|-------------|
| Diagnosis | Model | A | C | E | df | χ² | P Value | AIC |
| Broad† | ACE | 0.89 | 0 | 0.11 | NA | 2.70 | NA | NA |
| | AE | 0.89 | [0.0] | 0.11 | 1 | 2.70 | .52 | 0.695 |
| | CE | [0.0] | 0.64 | 0.36 | 1 | 21.02 | <.001 | 19.02 |
| | E | [0.0] | 0.15 | 0.1 | 2 | 73.61 | <.001 | 69.61 |
| Narrow‡ | ACE | 0.85 | 0 | 0.15 | NA | 0.03 | NA | NA |
| | AE | 0.85 | [0.0] | 0.15 | 1 | 0.03 | .86 | −1.97 |
| | CE | [0.0] | 0.69 | 0.31 | 1 | 12.75 | <.001 | 10.75 |
| | E | [0.0] | [0.0] | 1 | 2 | 103.03 | <.001 | 99.03 |

| Table 3. Within-Pair Concordances and Correlations in Liability, Within and Across Disorders |
|---------------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Diagnosis | Co-twin | No. (%) of Subjects | Total | Correlation in Liability (95% CI) |
| | Monozygot | Dizygotic | Monozygot | Dizygotic |
| Depression | Depression | 43 (48)/89 | 27 (20)/134 | 0.76 (0.65-0.85) | 0.37 (0.23-0.50) |
| Mania | Mania | 12 (40)/30 | 2 (5)/37 | 0.85 (0.73-0.93) | 0.41 (0.12-0.63) |
| Depression | Mania | 8 (10)/79 | 2 (11)/134 | 0.56 (0.44-0.66) | 0.23 (0.08-0.37) |
| Mania | Depression | 15 (50)/30 | 7 (19)/37 | |

| Table 4. Fitting the Correlated Liability Model of Depression and Mania* |
|---------------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Model | χ² (df) | P Value | AIC | r_t | r_s | Depression | Mania |
| | A | C | E | A | C | E |
| ACE | 145.2 (15) | <.001 | 115.2 | 0.76 | 0.54 | 0.66 | 0.04 | 0.30 | 0.81 | 0.07 | 0.12 |
| c and d Free | 14.5 (13) | .24 | −11.5 | 0.69 | 0.45 | 0.67 | 0.05 | 0.28 | 0.80 | 0.05 | 0.15 |
| AE | 14.6 (16) | .44 | −17.4 | 0.58 | 0.47 | 0.71 | [0.0] | 0.29 | 0.85 | [0.0] | 0.15 |
| c = 1; d Free | 36.9 (17) | .004 | 2.9 | 0.33 | 0.10 | 0.72 | [0.0] | 0.28 | 0.84 | [0.0] | 0.16 |
| c Free; d=1† | 14.6 (17) | .62 | −19.4 | 0.65 | 0.59 | 0.72 | [0.0] | 0.28 | 0.85 | [0.0] | 0.15 |
| | (0.58-0.75) | (0.15-0.84) | (0.60-0.81) | (0.19-0.40) | (0.74-0.93) | (0.07-0.26) |

Abbreviations: A, C, and E, proportions of variance explored by additive genetic, common environmental, and specific environmental effects, respectively; AIC, Akaike information criterion; NA, not applicable.

*Parameters in brackets are constrained.

†Pairs were classified as concordant if the co-twin had unipolar or bipolar disorder.
‡Pairs were classified as discordant if the co-twin had bipolar disorder.

Abbreviation: CI, confidence interval.

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We first applied a classic 2-threshold model and BPD by combining the 67 pairs in the BPD series with an estimated best explains the data on the grounds of parsimony and goodness of fit. The heritability estimate for mania based on this model was 0.85 (95% CI, 0.74-0.93) and that for depression was 0.72 (95% CI, 0.60-0.81). The genetic variance of mania explained by common genetic influences with depression was estimated to be 0.25, and the variance explained by specific genetic influences was estimated to be 0.60.

The genetic variance in liability to mania is determined by the effect of a common additive genetic factor, $A_s$, which influences the first and second disorder (represented by the path $a'$), and an additive genetic factor specific to mania, $A_s$ (with the corresponding path $a$). The proportion of variance in liability to mania explained by common genetic influences with depression ($a'/a'_1+a,s+e')$ was estimated to be 0.25 (2.499/9.971), and the proportion of variance explained by specific genetic influences was 0.60 ($a/a'_1+a,s+e')$. The sum of the proportions of variance in liability to mania explained by both specific and common $A$ factors sum to the heritability estimate (0.85). Therefore, 0.60/0.85, or approximately 71%, of the genetic variance in liability to mania is estimated to be specific to mania and not shared with depression.

COMMENT

We reported the concordance rates of a series of twins ascertained through 67 probands with BPD. This is the largest twin study of BPD since that of Bertelsen et al. and it has a very similar pattern of findings; we found a broad concordance of 67% in monozygotic twins and 19% in dizygotic twins compared with a broad proband concordance of 79% in monozygotic twins and 19% in dizygotic twins in the study by Bertelsen et al. However, our study includes several methodological advances; we made the diagnoses according to reliable operational criteria (DSM-IV), the diagnostic information on co-twins was assessed blind to zygosity and status (ie, whether the subject was a proband or co-twin), and modern model fitting procedures were applied.

Univariate model fitting resulted in estimates of heritability in excess of 80% (with a lower confidence limit of more than 70%) whether a broad or narrow diagnostic perspective was taken, suggesting that all of the familiality of BPD could be accounted for by additive genetic effects with no contribution from family environment.

We next examined the relationship between UPD and BPD by combining the 67 pairs in the BPD series with 177 twins ascertained via probands with UPD from the same register. We first applied a classic 2-threshold model to test the assumption that BPD and UPD occupy the same continuum of liability, whereby all affected individuals lie beyond the first threshold for being affected but only those who exceed a second, more extreme threshold are diagnosed with BPD. Applying the isocorrelational test, as suggested by Reich et al., we rejected this model. We were also able to reject a model in which BPD and UPD are etiologically distinct. It could be argued that an independent model is, in any case, implausible because in our 2-threshold analysis we classified subjects using conventional diagnostic rules, according to which individuals receive a single diagnosis and BPD trumps UPD. However, we then explored a correlated liability model, in which subjects were classified as having no disorder, 1 disorder (either mania or depression), or 2 disorders (mania and depression).

Fitting a model of this type necessitated applying an ascertainment correction to take into account the fact that we ascertained our twins through probands affected either by mania or depression. We also included estimation of ascertainment parameters in our model, which, perhaps unsurprisingly, suggested that the probability of ascertainment is higher for individuals with both mania and depression than for those with depression alone. The genetic correlation between mania and depression was substantial, 0.65, and could not be dropped from the model without worsening the fit. The heritability estimate for mania, 0.85, was similar to that obtained in the univariate model fitting of BPD. This left an estimated 15% of variance in liability to mania explained by individual specific or nonfamilial environmental effects. Given this comparatively modest estimate of environmental effects, it is of interest that the correlation between the environmental influences for mania and depression were estimated to be substantial (0.59, albeit with a large confidence interval), and environmental correlation could not be dropped from the model without worsening the fit. We were also able to estimate the size of the specific genetic influence for mania and found that, although the genetic effects on mania and depression are correlated, most of the genetic influence on liability to mania, approximately 71%, is distinct from the genetic liability to depression.

The main limitation of this study is the sample size. Our analyses were carried out on 67 twin pairs ascertained via probands with BPD and 177 pairs ascertained via probands with UPD, giving us a total of 244 pairs, which constitutes the largest clinically ascertained series of twins with affective disorder yet reported. However, the sample size is small by modern twin study standards, especially when compared with studies of other behaviors and disorders based on population-derived samples. This means that we are able to say with some confidence that BPD is substantially heritable. However, that we did not find any evidence of common environmental effects is not conclusive evidence that such effects do not exist; typically, much larger samples are required to detect small familial environmental effects.

Although most subjects underwent a structured or semi-structured interview, a substantial minority were not interviewed, so we relied on a combination of written material, such as case notes, and information provided by informants. Nevertheless, we were able to achieve high
levels of interrater agreement when data from all sources were combined.

Finally, our morbid risk estimates were extrapolated from local case register data rather than being based directly on population estimates. Nevertheless, the pattern of results and the estimates of heritability were similar to those of Kendler et al[2] from their population-based twin study. Kendler et al also assumed somewhat higher morbid risks of mania or mania plus hypomania. We therefore checked the effect of assuming a higher population risk of BPD of 1%. This resulted in a slight reduction in the estimate of heritability in the univariate analysis to 0.80 but did not change the pattern of results otherwise. In particular, the fit of the 2-threshold isocorrelational model became even poorer ($\chi^2 = 40.89; P < .001$).

Our study confirms that there is a large genetic contribution to the variance in liability for DSM-IV BPD and showed substantial genetic overlap with UPD. However, a liability threshold model in which UPD and BPD occupy the same continuum, but with BPD being the more severe of the two, does not fit. The relationship between BPD and UPD is better described by a correlated liability model. Fitting such a model shows us that there are significant genetic and nonfamilial environmental correlations between mania and depression but that most of the genetic variance in liability to mania is specific to the manic syndrome.

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Conclusions

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