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, dysthymic 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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CERTAIN PSYCHIATRIC disorders commonly occur together in individuals (co-occurrence) and in families (coaggregation), an observation suggesting that such disorders may share causal factors. Among proposed groups are the obsessive-compulsive spectrum of disorders,[1] the externalizing and internalizing disorders,[2] the bipolar spectrum of disorders,[3] disorders characterized by serotonin disturbance,[4] and schizotaxia.[5,6]

In 1990, we[7] proposed the affective spectrum disorder (ASD) hypothesis, suggesting that major depressive disorder (MDD) shares a causal factor (or set of factors) with 7 other psychiatric and medical disorders: attention-deficit/hyperactivity disorder, bulimia nervosa, cataplexy, irritable bowel syndrome, migraine, obsessive-compulsive disorder, and panic disorder. This hypothesis was based on the observa-

tion that each of these disorders had been shown to respond to at least 3 chemically unrelated classes of antidepressant medications. Since 1990, new pharmacologic data[8-12] have allowed 6 other disorders to be added to the ASD group: dysthymic disorder, fibromyalgia, generalized anxiety disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia. The term *ASD* reflects only the fact that the medications effective in these conditions were first used to treat MDD and thus were classified as antidepressants. However, this term does not imply that these conditions are caused by MDD; indeed, to the contrary, we hypothesize that MDD and the other forms of ASD share a common causal factor (or set of causal factors). Identification of these factors, if they exist, would potentially lead to the development of mechanism-based techniques for the treatment or prevention of these common and often disabling conditions.

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 with obsessive-compulsive disorder[24]; and little evidence for coaggregation in the one study of migraine[25] (a 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.

METHODS

SUBJECTS

We recruited probands with MDD from sequential admissions to psychiatric wards at Innsbruck University Clinics in Innsbruck, Austria, provided that they had (1) current MDD by *DSM-IV* criteria; (2) no history of psychotic symptoms in the absence of MDD; (3) no history of manic or hypomanic episodes; (4) age between 18 and 70 years; (5) at least 9 years of education; (6) 2 or more first-degree relatives within 500 km of Innsbruck; (7) consented to a personal interview; and (8) consented for the investigators to contact their first-degree relatives. We recruited non-MDD probands from the surgical and ophthalmologic units at Innsbruck University Clinics provided they met criteria 2 through 8 and reported no current or past episode of MDD. In both proband groups, we accepted subjects with current or past (lifetime) disorders other than MDD provided they met these criteria. First-degree relatives of all probands were eligible for study provided they were at least 18 years old and displayed no medical illness that prevented interviewing (eg, dementia). All probands and interviewed relatives signed informed consent for the study after the full study procedures were explained.

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,[35] 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.I.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[42,43] have discussed this model further elsewhere (see equation 1 in the article by Hudson et al[43]).

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[19,43] 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[19,43] have presented this bivariate proband predictive model in detail elsewhere (see model 4 in the article by Hudson et al[43]) and have demonstrated that it is more flexible in modeling and testing than previous univariate logistic regression[21] and multinomial[44] 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 coaggregation 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[43]) 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[43] 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[19,43] 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.[19] 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, $\chi^2_1 = 0.06$; $P = .81$). 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[43]). When there were insufficient data to fit even 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 θ parameters for each equation of model 4 in the article by Hudson et al[43]) 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.[45,46] 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 58 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

Table 1. Demographic Characteristics of Probands With and Without MDD and Their Relatives

| | Proband Group | |
| | Probands With MDD | Probands Without MDD |
Characteristic		
Probands, No.		
Total	64	58
Age, y, mean (SD) [range]	39.5 (15.0) [18-67]	40.9 (14.1) [18-63]
Female	49	23
Male	15	35
Relatives, No.		
Total interviewed and noninterviewed	355	350
Interviewed, No. (%)	178 (50)	152 (43)
Age, y, mean (SD) [range]	39.6 (13.7) [18-67]	37.4 (13.1) [18-65]
Mothers	28	19
Fathers	21	13
Sisters	45	38
Brothers	27	34
Daughters	32	22
Sons	25	26

Abbreviation: MDD, major depressive disorder.

Table 2. Lifetime Prevalence of Disorders in Depressed and Control Probands With and Without MDD*

| | No. (%) | |
| | Probands With MDD (n = 64) | Probands Without MDD (n = 58) |
Disorder		
Mood disorders		
MDD	64 (100)	0
Dysthymic disorder†	0	0
Bipolar disorder	0	0
Anxiety disorders		
Generalized anxiety disorder†	1 (2)	0
Obsessive-compulsive disorder	8 (13)	0
Panic disorder	7 (11)	0
Posttraumatic stress disorder	1 (2)	0
Social phobia	9 (14)	0
Agoraphobia without panic disorder	4 (6)	0
Simple phobia	2 (3)	0
Any anxiety disorder	26 (41)	0
Eating disorders		
Bulimia nervosa	6 (9)	1 (2)
Anorexia nervosa	13 (20)	0
Binge-eating disorder	0	0
Any eating disorder	14 (22)	1 (2)
Substance use disorders		
Alcohol abuse or dependence	7 (11)	3 (5)
Other substance abuse or dependence	4 (6)	1 (2)
Any substance use disorder	9 (14)	4 (7)
Other psychiatric disorders		
Body dysmorphic disorder	0	0
Kleptomania	2 (3)	0
Schizophrenia	0	0
Somatization disorder	0	0
Medical disorders		
Cataplexy	0	0
Fibromyalgia	1 (2)	0
Irritable bowel syndrome	9 (14)	0
Migraine	5 (8)	4 (7)
Chronic fatigue syndrome	0	0
Tourette disorder	0	0
Any medical disorder	13 (20)	4 (7)

Abbreviation: MDD, major depressive disorder.
*Forms of affective spectrum disorder in bold italics.
†Current diagnosis only.

probands without any form of ASD the prevalence was 29 (21%). We found that ASD, as a single entity, aggregated strongly within families: the estimated odds of ASD in a relative of a proband with ASD were 2.5 times (95% confidence interval [CI], 1.4-4.3) the odds of ASD in a relative of a proband without ASD (*P*=.001).

Importantly, there was some evidence for the specificity of aggregation of ASD. Specifically, we found no significant coaggregation of ASD, taken as a single entity, with alcohol use disorders (OR, 1.3; 95% CI, 0.74-2.1; *P*=.40), nonalcohol substance use disorders (OR, 0.97; 95% CI, 0.28-3.4; *P*=.96), or any substance use disorder (OR, 1.1; 95% CI, 0.69-1.8; *P*=.64). (For these analyses, we used the bivariate proband predictive logistic regression model described herein, with 1 or more forms of ASD as disorder A and a disorder within the given substance use disorder category as disorder B.)

COAGGREGATION OF MDD WITH NON-MDD FORMS OF ASD INDIVIDUALLY

As expected, there was limited power to assess the aggregation of individual disorders themselves or the coaggregation of MDD with other individual forms 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 sub-

stance use disorder (*P*=.005). Notably, alcohol use and other substance use disorders failed to show significant coaggregation with MDD (Table 4).

COAGGREGATION OF MDD WITH OTHER FORMS OF ASD COLLECTIVELY

We present the prevalence of MDD and at least one non-MDD form of ASD among relatives of probands with and without MDD in **Table 5**. We found that MDD coaggregated significantly with other forms of ASD collectively (OR, 1.9; *P*=.02) (Table 5). Furthermore, consistent with the assumption of interchangeability, the estimated ORs for the association between non-MDD forms of ASD in a relative and MDD in the proband and for the association between MDD in a relative and other forms of ASD in the proband were similar (Table 5).

Table 3. Lifetime Prevalence of Disorders in Interviewed Relatives of 64 Probands With and 58 Probands Without MDD*

	No. (%)	
Disorder	Relatives of Probands With MDD (n = 178)	Relatives of Probands Without MDD (n = 152)
Mood disorders		
MDD	33 (19)	12 (8)
Dysthymic disorder†	0	0
Bipolar disorder	2 (1)	0
Anxiety disorders		
Generalized anxiety disorder†	4 (2)	0
Obsessive-compulsive disorder	8 (4)	2 (1)
Panic disorder	13 (7)	3 (2)
Posttraumatic stress disorder	4 (2)	1 (1)
Social phobia	14 (8)	3 (2)
Agoraphobia without panic disorder	2 (1)	2 (1)
Simple phobia	14 (8)	6 (4)
Any anxiety disorder	38 (21)	14 (9)
Eating disorders		
Bulimia nervosa	11 (6)	1 (1)
Anorexia nervosa	6 (3)	0
Binge-eating disorder	3 (2)	1 (1)
Any eating disorder	17 (10)	2 (1)
Substance use disorders		
Alcohol abuse or dependence	20 (11)	13 (9)
Other substance abuse or dependence	8 (4)	5 (3)
Any substance use disorder	25 (14)	16 (11)
Other psychiatric disorders		
Body dysmorphic disorder	0	0
Kleptomania	1 (1)	0
Schizophrenia	0	0
Somatization disorder	1 (1)	1 (1)
Medical disorders		
Cataplexy	0	0
Fibromyalgia	3 (2)	0
Irritable bowel syndrome	28 (16)	10 (7)
Migraine	13 (7)	11 (7)
Chronic fatigue syndrome	0	0
Tourette disorder	0	0
Any medical disorder	39 (22)	20 (13)

Abbreviation: MDD, major depressive disorder.
*Forms of affective spectrum disorder in bold italics.
†Current diagnosis only.

COMMENT

MAIN FINDINGS AND IMPLICATIONS

The ASD hypothesis, developed from a pharmacologic treatment-response model,[7] proposes that a group of 14 psychiatric and medical disorders shares a common and possibly heritable pathophysiologic basis. Thus, the hypothesis predicts that this group of disorders, taken as a single entity, would aggregate in families, and that the individual disorders would coaggregate with one another in families. To test these predictions, we performed a family interview study, assessing 12 of the 14 forms of ASD, in 178 interviewed relatives of 64 probands with MDD, the most common form of ASD, and 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[7] 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[13-23] and twin studies,[26-29,31,32] described previously, that, with some exceptions,[24,25,47] have suggested coaggregation of MDD with most other individual forms of ASD. Our findings also seem congruent with additional studies[24,26,30,32] 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 one[32] of 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,[2,48] derived from co-occurrence data from 2 population-based studies and replicated in a more recent population study.[49] 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[50] (as operationalized by Andrews and associates[51]), which resembles the internalizing disorders but lacks simple phobia and agoraphobia without panic disorder. Peroutka and colleagues[52] found the third group—generalized anxiety disorder, MDD, migraine with aura, obsessive-compulsive disorder, panic disorder, and phobia—to be associated with the *Nco*I polymorphism within the dopamine D_2 receptor (*DRD2*) gene.

Table 4. Aggregation of Individual Disorders and Coaggregation of MDD With Other Disorders Individually*

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

Abbreviations: ASD, affective spectrum disorder; CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.

*Results on disorders where there were sufficient data to estimate aggregation parameters.

†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).

¶Because of interactions, analysis restricted to relatives without both MDD and alcohol abuse or dependence (see text).

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,[30,31,53-64] except dysthymic disorder and fibromyalgia. Finally, to our knowledge, no study has demonstrated a significant environmental cause for familial coaggregation among forms of ASD. Thus, genetic factors likely contribute substantially to the familial aggregation of ASD.

A second alternative explanation is that MDD shares a heritable abnormality with only some of the other forms of ASD. Weighing against this possibility, however, is the observation that each individual form of ASD diagnosed in our study, except migraine, was more frequent in the relatives of probands with MDD than relatives of probands without MDD. However, the 95% CIs for the coaggregation of these disorders with MDD do not exclude an OR of 1.0, and we had insufficient data to even estimate a coaggregation OR for cataplexy, dysthymic disorder, fibromyalgia, and generalized anxiety disorder. We also cannot exclude the corollary possibility that MDD itself is heterogeneous, with only some forms of MDD coaggregating with other forms of ASD.

A third explanation is that our findings reflect simply a nonspecific clustering of psychiatric and medical illness in general rather than ASD in particular. For example, MDD might occur as a final common pathway of psychiatric and medical disorder in general rather than being associated only

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

Prevalence of 1 or More Non-MDD Forms of ASD		Coaggregation OR*	
Relatives With MDD (n = 178, No. (%)	Relatives Without MDD (n = 152, No. (%)	Estimate (95% CI)	P Value
59 (33)	27 (18)	1.9 (1.1-3.2)	.02

Abbreviations: ASD, affective spectrum disorders; 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.

with a specific group of disorders. Against this possibility is our finding that substance use disorders were highly familial but coaggregated neither with ASD as a whole nor with MDD individually. These findings are consistent with the finding of Krueger and associates[2,48] that substance dependence clustered in individuals separately from MDD and other internalizing disorders and the finding of Kendler and colleagues[65] that substance use disorders plus antisocial personality disorder did not coaggregate with MDD and generalized anxiety disorder. Also, several other studies[66-68] have failed to find that MDD coaggregates with alcohol abuse or dependence, although some studies[69,70] have produced partially contradictory findings.

A fourth possibility is that our findings might be an artifact of ascertainment bias due to treatment seeking.[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*.[73] However, as we[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[72] or no evidence[71] 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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