Family Study of Affective Spectrum Disorder

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Background: Affective spectrum disorder (ASD) represents a group of psychiatric and medical conditions, each known to respond to several chemical families of antidepressant medications and hence possibly linked by common heritable abnormalities. Forms of ASD include major depressive disorder (MDD), attention-deficit/hyperactivity disorder, bulimia nervosa, cataplexy, dysthyemic disorder, fibromyalgia, generalized anxiety disorder, irritable bowel syndrome, migraine, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia. Two predictions of the ASD hypothesis were tested: that ASD, taken as a single entity, would aggregate in families and that MDD would coaggregate with other forms of ASD in families.

Methods: Probands with and without MDD, together with their first-degree relatives, were interviewed using the Structured Clinical Interview for DSM-IV and a supplemental interview for other forms of ASD. The familial aggregation and coaggregation of disorders were analyzed using proband predictive logistic regression models, including a novel bivariate model for the presence or absence of each of 2 disorders in a relative as predicted by the presence or absence of each of 2 disorders in the associated proband.

Results: In the 178 interviewed relatives of 64 probands with MDD and 152 relatives of 58 probands without MDD, the estimated odds ratio (95% confidence interval) for the familial aggregation of ASD as a whole was 2.5 (1.4-4.3; P=.001) and for the familial coaggregation of MDD with at least one other form of ASD was 1.9 (1.1-3.2; P=.02).

Conclusions: Affective spectrum disorder aggregates strongly in families, and MDD displays a significant familial coaggregation with other forms of ASD, taken collectively. These results suggest that forms of ASD may share heritable pathophysiologic features.

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If the hypothesized common causal factors in ASD are heritable, then ASD as a whole should aggregate within families, and the individual forms of ASD should coaggregate in families. (We use aggregate to refer to the clustering of a single disorder within families and coaggregate to refer to the clustering of 2 disorders with one another in families.) To date, however, most studies that tested these questions have examined only the coaggregation of individual pairs of disorders, where one member of the pair is almost always MDD (eg, MDD with bulimia nervosa). Collectively, studies of this design have provided evidence for a significant coaggregation of MDD with attention-deficit/hyperactivity disorder, 13 bulimia nervosa, 14-19 panic disorder, 20-22 and social phobia 23; equivocal evidence for coaggregation of MDD and generalized anxiety disorder 24,25; and little evidence for coaggregation in the one study of migraine 26 (meta-analysis evaluating these studies is available from the authors on request). However, these results are tentative in that only a small number of studies meet minimum standards to permit analysis.

Twin studies have provided similar evidence for coaggregation and have additionally suggested common genetic factors among various forms of ASD. These forms include MDD and generalized anxiety disorder, 26,27 MDD and social phobia, 28 MDD and bulimia nervosa, 29 and generalized anxiety disorder and panic disorder. 30 A study 31 of MDD and premenstrual dysphoric disorder, however, suggested only a small common genetic factor. Finally, in the only study large enough to evaluate adequately the coaggregation of several forms of ASD simultaneously, Kendler and colleagues 32 found evidence of a common genetic factor in panic disorder and bulimia nervosa and in MDD and generalized anxiety disorder. To date, however, no study has examined how ASD, viewed as a single entity, aggregates within families. Accordingly, we undertook a family interview study to evaluate the familial aggregation of ASD and the coaggregation of MDD (the most common form of ASD) with other forms of ASD, taken individually and collectively.

An administrator approached and screened candidate subjects for both proband groups. Potentially qualifying probands were then seen by a proband interviewer (C.D. or A.H.) blinded to information about the proband’s relatives. If this interview confirmed that the proband qualified for the MDD or non-MDD groups, the administrator then scheduled consenting first-degree relatives to see the family interviewer (B.M.), who was blinded to information about the proband. The administrator mingled relatives of MDD and non-MDD probands together so that the family interviewer remained blinded regarding the group status of relatives.

INTERVIEW PROCEDURES

We interviewed probands and relatives using the German version 33 of the Structured Clinical Interview for DSM-IV (SCID) 34 together with a supplemental interview in SCID format 35 (German version available on request), covering fibromyalgia, irritable bowel syndrome, migraine, chronic fatigue syndrome, narcolepsy, cataplexy, Tourette disorder, and kleptomania. The only forms of ASD not covered by these instruments were attention-deficit/hyperactivity disorder and premenstrual dysphoric disorder, because the former was difficult to diagnose reliably without contemporaneous records of childhood behavior and the latter without diaries of mood states. 36 We diagnosed psychiatric forms of ASD by DSM-IV criteria and medical forms using criteria published by official bodies 37-40 as described previously, 13 except that our criteria for migraine used modifications for epidemiologic studies derived from Merikangas et al 41 that required (1) severe headaches and (2) the presence of both photophobia or phonophobia and nausea or vomiting. We assessed lifetime diagnoses except for generalized anxiety disorder and dysthymia, which the SCID assesses only as current diagnoses.

The family interviewer also interviewed the available relatives regarding deceased or unavailable relatives, but this information was not used in the analysis because it proved to be too insensitive and because sensitivity varied by diagnosis. Specifically, there were only 25 diagnoses of forms of ASD (20 MDD and 5 non-MDD forms of ASD) made among the 375 noninterviewed relatives (average 0.067 per relative compared with 0.53 per relative among the interviewed relatives).

The proband interviewers reviewed interview results with an American investigator (H.G.P.) blinded to family history information. We assigned diagnoses only by consensus of both the Austrian and American investigators. The only exception to this conservative rule occurred in the case of the diagnosis of possible MDD in a control proband; if either of the 2 investigators suspected MDD in a control proband, that proband and family were excluded. The family interviewer similarly reviewed all of her results with another American investigator (J.H.H.) blinded to proband information, with diagnoses again assigned to interviewed relatives only by consensus of the 2 investigators.

STATISTICAL ANALYSIS

Hypotheses

The main hypotheses of the study were (1) that ASD, viewed as a single entity, would aggregate in families and (2) that MDD would coaggregate with other forms of ASD, individually and collectively. In the latter analysis, we recognized that we would have limited power to detect the coaggregation of MDD with other individual forms of ASD.

Familial Aggregation of ASD

To evaluate the aggregation of ASD as a whole, we used a logistic regression model, with the presence or absence of 1 or
more forms of ASD in a relative as the outcome and the presence or absence of 1 or more forms of ASD in the proband associated with that relative as the predictor. (Probands with ASD included all probands with MDD plus probands without MDD who had at least one other form of ASD.) We have discussed this model further elsewhere (see equation 1 in the article by Hudson et al).

Familial Coaggregation of MDD With Other Forms of ASD

To test the coaggregation of MDD with other forms of ASD, either individually or collectively, we used a multivariate logistic regression model that we have developed, with bivariate disorder status of a relative (that is, the presence or absence of each of 2 disorders, denoted disorder A and disorder B) as the outcome and bivariate disorder status of the corresponding proband as the predictor. We have presented this bivariate proband predictive model in detail elsewhere (see model 4 in the article by Hudson et al) and have demonstrated that it is more flexible in modeling and testing than previous univariate logistic regression and multinomial regression models. The model estimates 4 main parameters simultaneously, yielding odds ratios (ORs) for 4 main effects: the aggregation of disorder A, the aggregation of disorder B, the co-aggregation of disorder A with disorder B, and the co-occurrence of disorder A with disorder B.

This basic model incorporates 2 assumptions. The first is that the ORs for aggregation and coaggregation are not influenced by a proband or a relative simultaneously displaying disorders A and B, over and above the additive effects of disorders A and B individually; that is, there are no interaction effects caused by the simultaneous presence of 2 disorders. We applied an augmented model with terms for these interactions (see model 7 in the article by Hudson et al) to the data in this study and found that none was significantly different from zero, except for the coaggregation of MDD with alcohol abuse or dependence. In this case, we restricted the analysis to relatives without both disorders simultaneously.

A second assumption is what we have termed interchangeability of probands and relatives; specifically, the coaggregation of disorder A with disorder B is independent of whether the proband has A and the relative has B or the relative has A and the proband has B. More technically, the model assumes that the association parameters are the same for probands and relatives, when adjusted for the covariates in the model. As we have explained previously, this assumption is plausible when we can view probands with a given combination of disorders as being randomly selected from among all family members with the same combination of disorders. We can test this assumption by estimating 2 coaggregation parameters, one for the association between disorder A in a proband and disorder B in the relative and one for the association between disorder A in a relative and disorder B in the proband, and then testing whether these 2 parameters are equal, as they are when interchangeability holds. We found no evidence in these analyses to reject the hypothesis that these parameters were equal. For example, for the analysis of coaggregation of MDD with other forms of ASD collectively, there was little difference between the estimates for the 2 coaggregation parameters (Wald test, χ² = 0.06; P = .81). Thus, the assumption of interchangeability seemed plausible in this analysis.

Coaggregation of MDD
With Other Individual Forms of ASD

In the analysis of coaggregation of MDD with other individual forms of ASD, disorder A is always MDD and disorder B is another specific form of ASD. This analysis also generated an OR for the aggregation of that specific form of ASD individually, as explained in the description of the bivariate proband predictive model. When there were insufficient data to fit this bivariate model, we fitted a univariate model for the given form of ASD in a relative as a function of the presence or absence of MDD in that relative and the presence or absence of MDD and of the other form of ASD in the corresponding proband (see first equation of model 4 in the article by Hudson et al). When there were insufficient data to fit this model, we restricted this univariate model to consider only relatives of probands who did not have the given form of ASD. To assess the familial aggregation of MDD individually, we used the same univariate model as for the aggregation of ASD as a whole.

Coaggregation of MDD
With Other Forms of ASD Collectively

To test the coaggregation of MDD with other forms of ASD collectively, we used the bivariate proband predictive logistic regression model, with disorder A defined as MDD and disorder B as any other form of ASD (ie, 1 or more other forms of ASD).

Covariates, SEs, and Model Fitting

We included terms in all models for the relative’s sex, age, and relationship to the proband (parent, sibling, or child) to adjust for the effect of these covariates on the odds of disorder (eg, to allow for the possibility that a sibling might have different odds of a disorder than a parent). We also tested whether addition of separate covariates for each of the 2 outcomes (that is, including a separate vector of 0 parameters for each equation of model 4 in the article by Hudson et al) changed the estimates of the coaggregation OR, indicating possible confounding. However, since introduction of these parameters had virtually no effect on these estimates (<2% change), we did not include them in the final models. In addition, although we found no evidence for interactions between the covariates and the association effects, we had limited power to detect these interactions.

Because observations within families are correlated, we used generalized estimating equations to estimate SEs. We used independence as the working covariance structure. We fitted the models using Stata version 7.0 computer software (Stata Corp, College Station, Tex).

RESULTS

PROBANDS AND INTERVIEWED RELATIVES

Between September 23, 1996, and June 16, 2000, we interviewed 178 relatives of 64 probands with MDD and 152 relatives of 38 probands without MDD (see Table 1 for demographic characteristics). We present the prevalence of disorders in probands in Table 2 and interviewed relatives in Table 3. These are lifetime diagnoses, except dysthymic disorder and generalized anxiety disorder, which were restricted by our SCID-based criteria to current cases only. Thus, the figures obtained for the prevalence of these 2 disorders are lower than would be the case had they been diagnosed on a lifetime basis.

FAMILIAL AGGREGATION OF ASD

The prevalence of at least 1 form of ASD among relatives of 69 probands with ASD (of whom 64 had MDD and 5 did not have MDD) was 74 (39%), and among 53
As expected, there was limited power to assess the aggregation of individual disorders themselves or the coaggregation of MDD with another individual form of ASD (Table 4). The findings favored aggregation of most individual forms of ASD, although they reached statistical significance only for MDD (P = .01) and social phobia (P = .03). Furthermore, with the possible exception of migraine (OR, 1.4), the evidence also seemed to favor coaggregation of MDD with other individual forms of ASD, with estimated ORs ranging from 2.3 to 6.1. However, the only marginally significant findings were for bulimia nervosa (P = .09) and irritable bowel syndrome (P = .06). The evidence also supported the aggregation of substance use disorders, with statistically significant results for alcohol use disorder (P = .02) and any substance use disorder (P = .005). Notably, alcohol use and other substance use disorders failed to show significant coaggregation with MDD (Table 4).

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in 152 interviewed relatives of 58 nondepressed control probands. We found that ASD, viewed as a single entity, aggregates strongly in families. We also found that MDD displays strong coaggregation with other forms of ASD, taken collectively. These findings are consistent with the hypothesis that the various forms of ASD may share a heritable physiologic abnormality critical to their origin; for example, the forms of ASD might represent in part pleiotropic manifestations of a common genetic defect.

This hypothesis has important clinical and theoretical implications. Clinically, it would argue that treatments for this putative abnormality should benefit all forms of ASD not merely in a palliative sense, such as analgesics for pain, but by fundamentally interrupting the chain of etiologic steps that causes these disorders to occur. As we have suggested previously, the antidepressants may benefit all forms of ASD by treating (albeit imperfectly) this putative abnormality in some common manner. The hypothesis would also suggest that individuals with a family history of one form of ASD would likely be at increased risk for other forms of ASD as well. Recognition of this possibility might lead to earlier diagnosis and treatment of these many conditions and may suggest prevention strategies.

From a theoretical perspective, the hypothesis would predict that individuals with the various forms of ASD might share distinctive neuropsychological or biological abnormalities, such as specific cognitive deficits, neurotransmitter abnormalities, or abnormalities detectable on structural or functional neuroimaging. The hypothesis would also argue that studies of any individual form of ASD, such as MDD, should take account of the co-occurrence of other forms of ASD; failure to address this issue might lead to biased results and erroneous conclusions.

Our results are consistent with the family studies and twin studies described previously, that, with some exceptions, have suggested coaggregation of MDD with most other individual forms of ASD. Our findings also seem congruent with additional studies that have demonstrated relationships among various pairs of non-MDD forms of ASD, although our data are insufficient to test some of the distinctions suggested by these studies.

Our familial data also seem consistent with 3 other empirically supported groupings of disorders that are similar to the ASD cluster. The first is the internalizing disorders described by Krueger and colleagues, derived from co-occurrence data from 2 population-based studies and replicated in a more recent population study. The internalizing disorders include agoraphobia, dysthymic disorder, generalized anxiety disorder, MDD, obsessive-compulsive disorder, panic disorder, and social phobia. The second is the general neurotic syndrome described by Tyrer as operationalized by Andrews and associates, which resembles the internalizing disorders but lacks simple phobia and agoraphobia without panic disorder. Peroukta and colleagues found the third group—generalized anxiety disorder, MDD, migraine with aura, obsessive-compulsive disorder, panic disorder, and phobia—to be associated with the NcoI polymorphism within the dopamine D2 receptor (DRD2) gene.
Table 4. Aggregation of Individual Disorders and Coaggregation of MDD With Other Disorders Individually

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Aggregation OR for Disorder†</th>
<th>Coaggregation OR for MDD With Disorder‡</th>
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<tr>
<td></td>
<td>Estimate (95% CI) P Value</td>
<td>Estimate (95% CI) P Value</td>
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<tr>
<td>Forms of ASD</td>
<td></td>
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<tr>
<td>Bulimia nervosa§</td>
<td>4.5 (0.54-38) .17</td>
<td>6.1 (0.74-51) .09</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>1.9 (0.83-4.4) .13</td>
<td>2.3 (0.97-5.4) .06</td>
</tr>
<tr>
<td>MDD</td>
<td>2.9 (1.3-6.6) .01</td>
<td></td>
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<tr>
<td>Migraine</td>
<td>2.8 (0.62-9.0) .21</td>
<td>1.4 (0.63-3.0) .43</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td></td>
<td>2.6 (0.51-13) .25</td>
</tr>
<tr>
<td>Panic disorder§</td>
<td>3.4 (0.61-19) .16</td>
<td>2.5 (0.64-10) .19</td>
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<tr>
<td>Posttraumatic stress disorder</td>
<td></td>
<td>2.4 (0.25-23) .45</td>
</tr>
<tr>
<td>Social phobia§</td>
<td>4.6 (1.2-18) .03</td>
<td>2.7 (0.59-12) .20</td>
</tr>
<tr>
<td>Other disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse or dependence¶</td>
<td>3.6 (1.2-10) .02</td>
<td>1.4 (0.70-2.8) .33</td>
</tr>
<tr>
<td>Other substance abuse or dependence</td>
<td>6.7 (0.49-93) .16</td>
<td>0.9 (0.31-2.8) .91</td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>3.8 (1.5-9.8) .005</td>
<td>1.3 (0.69-2.3) .43</td>
</tr>
<tr>
<td>Simple phobia§</td>
<td></td>
<td>1.9 (0.66-5.3) .24</td>
</tr>
</tbody>
</table>

Abbreviations: ASD, affective spectrum disorder; CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.
†The ORs of the given disorder in a relative of a proband with that disorder compared with a relative of a proband without that disorder, adjusted for relative’s age, sex, and relationship to proband.
‡Unless noted otherwise, ORs (adjusted for relative’s age, sex, and relationship to proband) of (1) the given disorder in a relative of a proband with MDD compared with a relative of a proband without MDD and (2) MDD in a relative of a proband with the given disorder compared with a relative of a proband without that disorder.
§Because of sparse data, only ORs of the given disorder in a relative of a proband with MDD compared with a relative of a proband without MDD (see text).
¶Because of sparse data, only ORs of the given disorder in a relative of a proband with MDD compared with a relative of a proband without MDD, with analysis restricted to relatives of probands who did not have the given form of ASD (see text).

Table 5. Familial Coaggregation of MDD With Non-MDD Forms of ASD in Interviewed Relatives of 64 Probands With and 58 Probands Without Depression

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of 1 or More Non-MDD Forms of ASD</th>
<th>Coaggregation OR*</th>
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<tr>
<td></td>
<td>Relatives With MDD (n = 178, No. (%))</td>
<td>Relatives Without MDD (n = 152, No. (%))</td>
</tr>
<tr>
<td></td>
<td>59 (33)</td>
<td>27 (18)</td>
</tr>
</tbody>
</table>

Abbreviations: ASD, affective spectrum disorder; CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.
*Odds (adjusted for relative’s age, sex, and relationship to proband) of (1) ≥1 non-MDD form of ASD in a relative of a proband with MDD compared with a relative of a proband without MDD, or (2) MDD in a relative of a proband with ≥1 non-MDD form of ASD compared with a relative of a proband without ≥1 non-MDD form of ASD. Separate estimates (OR [95% CI]) of (1) and (2) described herein are 2.0 (1.1-3.8) and 1.7 (0.6-4.7), respectively.

ALTERNATIVE EXPLANATIONS

We should consider several alternative explanations for our findings. One is that the forms of ASD share common familial factors but that these are primarily environmental rather than genetic. Against this possibility are the data from twin studies cited herein, together with evidence supporting a genetic basis for each individual form of ASD. We should consider several alternative explanations for our findings. One is that the forms of ASD share common familial factors but that these are primarily environmental rather than genetic. Against this possibility are the data from twin studies cited herein, together with evidence supporting a genetic basis for each individual form of ASD.30,31,53-64

We recognize that substance use disorders plus antisocial personality disorder did not coaggregate with MDD and generalized anxiety disorder. Also, several other studies56,60 have failed to find that MDD coaggregates with alcohol abuse or dependence, although some studies59,70 have produced partially contradictory findings.
A fourth possibility is that our findings might be an artifact of ascertainment bias due to treatment seeking.\textsuperscript{71,72} For example, since our probands with MDD were seeking inpatient treatment, both they and their relatives might display a higher prevalence of other forms of ASD than comparable individuals in the general population, a phenomenon sometimes called spurious comorbidity.\textsuperscript{73} However, as we\textsuperscript{19,43} have explained elsewhere, our analysis is relatively immune to the effects of spurious comorbidity, because it does not require that the prevalence of co-occurring disorders in our probands with MDD be comparable with that in individuals with MDD in the source population. Thus, our findings could not be explained by ascertainment bias, barring a residual bias that influences rates of non-MDD forms of ASD in relatives even after controlling for effects of co-occurring non-MDD forms of ASD in the probands. Two studies that examined the effects of treatment seeking on aggregation of individual disorders found little\textsuperscript{72} or no evidence\textsuperscript{11} of such residual bias.

Finally, it might be asked whether the study would produce different results had it used probands with other forms of ASD rather than exclusively probands with MDD. However, as noted in Table 5, the coaggregation estimates are similar regardless of whether we consider the association between non-MDD forms of ASD in a relative and MDD in the proband or between MDD in a relative and other forms of ASD in the proband. The wide CI on the second estimate, however, highlights the utility of further studies using probands with non-MDD forms of ASD.

In short, none of these alternative possibilities offers compelling evidence against the predictions of the ASD hypothesis. Therefore, the present findings would encourage searching for common factors among the various forms of ASD, including possible biological markers, common treatments, and perhaps shared genetic abnormalities that might help explain the origin of these many conditions.

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