Psychiatric Disorder and the Broad Autism Phenotype: Evidence From a Family Study of Multiple-Incidence Autism Families

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Objective: Several studies have shown familial aggregation of some axis I psychiatric disorders in families ascertained through a single autistic proband. In this study the authors examined the rate of axis I psychiatric disorders in nonautistic relatives from multiple-incidence autism families and the possible relationship of these disorders to the broad autism phenotype. **Method:** The rates of axis I psychiatric disorders, assessed by using semistructured and family history interviews, were compared in parents, grandparents, and aunts and uncles ascertained through 25 families of multiple-incidence autism probands and 30 families of probands with Down's syndrome. The possible association between selected psychiatric disorders and the broad autism phenotype, assessed directly through semistructured interviews and observational rating measures, was also examined in the two groups of parents. **Results:** The parents of the autistic probands had significantly higher rates of major depressive disorder and social phobia than the parents of the Down's syndrome probands. The high rate of depression in the parents of the autistic probands was consistent with the high rates of depression and anxiety detected in the grandparents and aunts and uncles in the autism families by family history. There was no evidence of an association, within individuals, between either depression or social phobia and the broad autism phenotype. **Conclusions:** Relatives of autistic individuals have high rates of major depression and social phobia that are not associated with the broad autism phenotype and cannot be explained by the increased stress associated with raising an autistic child. Alternative mechanisms and the scientific and clinical implications of these findings are discussed.

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While there is now considerable evidence from twin and family studies to support the importance of genetic factors in the etiology of autism (1–4), the nature and broad range of phenotypic expression of the underlying genetic liability for this disorder are still matters of debate. Since the landmark twin study by Folstein and Rutter (3), data have emerged that suggest that, in addition to causing autism, the genetic liability for this disorder may also be expressed, in the nonautistic relatives of autistic probands, in behavioral and cognitive characteristics that are milder but qualitatively similar to the defining features of autism. This set of behaviors and characteristics has been referred to as the broad autism phenotype (5) and has been mainly conceptualized as being limited to milder aspects of the defining features of autism, including social and communication deficits and stereotyped-repetitive behaviors (2, 5–7). The relationship of the broad autism phenotype to the particular cognitive deficits shown in some studies to aggregate in families of autistic individuals (8) is not yet clear.

Of particular interest in the debate over the nature and range of expression of the underlying genetic liability for autism have been studies suggesting that there is a higher than expected rate of some psychiatric disorders in the relatives of autistic individuals. Three family studies, employing comparison groups and direct psychiatric assessment, have shown high rates of some psychiatric disorders in relatives ascertained through a single autistic proband. We examined (9) 81 parents of 42 autistic probands and 34 parents of 18 Down's syndrome probands by using a semistructured psychiatric interview, the Maudsley version of the Schedule for Affective Disorders and Schizophrenia—

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Lifetime Version (SADS-L), and reported a significantly higher rate of "any anxiety disorder" (generalized anxiety, panic, or phobic disorder) and a somewhat higher rate (27% versus 14%) of major depressive disorder (4 weeks' duration) in the parents of the autistic probands. Subsequently, Smalley et al. (10) examined the first-degree relatives in 36 families ascertained through a single autistic proband, using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (K-SADS-E) and the Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (SADS-LA). In relation to comparison subjects, the first-degree relatives of the autistic probands had significantly higher rates of major depressive disorder (2 weeks' duration) and social phobia. In both our study and the study by Smalley et al., a substantial proportion of the subjects with major depressive disorder experienced the first depressive episode before the birth of the autistic child, suggesting that the higher rate of depression was not merely a result of stress related to caring for the handicapped child. Most recently, Bolton et al. (11) reported a higher rate of major depressive disorder (4 weeks' duration according to the Maudsley SADS-L) but not generalized anxiety, phobic (excluding simple phobias), or panic disorder in 218 first-degree relatives of 99 autistic probands than in 87 first-degree relatives of Down's syndrome probands, after direct assessments. Bolton et al. further reported no evidence of a relationship between major depression (on the Maudsley SADS-L) and the broad autism phenotype (defined as the presence of either communication/social impairments or restrictive patterns of interest or activities on an autism family history interview) in the relatives of the autistic probands. While there was no evidence of a high rate of obsessive-compulsive disorder (OCD) in the first-degree relatives of the autistic probands on direct assessment, in assessments using the family history method there was a significantly higher rate of "possible" OCD in the combined group of all first-, second-, and third-degree relatives of the autistic probands than in the relatives of the Down's syndrome probands (15% versus 0%), and the family history method also indicated a significant relationship between "possible" OCD and the broad autism phenotype.

The results of these studies raise two major questions. First, which psychiatric disorders aggregate in the families of autistic individuals? While major depressive disorder has consistently appeared more commonly in autism relatives, there has been less consistency in the results regarding anxiety disorders, in particular social phobia. Second, if particular psychiatric disorders do occur more commonly in the relatives of autistic individuals than in the general population, what are the possible underlying mechanisms? Are high rates of psychiatric disorder accounted for by the psychological stresses associated with raising an autistic child? The available data suggest that they are not. Is the excess of psychiatric disorder in autism relatives associated with the social or communication deficits or stereotyped-repetitive behaviors that have recently been conceptualized as defining the broad autism phenotype, or does the risk for psychiatric disorder occur independent of this definition of a broad autism phenotype? And, finally, if the risk of psychiatric disorder is associated with the occurrence of the broad autism phenotype in autism relatives, does it occur as a consequence of these characteristics and vulnerabilities, or is it simply the variable expression of a common underlying etiologic factor?

In the present study we addressed these research questions in a case-control comparison of the rates of psychiatric disorder in parents of two autistic individuals (multiple-incidence autism families) and parents of a Down's syndrome child. Multiple-incidence autism families offer several advantages over families ascertained through a single autistic proband. Probands in multiple-incidence autism families are less likely than probands in single-incidence families to have autism as a result of nongenetic causes (12), and therefore their relatives are likely to constitute a more etiologically homogeneous study group than those ascertained through a single autistic proband. In addition, relatives ascertained through multiple-incidence autism families may have a higher genetic liability for autism (as well as the broad autism phenotype and possibly psychiatric disorder) than relatives ascertained through probands in families with single-incidence autism or pervasive developmental disorder. However, they also may have more stress than either families with only one autistic child or families with a Down's syndrome child, complicating the interpretation of the results.

The sensitivity of the family history method for detecting the broad autism phenotype is unknown and is likely to yield an underestimate of the true rate of the broad autism phenotype in relatives. Therefore, in addition to the direct assessment of parents for psychiatric disorder, we also blindly and directly assessed parents for the presence of the broad autism phenotype. In this paper we examine rates of axis I psychiatric disorders in parents from multiple-incidence autism families and the relationship between psychiatric disorder and the broad autism phenotype, as conceptualized in a previous article on this same group of subjects (7). In addition to further clarifying the findings from previous reports on the familial aggregation of particular psychiatric disorders in relatives of autistic individuals, the design of this study provides the potential for further insight into possible mechanisms underlying this phenomenon.

METHOD

Selection of Study Groups

Autism families. Families that each had at least two autistic children were systematically ascertained from all such multiple-incidence autism families in Iowa and from families known to two tertiary evaluation centers for autism in the Midwest at the start of the study. The goal of this systematic ascertainment scheme was to reduce any potential bias with respect to familial aggregation of possi-

bly related disorders, including social and communication deficits, stereotyped behaviors, and psychiatric disorders. Families of autistic probands were eligible for this study if 1) two children (age 4–30 years) showed evidence of autism, either on the basis of a previous clinical diagnosis or, in the case of public school screening, on the basis of an experienced teacher's behavioral observations; and 2) medical records indicated that neither proband had evidence of a significant co-occurring medical condition thought to be possibly etiologically related to autism, such as tuberous sclerosis, neurofibromatosis, phenylketonuria, a chromosomal anomaly identified through karyotyping, fragile X syndrome, or significant CNS injury (12). The lower age limit of 4 years was specified to eliminate the uncertainty often present in diagnosing autism in mentally retarded children below this chronological age.

Twenty-five multiple-incidence autism families participated in this study, including 42 male and eight female autistic probands ranging from 4 to 28 years of age. Details of the ascertainment of these families are available elsewhere (6). Adequate performance IQ estimates were available from the medical record for 45 of the 50 probands. The performance IQs of 51% of the subjects were 70 or higher, 22% were in the 50–69 range, 27% were in the 30–49 range, and none of the subjects tested had performance IQs less than 30. Five were felt to not have had adequate testing at the time this study was undertaken either because of the test used or because of the subjects' inability to cooperate with testing. Resources were not available to attempt further testing of these five individuals.

Comparison families. The comparison group in this study comprised 30 families that each had a child with Down's syndrome due to a nondysjunction of chromosome 21. The rationale for choosing this group was our need to control for the effect of caring for a handicapped child on the emotional and social functioning of parents and siblings. Also, relatives of a Down's syndrome child would not be expected to have an increased genetic liability, over that of the general population, for social or communication deficits or for stereotyped behaviors—the behavioral variables of interest in this study. The group of Down's syndrome families included 13 male and 17 female Down's syndrome probands ranging in age from 2 to 27 years. Further details on the ascertainment of this study group are available elsewhere (6).

Assessment of Autistic Probands

Diagnosis. Parental informants for all subjects were interviewed regarding the subject's diagnosis by means of a standardized interview, the Autism Diagnostic Interview (13). An algorithm constructed for use with the Autism Diagnostic Interview (based on the ICD-10 criteria for autism) has been shown to adequately discriminate autistic subjects and nonautistic IQ-matched comparison subjects (13). Adequate interrater agreement (kappa >0.90) on the Autism Diagnostic Interview algorithm (on the basis of 10 videotaped interviews) for a diagnosis of autism was established by all raters before the start of data collection. In addition, the probands were directly assessed by means of the Autism Diagnostic Observation Schedule (14), a structured observation and interview schedule developed to aid in the diagnosis and assessment of autistic individuals. The information from the Autism Diagnostic Observation Schedule functioned as a check on the proband's current behavior as reported by the parents on the Autism Diagnostic Interview.

Physical examination. All subjects were evaluated in a screening neurodevelopmental examination for evidence of significant neurological impairment or medical conditions thought to be etiologically related to autism (as already listed). Almost all of the subjects had been previously screened through a medical evaluation at a tertiary care center and found not to have evidence of any exclusionary criteria for this study. No subject was excluded on the basis of our additional neurodevelopmental screening examination.

Assessment of Relatives for Psychiatric Disorder

All available parents were interviewed by two trained interviewers (with supervision by a psychiatrist, J.P.) with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders, Revised (SADS-LA-R), a semistructured interview for the diagnosis of psychiatric disorder (15). This instrument was selected because of its expanded anxiety section and similarity to interviews used in prior studies. Adequate reliability has been demonstrated for this semistructured interview. The parents were also interviewed with a standardized family history interview, the Family History Interview for Developmental Disorders of Cognition and Social Functioning, as described in previous publications (5, 6). Each parent was interviewed about himself or herself and about the proband's siblings, grandparents, uncles, aunts, and first cousins. The items from the family history interview concerning history of psychiatric disorder were a subset of those used by Bolton et al. (11) in their case-control family history study. For this portion of the study we were interested in examining family history data on the probands' grandparents and aunts and uncles for evidence of the psychiatric disorders detected at high rates in the direct interviews of the parents. This approach, although less sensitive than the direct assessment method, offers the potential for complementary and converging evidence for the validity of any findings in relatives of autistic probands.

Broad Autism Phenotype

Each parent in the autism families and an informant for the parent (usually a spouse) were interviewed by one of two interviewers with the subject and informant versions of the Modified Personality Assessment Schedule, Revised. This measure was part of an interview that included a semistructured instrument to elicit the subject's life story (i.e., nodal life events, social life, and school and work history), the Friendship Interview, and the semistructured psychiatric interview already described. The Modified Personality Assessment Schedule is a semistructured instrument designed to assess eight personality characteristics hypothesized to contribute to the broad autism phenotype. Best-estimate ratings ("present" or "absent") derived from blind videotaped ratings of the subject and informant interviews were made for each of the eight characteristics for each subject. This instrument was described in detail in a previous publication by our group (7). Results of this study revealed that four characteristics—aloof, rigid, anxious, and hypersensitive to criticism—occurred more commonly (after correction for multiple comparisons) in the multiplex autism parents than in the comparison subjects. Interrater reliability for all four characteristics was good (kappa >0.80).

The Pragmatic Rating Scale was used to provide an assessment of pragmatic language (19 items) and speech (six items) behaviors observed during the subject interview. A detailed description of the Pragmatic Rating Scale, including its development, is included in two previous reports that examined social language use in the parents of autistic individuals (7, 16). In brief, the ratings were based on conversational behavior observed throughout the interview session, including a 15-minute conversation held midway through the session. The 25 behaviors of the Pragmatic Rating Scale were each blindly rated on a 3-point scale, with 0 indicating normal behavior, 1 indicating moderately abnormal behavior (not considerably disruptive to the conversation), and 2 indicating that the behavior was strikingly abnormal (causing the conversational partner to use compensatory strategies to maintain the flow of conversation). For the purposes of analysis, ratings were collapsed into "present" (rating= 1 or 2) and "absent" (rating=0). For each subject, the 19 pragmatic language items and the six speech items were summed separately (1 point was assigned for each item rated as present) to produce a total pragmatic language score and a total speech score. Interrater reliability for the total score for pragmatic language was shown previously to be high (intraclass correlation coefficient=0.95), and the 3-month test-retest reliability was shown to be adequate (i.e., mean scores did not significantly differ) (16). Interrater reliability for the total speech score has not yet been examined.

The Friendship Interview is a semistructured interview instrument that assesses the number and quality of an individual's friendships. The subject is asked a number of questions about the quality of what the subject considers his or her three closest friendships. In our use of the instrument, the subjects were rated on the extent to which the friendships were characterized by mutual emotional support (rating of 0, 1, 2, or 3) and the extent to which the subject was able to con-

fide in his or her friend(s) about private worries and hopes (rating of 0, 1, or 2). Scores on these two items were summed across three potential friendships for each individual to produce a "friendship score." High-quality friendships were denoted by a low score, with 0 being the lowest, whereas the absence of friends was indicated by a high score, with 15 being the highest possible score. Interrater reliability for the friendship score was high (intraclass correlation=0.97) for two raters across 10 subjects. This instrument is available on request from the first author. Further details are described in a previous report by our group (7) and by Santangelo and Folstein (17).

Analysis

Subject characteristics (e.g., parental age, education level), rates of psychiatric disorders, and the relationships of psychiatric disorders to scores on the broad autism phenotype and its various components were examined by using univariate test statistics (chi-square likelihood ratio test and t test). Differences were considered significant at $p<0.05$ (two-tailed).

In a previous study (7) we developed an algorithm for determining the broad autism phenotype, based on personality and language items from the Modified Personality Assessment Schedule, the Pragmatic Rating Scale, and the Friendship Interview. The 11 personality and language variables derived from these three instruments (aloof, rigid, anxious/worrying, hypersensitive to criticism, undemonstrative, unresponsive, untactful, and overly conscientious personality characteristics and the pragmatic language, speech, and friendship scores) were entered into a logistic regression that produced an equation that best distinguished the autism and Down's syndrome parents (7). The final equation included four items—friendship score, speech score, and the personality characteristics rigid and hypersensitive to criticism—paralleling the major behavioral domains that define the syndrome of autism (social and communication deficits and stereotyped-repetitive behaviors), along with an additional component reflecting an anxiety dimension (i.e., hypersensitivity to criticism). In order to develop an empirical definition of the broad autism phenotype, each item was assigned 1 point if present in an individual and 0 points if absent. For the items rigid and hypersensitive to criticism, presence or absence was based on the rating of present or absent on the Modified Personality Assessment Schedule. Friendship deficits and speech deficits were determined to be present if an autism parent scored 1.5 standard deviation or more beyond the mean for the Down's syndrome comparison subjects on that item. In an effort to maximize specificity (96%) without severely limiting sensitivity (56%), an arbitrary threshold of 2 or greater was set for defining the presence of the broad autism phenotype out of a total of 4 possible points. Additional details on the development of this algorithm can be found in our previous report (7).

RESULTS

In the 25 multiple-incidence autism families, 25 mothers and 23 fathers were eligible to participate; all of the mothers and fathers in the 30 Down's syndrome families participated. A parent in a family with autism was included in the analysis only if he or she was the parent of two autistic children. Two mothers had autistic children with two different fathers, resulting in inclusion of only 23 autism fathers in this analysis. There was no significant difference between the families with autism and those with Down's syndrome in father's age ($t=0.76$, $df=51$, $p>0.45$), father's level of education ($\chi^2=1.39$, $df=4$, $p=0.85$), mother's age ($t=0.29$, $df=53$, $p=0.77$), or mother's level of education ($\chi^2=6.95$, $df=4$, $p=0.14$). Father's occupational level, as specified by the British Manual of the Classification of Occupations (18), also did not differ significantly between the two groups ($\chi^2=6.23$, $df=4$, $p=0.18$).

Psychiatric Disorder in Relatives

The results of a comparison of the autism and Down's syndrome parents on rates of psychiatric disorders, as defined by the Research Diagnostic Criteria (RDC), revealed that the autism parents had a significantly higher lifetime rate (33.3% versus 11.7%) of definite RDC major depressive disorder than did the Down's syndrome parents ($\chi^2=7.51$, $df=1$, $p=0.006$). The parents of the autistic probands also had a significantly higher rate of social phobia (14.6% versus 3.3%) than the parents of the Down's syndrome probands ($\chi^2=4.54$, $df=1$, $p=0.03$). There was no significant association between major depressive disorder and social phobia in the autism parents ($\chi^2=0.32$, $df=1$, $p=0.57$). No significant group differences were detected in the rates of the other axis I psychiatric disorders examined, including alcoholism (10.4% versus 3.3%), drug abuse (2.1% versus 1.7%), bipolar disorder (0.0% versus 0.0%), panic disorder (0.0% versus 1.7%), generalized anxiety disorder (4.2% versus 3.3%), simple phobia (4.2% versus 5.0%), and obsessive-compulsive disorder (2.1% versus 0.0%). Of the 16 autism parents with RDC major depressive disorder, 12 (75.0%) were female.

As in our previous study (9), we sought to apply more stringent criteria to the diagnosis of major depressive disorder (recurrent disorder with symptoms of 4 weeks' duration rather than the 2 weeks required by the RDC). In addition to increasing the required number of episodes (i.e., recurrent disorder) and duration of symptoms (i.e., 4 weeks), in this analysis we also excluded episodes that were temporally related to particularly stressful life events (e.g., occurred within 3 months of the death of a close friend or relative, the diagnosis of autism in a proband, or a divorce or marital separation or occurred in close association with a known organic etiology for depression, severe medical illness, or pregnancy). When these modified criteria for major depression were used, the autism parents continued to show a significantly higher rate of major depressive disorder (18.8% versus 1.7%) than the Down's syndrome parents ($\chi^2=10.12$, $df=1$, $p=0.001$). Eight out of the nine autism parents meeting this modified definition of major depressive disorder experienced his or her first depressive episode before the birth of either autistic child.

To further explore the evidence for an excess of depressive disorders in autism relatives, we examined family history data from the Family History Interview for Developmental Disorders of Cognition and Social Functioning for the probable or definite (i.e., 1 month of symptoms with evidence of impairment or treatment) presence of depressive or anxiety disorder in grandparents and in aunts or uncles. Too few siblings (in addition to the two autistic probands) were available in the multiple-incidence autism families for a meaningful comparison of rates in siblings. Also, the available data on first cousins were not thought to be sufficiently reliable for analysis. In sex-specific comparisons of the two groups of extended relatives (grandparents and aunts/uncles), there were no differ-

ences between the autism and Down's syndrome families in the grandfathers' age (t=0.66, df=10, p=0.76), grandmothers' age (t=0.71, df=8, p=0.64), uncles' age (t=0.58, df=13, p=0.63), or aunts' age (t=0.37, df=9, p=0.77) or in the grandfathers' level of education (χ^2=3.33, df=7, p=0.59), grandmothers' education (χ^2=2.43, df=10, p=0.61), uncles' education (χ^2=2.77, df=10, p=0.59), or aunts' education (χ^2=5.41, df=7, p=0.85). The rate of depression or anxiety was significantly higher in the grandparents (χ^2=4.26, df=1, p=0.04) and the aunts and uncles (χ^2=6.0, df=1, p=0.01) of the autism probands. Probable or definite depression or anxiety was found in 17.7% of the grandparents in the autism families, compared to only 8.4% of the grandparents in the Down's syndrome families, and in 13.2% of the aunts and uncles in the autism families, versus 5.4% of those in the Down's syndrome families.

Psychiatric Disorder and the Broad Autism Phenotype

To explore the relationship between major depressive disorder and the broad autism phenotype and between social phobia and the broad autism phenotype (i.e., defined as characteristics that are qualitatively similar but milder than those that define autism—social and communication deficits and stereotyped-repetitive behaviors—and show familial aggregation in autism families), we first examined the relationship between the presence (score ≥2) or absence (score=0) of the broad autism phenotype, as already empirically defined (see Analysis section) and the presence of RDC major depressive disorder and social phobia. The broad phenotype status of the autism parents with a score of 1 was considered unknown, and these individuals were not included in this analysis. Using this approach, we found no evidence of a significant association between the presence of the broad autism phenotype and either major depressive disorder (χ^2=0.87, df=1) or social phobia (χ^2=0.02, df=1). Further analysis also revealed no evidence of a significant relationship between total score for the broad autism phenotype (i.e., a continuous variable rated 0 through 4) and the presence or absence of major depressive disorder (t=0.70, df=44) or social phobia (t=0.11, df=44). More fine-grained analysis also revealed no evidence of a significant relationship between the presence of major depressive disorder and components of the broad autism phenotype, including the personality characteristics aloof, rigid, and anxious, the scores on the Pragmatic Rating Scale and speech measures, and the friendship score, except for a significant relationship between hypersensitivity to criticism and major depressive disorder (χ^2=4.91, df=1, p=0.03). Social phobia did show a significant relationship to the scores on the Pragmatic Rating Scale for pragmatic language (t=2.55, df=31, p=0.02 for unequal variances) and for speech (t=3.26, df=42, p=0.002 for unequal variances), i.e., significantly correlated with variables measuring pragmatic language deficits. However, the presence of social phobia was not significantly related to the other components of the broad autism phenotype examined, including friendship score and the personality characteristics aloof, anxious, and hypersensitivity to criticism.

DISCUSSION

Strengths and Limitations

There are several strengths of this study that distinguish it from previous studies. First, direct assessment was used for determining both the presence of psychiatric disorder (with an emphasis on more fully characterizing anxiety disorders by using the SADS-LA-R) and the broad autism phenotype. Assessment of the broad autism phenotype, and its components, was based on the blind rating of videotaped interviews, and determination of the presence of the broad autism phenotype was based on an empirically derived algorithm. Second, in this study we examined a group of parents ascertained systematically through two autistic probands per family. Systematic ascertainment limited the potential bias that could have occurred through the use of other ascertainment schemes (e.g., a clinic sample or advertisements for multiple-incidence families). Also, use of a group of multiple-incidence autism families, as opposed to a group ascertained through a single autistic proband, theoretically increased the etiologic homogeneity of our study group and possibly increased the genetic liability for both autism and the broad autism phenotype in relatives. However, several limitations of this study should also be considered. First, while we made efforts to systematically ascertain and retain comparison families in this study, the extent to which our comparison subjects accurately estimate the rate of psychiatric disorder in a population sample of nondysjunction Down's syndrome families is unclear. The demands on a family participating in this study were considerable. The results of cognitive and other tests are not reviewed in this article, but these tests also added to the demands on participants. It is possible that the demands and motivation for participation in this study, aimed at understanding issues primarily relevant to the genetics of autism, may have resulted in systematic ascertainment of a comparison group that was more compliant and that may have had fewer of the characteristics of interest in this study. We have no good way to assess the extent of this potential ascertainment bias. However, the fact that our findings with regard to axis I psychiatric disorder were also present in extended relatives (grandparents and aunts and uncles) suggests that, at least with regard to axis I conditions, the findings of this study are not the result of a bias of ascertainment. Second, the number of subjects in this study, while providing sufficient power to detect differences in the rates of major depressive disorder in case and control subjects, was limited with regard to our ability to detect associations within the smaller group of only autism parents. So, for example, while we had adequate power (0.92) to detect a large

relationship (Cohen's W or phi of 0.5) (e.g., between major depressive disorder and the broad autism phenotype), we had only marginal power (0.52) to detect a more modest relationship (e.g., phi of 0.3).

Psychiatric Disorder in Autism Parents

This study confirms previous reports suggesting that the relatives of autistic individuals have high rates of major depressive disorder and social phobia. Significant differences in rates of RDC major depressive disorder and social phobia were detected in a case-control comparison of the rates in parents, based on direct assessment, and in rates of depression or anxiety disorder in both grandparents and aunts and uncles, based on family history. The difference in rates of major depressive disorder was also demonstrated by using a conservative definition of major depression (i.e., modified major depression).

The study by Smalley et al. (10) is the only one of which we are aware in which rates of major depressive disorder comparable to those found in the present study were observed through use of identical criteria (RDC or a single 2-week episode of depressive symptoms) and very similar instruments. Smalley et al. (10) used the SADS-LA, and we employed an updated, revised version of this same instrument, the SADS-LA-R. Major depressive disorder in the Smalley et al. study was detected in 32% of autism first-degree relatives versus 11% of relatives from the comparison group. In the present study, the rate of a modified definition of major depressive disorder (i.e., recurrent episodes, 4 weeks of major depressive disorder) was also similar to that found in our earlier study (9) of parents ascertained through a single autistic proband (16.0% in that study versus 18.8% in the present study), although the rate in the comparison group of Down's syndrome parents in our previous study was slightly higher (6.0% in that study versus 1.7% in the present study). The rates of major depressive disorder (single episode of 4 weeks, RDC) in the study by Bolton et al. (11) were intermediate between those reported in the three studies just noted (19.7% in first-degree relatives of autistic probands versus 5.7% in comparison subjects), showing lower rates than in the two studies using RDC criteria (Smalley et al. [10] and the present study) and higher rates than in the study in which recurrent 4-week episodes of RDC depressive symptoms were required (9). Thus, in the four published reports of studies that used direct assessment for a variety of definitions of major depressive disorder in relatives of autism and comparison families, the results appear to be remarkably consistent. The higher rate of social phobia we detected in parents of autistic probands is also in agreement with the rate in the only other published report of a study employing the SADS-LA (10), and it is consistent with our previously reported high rate of "any anxiety disorder" in autism parents (9).

While the study by Bolton et al. (11) did not detect a high rate of OCD in first-degree relatives on direct assessment, when the family history method was used to assess nuclear and extended relatives, a high rate of OCD was found. As in our previous study (9), in this study we found no evidence of a high rate of OCD in autism parents. The discrepancy between the results obtained through direct assessment and through the family history method may reflect a failure of the family history method to distinguish the conceptually related phenomena of rigidity (a personality characteristic defined as "having little interest in or difficulty adjusting to change") and OCD. Rigidity was present at a high rate in the multiple-incidence autism parents in our study (6), whereas OCD was not.

Psychiatric Disorder and the Broad Autism Phenotype

The finding of the familial aggregation of major depressive disorder and social phobia in autism families raises several questions about possible mechanisms underlying these phenomena that can partially be addressed by the findings of this study. First, these results are in agreement with those of earlier studies (9–11) in showing no evidence for the hypothesis that the high rate of major depressive disorder (where discrete episodes and onset are generally discernible) in autism parents is entirely explained by the stress of raising an autistic child or children, as the majority of cases of major depression had onsets before the birth of either autistic proband. Second, the absence of any association between the presence of major depressive disorder or social phobia and either the broad autism phenotype (defined both categorically and as a continuous variable) or components of the broad autism phenotype (except for a relationship between social phobia and pragmatic language) suggests that the high rates of major depressive disorder and social phobia we observed are not likely to be either an indirect result of the broad autism phenotype (i.e., secondary to vulnerabilities created by the presence of particular personality and language characteristics) or the direct result of the gene or genes causing the broad autism phenotype. The absence of a relationship between major depressive disorder and the broad autism phenotype is also in agreement with the findings by Bolton et al. (11), who failed to find a significant association between the broad autism phenotype and depression, based on family history data, in first-degree relatives from families ascertained through a single autistic proband. However, it should also be noted that our study had only marginal power (0.50) to detect a modest relationship between major depressive disorder and the broad autism phenotype.

The absence of a relationship, within individuals, between major depressive disorder or social phobia and our conceptualization of the broad autism phenotype raises several additional possibilities to consider in attempting to understand the high rates of these psychiatric disorders in these families. First, both of these conditions (major depressive disorder and social phobia) are generally considered to be etiologically

heterogeneous, and therefore more than one factor or the interaction of a combination of factors may be responsible for this finding. Second, a leading hypothesis for the etiology of autism is that it is the result of multiple, interacting genes (19) and that it may be an etiologically heterogeneous disorder (12). Thus, it is possible that major depressive disorder and social phobia in these families are caused by a gene or genes different from those contributing to the broad autism phenotype, that these findings merely reflect the etiologic heterogeneity thought to be present in the autistic syndrome, or both. The use of multiple-incidence families, while likely to decrease the phenocopies included in this study group, cannot eliminate the possibility of the genetic heterogeneity that almost certainly exists within our study group. However, the idea that there is a gene or set of genes that cause both autism and the broad autism phenotype and that there is a separate gene or genes that cause both autism and major depressive disorder (or social phobia) seems unlikely.

A third possibility for consideration is that the familial aggregation of major depressive disorder and social phobia in these families may reflect, in part, the assortative mating of parents with the broad autism phenotype for spouses with major depression (and social phobia). We examined this possibility in our data and discovered that of the 27 parents with definite evidence of the broad autism phenotype (i.e., a score of 2 or greater), 11 (40.7%) married a spouse with a history of major depressive disorder, whereas of the 11 without evidence of the broad autism phenotype, only two (18.2%) married a spouse with a history of major depressive disorder. While the odds of a parent with the broad autism phenotype marrying a spouse with major depressive disorder do not significantly differ from 1 (odds ratio=3.1, 95% confidence interval=0.6–17.1), the power of our study to detect a modest but significant effect of assortative mating is marginal. Against the hypothesis of assortative mating, however, are the findings by Bolton et al. (11) of an absence of an association between depression and the broad autism phenotype within families, based on family history data.

In summary, we confirm the previous reports of high rates of several psychiatric disorders in the parents of autistic individuals. While the results of this study suggest several mechanisms that probably do not play important roles in the high rates of major depressive disorder in these families, and suggest other mechanisms that should continue to be considered in elucidating the reasons for high rates of other conditions, additional studies will be necessary to more definitively understand the pathogenesis of this finding. In particular, identification of susceptibility loci for autism may enable us to more definitively tease apart the factors contributing to high rates of psychiatric disorders in autism parents. Finally, while we have suggested that the stress of having an autistic child or children does not entirely explain the high rate of major depressive disorder in autism families, we cannot conclude from this study that it does not, in some way, increase the risk for major depression or the number or duration of episodes in these vulnerable individuals. While the findings of this study do not provide a definitive understanding of the pathogenesis of selected psychiatric disorders in these families, the high risk of major depressive disorder and social phobia clearly have clinical relevance and should be kept in mind by all clinicians working with families of autistic individuals.

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