Broader Autism Phenotype: Evidence From a Family History Study of Multiple-Incidence Autism Families

Joseph Piven, M.D., Pat Palmer, Ph.D., Dinah Jacobi, B.A., Debra Childress, B.S., and Stephan Arndt, Ph.D.

Objective: *Studies of families ascertained through a single autistic proband suggest that the genetic liability for autism may be expressed in nonautistic relatives in a phenotype that is milder but qualitatively similar to the defining features of autism. The objective of this study was to examine behaviors that may define this broader phenotype in relatives ascertained through two autistic siblings.* *Method:* *The authors used a semistructured family history interview to compare the rates of social and communication deficits and stereotyped behaviors in relatives ascertained through two autistic siblings (families with multiple-incidence autism; 25 families) with the rates in relatives of Down syndrome probands (30 families).* *Results:* *Higher rates of social and communication deficits and stereotyped behaviors were found in the relatives in the families with multiple-incidence autism.* *Conclusions:* *These data suggest that further studies should be undertaken to delineate the boundaries of the broader autism phenotype and that this broader phenotype should be included in some future genetic analyses of this disorder.*

(Am J Psychiatry 1997; 154:185–190)

Autism is a behavioral syndrome defined by the presence of social deficits, communication abnormalities, stereotyped or repetitive behaviors, and a characteristic course. There is now considerable evidence from family and twin studies that, for a subgroup of autistic individuals, the etiology is mainly genetic (1). The risk of recurrence of autism in families (i.e., the frequency of autism in subsequently born siblings) is estimated at 6%–8%, or up to 200 times the risk in the general population (2). Three twin studies of geographically defined populations (3–5) detected pairwise concordance rates of approximately 65% (the average over the three studies) and 0%, in monozygotic and dyzygotic pairs, respectively, producing a heritability estimate of over 90%. Further, there is no convincing evidence that perinatal factors play an important role in the etiology of most cases of autism (6).

Although the importance of genetic factors in autism has been firmly established, the definition of the phenotype for use in genetic studies continues to be in question. A number of family and twin studies have suggested that a behavioral phenotype that is qualitatively similar to but more broadly defined than that which defines autism occurs more commonly in relatives of autistic individuals than in the general population. In the first twin study of autism, in addition to finding a pairwise concordance rate for autism of 36% among 11 monozygotic pairs, Folstein and Rutter (3) reported an even higher concordance rate (82%) for a more broadly defined cognitive impairment that included autism, mental retardation, language delay, reading disorder, spelling disorder, or articulation disorder. August et al. (7) reported further possible evidence to support the relationship of cognitive disorders to autism, showing the familial aggregation of these disorders in the siblings of autistic probands. However, these investigators questioned whether the aggregation of cognitive disorders in autism families was confounded by the co-occurrence of mental retardation in the majority of the autistic probands. A subsequent study by Freeman et al. (8), directly testing the relatives of autistic probands and comparing data on them to published norms, failed to detect higher rates of cognitive disorders in the autism relatives. Similarly, Szatmari et al. (9) reported no differences on direct testing in a comparison of the relatives of probands with pervasive developmental disorder and the relatives of Down syndrome probands. More recently, Szatmari et al. (10) used the family history method and also failed to find a higher rate of cognitive deficits in relatives of probands with pervasive developmental disorder.

Accompanying the reports of possible cognitive deficits in relatives of autistic individuals have been parallel reports of the aggregation of social deficits in family mem-

Received Nov. 29, 1995; revision received July 15, 1996; accepted Sept. 3, 1996. From the Department of Psychiatry, University of Iowa College of Medicine. Address reprint requests to Dr. Piven, 1875 John Pappajohn Pavilion, Department of Psychiatry, University of Iowa Hospitals and Clinics, Iowa City, IA 52242-1057; jpiven@blue.weeg.uiowa.edu (e-mail).

Supported by NIMH grants MH-51217 and MH-01028.

The authors thank Edwin Cook, M.D., Elizabeth Reeves, M.D., Debra Scott-Miller, Gerald Gritzmacher, and the Iowa Department of Education for help with the ascertainment of families for this study.

bers. Wolff et al. (11), blind to proband diagnosis, interviewed the parents of autistic children and the parents of nonautistic mentally retarded comparison subjects and found that the parents of the autistic children were more often judged to lack emotional responsiveness and empathy, show impaired rapport with the examiner, and have histories of oversensitivity to experience, special interest patterns, and oddities of social communication. Landa et al. (12, 13) reported significant differences between parents of autistic and Down syndrome probands who were rated blindly on measures of social language use and spontaneous narrative discourse. Gillberg (14), in a study of the parents of 23 children with Asperger syndrome, reported social deficits in 11 of the 23 fathers that were similar to, but milder than, those seen in Asperger syndrome. In a study using best-estimate ratings of subjects and informants directly interviewed with a semistructured personality interview, Piven et al. (15) detected significantly higher rates of social deficits in the parents of autistic children than in the parents of children with Down syndrome.

Most recently, Bolton et al. (16) used a semistructured family history interview, designed to examine features hypothesized to be part of a more broadly defined autism phenotype, to examine the family histories of the first-degree relatives of 99 autistic and 36 Down syndrome probands. The results indicated that the relatives of the autistic probands had significantly higher rates of communication and social deficits and stereotyped behaviors than the relatives of the Down syndrome probands. Similarly, in their twin study of autism Bailey et al. (5) found a 92% concordance rate for the presence of either a social or cognitive abnormality in monozygotic twins, compared to a 10% rate in dizygotic twins. In contrast to these results, however, is the report by Szatmari et al. (10), who used the same family history schedule used by Bolton et al. (16) and found no difference in the rate of social or communication deficits between comparison subjects and relatives ascertained through a proband with pervasive developmental disorder.

In the present study we used the family history method to examine rates of a more broadly defined autism phenotype (as defined previously by Bolton et al. [16]) in a sample of relatives ascertained through two autistic siblings (multiplex autism families) and comparison subjects. To our knowledge, rates of the broader autism phenotype have not been previously reported for families with multiple-incidence autism. These families offer several advantages over families ascertained through a single autistic proband. Probands in multiple-incidence autism families are less likely than those in single-incidence families to have autism as a result of nongenetic causes (see review by Piven and Folstein [1]) and are therefore likely to represent a more etiologically homogeneous sample than probands from families ascertained through a single autistic proband. In addition, relatives ascertained through families with multiple-incidence autism may have a higher genetic liability for autism than relatives ascertained through families with single-incidence autism or pervasive developmental disorder. For these reasons, relatives in families with multiple-incidence autism provide a potentially important study group for exploring the boundaries of the phenotype in autism.

METHOD

Selection of Autism Families

Families with at least two autistic children were ascertained for this study through a systematic search for 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 possibly 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 (aged 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) a review of medical records indicated that neither proband had evidence of a major co-occurring medical condition thought possibly to be etiologically related to autism, such as tuberous sclerosis, neurofibromatosis, phenylketonuria, a chromosomal anomaly identified on karyotype or fragile X screening, or noteworthy CNS injury (1).

Iowa families. Through a medical record review of patients seen over the last 24 years in the child psychiatry clinic at the University of Iowa and currently living in Iowa, 23 families were identified as possibly having two autistic children. These families were recontacted regarding participation in the study. Four families refused to participate, and one could not be located, leaving 18 potential families for further screening. Letters requesting referral of families with at least two children suspected of having autism were subsequently sent to all pediatricians and family practitioners in Iowa (N=1,260). After two mailings, 79% of the physicians responded, identifying 28 unique families with potential multiple-incidence autism sibships. Eleven families were already known through our medical record review at the University of Iowa. Six were excluded on the basis of a telephone discussion with the referring physician or a review of medical records that indicated that a diagnosis of autism was unlikely. One pair of adopted siblings met the diagnostic criteria for the study but were excluded because the biological parents were unavailable for participation. Four families refused to participate or could not be located. Therefore, of the 28 potential multiple-incidence sibships identified by the Iowa pediatricians and family practitioners, six were left for further screening.

During the first six months of 1994, all public schools in Iowa were systematically screened by area special education directors, who contacted the schools in their districts to learn of sibships with potential multiple-incidence autism. Sixteen sibships were identified. Fourteen were already known to us, and one family refused further contact, leaving one sibship with potential multiple-incidence autism.

At this level of screening, 25 sibships with potential multiple-incidence autism were identified in Iowa. After direct evaluation (to be described), seven families were excluded as both probands did not meet the study criteria for autism, leaving 18 families. No proband was found on physical examination to have evidence of a major co-occurring medical condition. Of the 36 identified probands, at least one in each of the 18 multiple-incidence sibships had been cytogenetically tested for fragile X or was subsequently tested before entry into our study. All subjects were negative for the fragile X anomaly.

Non-Iowa families. At the start of this study five families with multiple-incidence autism were known to Dr. Edwin Cook at the University of Chicago and were referred to our study. All agreed to participate. Four families known to Dr. Elizabeth Reeves at the St. Paul-Ramsey County Hospital in Minnesota were also referred to our study; two refused to participate, leaving a total of seven families with multiple-incidence autism ascertained from outside of Iowa. Direct examination (to be described) indicated that they all met the study criteria for autism, and none was excluded because of a major medical condition or cytogenetic evidence of fragile X syndrome.

Final sample. The final 25 multiplex autism families included 42

male and eight female autistic probands ranging in age from 4 to 28 years. Adequate estimates of performance IQ were available from the medical records of 45 of the 50 probands. The following IQ measures, if administered by a psychologist, were considered adequate for estimation of performance IQ: the Wechsler Intelligence Scale for Children—Revised (17), the Wechsler Intelligence Scale for Children—III (18), the Wechsler Adult Intelligence Scale—Revised (19), the Leiter International Performance Scale (20), and the Merrill-Palmer Scale of Mental Tests (21). When results of multiple tests were available, the test (with priority as indicated in the preceding list) performed closest to 12 years of age was used for estimating performance IQ. The performance IQs of 51% of the subjects were 70 or higher, 22% were 50–69, 27% were 30–49, and none was less than 30. Five probands were felt to not have had adequate testing at the time this study was undertaken, either because the test used was inappropriate or the proband had difficulty taking the test. Resources were not available to attempt further testing of these five individuals.

After complete description of the study to the subjects, written informed consent was obtained from the adults and written informed assent was obtained from the minors.

Selection of Comparison Families

Thirty families each having a child with Down syndrome secondary to a nondysjunction of chromosome 21 constituted the comparison group in this study. 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 child with Down syndrome would not be expected to have a greater genetic liability, over that of the general population, for social or communication deficits or stereotyped behaviors—the behavioral variables of interest in this study.

An attempt was made to obtain equal numbers of families in each of three proband age groups: 4–12, 13–18, and >18 years. Initially, a letter to parents was sent home with children in the public schools in eastern Iowa. Nine families, all in the lowest proband age group, were recruited by this means. Using a second strategy, we randomly recruited the remaining 21 families (70%) from a list of the families of newborns diagnosed with Down syndrome at the University of Iowa who lived within 150 miles of the university. To obtain comparable numbers of families in the three proband age groups, preference was given first to families who had probands in the middle and oldest age groups. The final group of Down syndrome families included 13 male and 17 female Down syndrome probands. The probands' ages ranged from 2 to 27 years.

After description of the study, written informed consent was obtained from the adults, and written informed assent was obtained from the minors.

Assessment of Autistic Probands

Diagnosis. Parents of all subjects were interviewed regarding the subjects' diagnosis with a standardized interview, the Autism Diagnostic Interview (22). An algorithm constructed for use with the Autism Diagnostic Interview (which uses the ICD-10 criteria for autism [23]) has been shown to adequately discriminate autistic and nonautistic IQ-matched subjects (22). For 10 videotaped interviews, adequate interrater agreement (kappa <0.90) on diagnoses of autism made by using the algorithm was established by all raters before the start of data collection. In addition, the probands were directly assessed by using the Autism Diagnostic Observation Schedule (24), 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 major neurological impairment or medical conditions thought to be etiologically related to autism (listed earlier). Almost all subjects had been previously screened through a medical evaluation at a tertiary care center and not found to have evidence of any exclusionary criteria for this study. No subject was excluded on the basis of our additional neurodevelopmental screening examination.

Family history interview. The parents were interviewed through use of a standardized family history interview—the Family History Interview for Developmental Disorders of Cognition and Social Functioning—to query for the presence of a range of abnormalities that have been previously reported to occur at high rates in members of families of autistic probands or have been hypothesized to possibly be genetically related to autism. This instrument was jointly developed by researchers at the Institute of Psychiatry in London (under the direction of Professor Michael Rutter) and the Johns Hopkins University (under the direction of Dr. Susan Folstein) for use in a cross-national collaborative family study of autism. This interview includes additional probes for a range of developmental characteristics (including motor development, IQ, communication skills, academic skills, and social behaviors) and psychiatric disorders and symptoms. Questions about adult and childhood functioning are also asked separately. Characteristics are generally rated as absent (rating=0), mild or probably present (rating=1), or severe or definitely present (rating=2). A more detailed description of this interview schedule has been provided by Bolton et al. (16).

The items from the family history interview to be examined in this study were those that were contrasted in the autistic and comparison subjects in the autism family study of Bolton et al. (16). In the study by Bolton et al., items were selected for comparison on the basis of a confirmatory factor analysis demonstrating loading of items onto three principal factors that parallel the defining features of autism: deficits in communication, deficits in reciprocal social interaction, and the presence of selected stereotyped or repetitive behaviors. With guidance from the factor analysis and conceptual notions about a latent autism phenotype, relevant items on the family history interview were combined to produce operational definitions for the three domains of behavior examined. Except for some minor changes, the definitions used in the present study for communication and social deficits and stereotyped behaviors are identical to those used in the Bolton et al. study; these are listed in table 1. In general, a subject was considered affected in a particular behavioral domain if at least two behaviors were present to a mild or probable degree (i.e., had a rating of 1) or if at least one behavior in the domain was rated as severe or definitely present (i.e., had a rating of 2). Several items included in the Bolton et al. study (16) were not included in the version of the interview used in this study (including the items "childhood social dysfunction," "adult social dysfunction and isolation," and "adult repetitive behaviors") and therefore are not included in our analyses. In addition, the item "obsessions and compulsions" was not included in our definitions of stereotyped behaviors on the basis of a previous study (25) in which we failed to detect high rates of obsessive-compulsive disorder in the parents of autistic individuals.

The parents in each family were interviewed about themselves and about the siblings, grandparents, aunts and uncles, and first cousins of the probands. Because of the extensive involvement with families required in this study and the limited resources available, we could not remain blind to the case-control status of the subjects. To limit any bias resulting from this practice, case vignettes based on the information gathered with the family history interview were composed for all parents and rated blindly by one of us (J.P.).

Analysis

Sample characteristics for the autistic and comparison subjects (e.g., parental age, education level) were compared by using simple statistics. The analysis of family data required that we account for the fact that relatives within the same family (aunts/uncles, grandparents, and parents) are not statistically independent. To take this into account in the analysis, we treated the family as the unit of analysis. For example, the presence of a history of social deficits in one parent or the other was treated as the independent variable in a logistic regression predicting family diagnosis (autism versus Down syndrome). Similarly, logistic regression was used in case-control comparisons by family of aunts and uncles and by family of grandparents. There was no significant difference between the autism families and the Down syndrome families in either the number of aunts and uncles ($t=0.26$, $df=53$, $p=0.78$) or the number of grandparents ($t=1.41$, $df=53$, $p=0.16$). Results were considered significant if they passed the $p<0.05$ level of significance (two-tailed).

TABLE 1. Definitions of Behavioral Deficits Used in Family History Study of Multiple-Incidence Autism Families[a]

Behavioral Deficit	Definition
Communication deficits	
Language delay	No single words at age 2 years; no phrases by 33 months
Reading retardation (8 years or older)	Educational assessment for reading problems; remedial help
Articulation disorder (5 years or older)	Speech therapy; strangers unable to understand at age 5
Spelling difficulties (8 years or older)	Frequent errors with common words
Social deficits	
Lack of affection (4 and 5 years)	Little or no spontaneous affection
Impaired social play (1 to 6 years)	Little to-and-fro social play
Impaired friendships (6 to 16 years)	Limited or no friendships
Lack of conversation (4 to 15 years)	Limited or no to-and-fro conversation
Lack of friends (adulthood)	Few or no friends
Impaired conversation (adulthood)	Limited or no conversation
Social inappropriateness (adulthood)	Striking, frequent inappropriate behavior
Stereotyped behaviors	
Circumscribed interests (16 years or older)	All-encompassing interest that is unusual in its intensity and exclusion of other activities but is not odd or socially inappropriate; all-encompassing odd or socially inappropriate interest that is unusual in its intensity and exclusion of other activities
Rigidity (16 years or older)	Rigid or perfectionistic style that is commented on by others outside the family but not associated with impairment; rigid or perfectionistic style of behavior that is associated with impairment

[a]Items were selected from the Family History Interview for Developmental Disorders of Cognition and Social Functioning. Communication deficits and stereotyped behaviors were considered present if one item was given a rating of 2 or two items were given ratings of 1. Social deficits were considered present if one item was rated as "definitely present" or two items were rated as "probably present."

RESULTS

Twenty-five mothers and 23 fathers from the 25 multiple-incidence autism families and 30 mothers and 30 fathers from the 30 Down syndrome families participated in this study. A parent in an autism family 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, and so only 23 autism fathers were included in this analysis. There was no significant difference between the autism and comparison families 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 ($\chi^2=6.95$, $df=4$, $p=0.14$). The father's occupational level, as specified by the British Manual of the Classification of Occupations (26), also did not differ significantly between the two groups ($\chi^2=6.2$, $df=4$). Although the parent groups did not differ on these demographic variables, it is notable that seven (30%) of the 23 autism fathers versus one (3%) of the 30 Down syndrome fathers ($\chi^2=5.50$, $df=1$, $p=0.02$) each reported two or more episodes of either resigning or being fired from his job because of inability to get along with a colleague or supervisor.

Comparison of the autism and Down syndrome parents by means of multivariate logistic regression, with social and communication deficits and stereotyped behaviors included in the model, revealed significant differences between the two groups (–2 log likelihood $\chi^2=19.9$, $df=3$, $p<0.0002$). The results of comparisons of the parental groups separately on social deficits, communication deficits, and stereotyped behaviors are presented in table 2. The autism parents showed significantly higher rates of social deficits and stereotyped behaviors but not communication deficits than did the Down syndrome parents. One autism father met the criteria for autism on the basis of current behavior, but no informants could be obtained to verify the presence of autistic behavior in childhood.

To examine these differences in more distantly related relatives and attempt replication of the findings for the parents, we similarly compared the grandparents and the aunts and uncles in the autism and Down syndrome families (autism families: 96 grandparents, 145 aunts and uncles; Down syndrome families: 120 grandparents, 168 aunts and uncles). The results, presented in table 2, demonstrate that a pattern of group differences similar to those found in the parents was detected in both the grandparent and aunt/uncle groups. As it was felt that childhood communication behaviors could not be reliably assessed in grandparents, rates of communication deficits in the grandparents were not analyzed. Differences in communication between the autism and Down syndrome aunt/uncle groups were also detected. One maternal uncle in the autism group had received a previous clinical diagnosis of autism.

The sample of multiple-incidence autism families included only 12 siblings in addition to the probands (one of whom also met the criteria for autistic disorder of the Autism Diagnostic Interview); the Down syndrome group contained 53 siblings. The small number of siblings in the autism group precluded meaningful comparisons; however, even within this small sample of siblings there was evidence of a higher rate of social deficits—33% (N=4) versus 0% among the siblings in the Down syndrome families. No differences were suggested from comparison of the rates of communication deficits—0% versus 8% (N=4)—or stereotyped behaviors—0% versus 2% (N=1)—in siblings. Information on first cousins was not uniformly available to the parents, and therefore data on first cousins were not analyzed.

To take into account possible bias of ascertainment due to inclusion of families recruited from outside of Iowa (i.e., families not ascertained epidemiologically), we examined rates of social and communication deficits and stereotyped behaviors in the parents from the 18 families ascertained epidemiologically in Iowa. Differences simi-

TABLE 2. Logistic Regression Comparison of 25 Families With Multiple-Incidence Autism and 30 Families With One Down Syndrome Proband on Three Types of Behavioral Deficits in Parents, Grandparents, and Aunts and Uncles

Type of Relative	–2 Log Likelihood χ^2 (df=1)		
	Social Deficits	Communication Deficits	Stereotyped Behaviors
Parents	10.1***	0.9	5.1**
Grandparents	2.8*	—	4.1**
Aunts and uncles	6.6**	6.3**	4.1**

*p<0.10. **p<0.05. ***p<0.01.

TABLE 3. Comparison of 25 Families With Multiple-Incidence Autism and 30 Families With One Down Syndrome Proband on Frequency of Three Types of Behavioral Deficits in Fathers and Mothers

Type of Relative and Behavioral Deficit	Autism		Down Syndrome		–2 Log Likelihood χ^2 (df=1)	
	N	%	N	%	χ^2	p
Fathers[a]						
Social deficits	13	57	4	13	11.46	0.0007
Communication deficits	5	22	6	20	0.02	n.s.
Stereotyped behaviors	6	26	1	3	6.22	0.01
Mothers						
Social deficits	9	36	4	13	3.92	0.05
Communication deficits	5	20	0	0	8.49	0.004
Stereotyped behaviors	3	12	0	0	4.91	0.03

[a]Only 23 fathers from the autism families participated.

lar to those found in the total sample were again detected; i.e., the autism parents showed significantly higher rates of social deficits and stereotyped behaviors, but not communication deficits, than the parents in the Down syndrome families.

To explore possible gender effects in the features of the broader autism phenotype, we compared the rates of social and communication deficits and stereotyped behaviors in the autism and Down syndrome fathers and in the autism and Down syndrome mothers. The results are presented in table 3. Significantly higher rates of social deficits and stereotyped behaviors, but not communication deficits, were detected in the autism fathers, whereas higher rates of communication deficits, social deficits, and stereotyped behaviors were detected in the autism mothers. The significant difference in stereotyped behaviors in the mothers was based on a low rate of occurrence (12%) and reached significance, in part, because of the absence of any Down syndrome mothers with these behaviors. Similarly, high specificity was demonstrated for communication deficits in the autism mothers; communication deficits occurred in 20% of the autism mothers and none of the Down syndrome mothers.

To avoid performing multiple comparisons and potentially inflating our rate of type I errors, we did not undertake statistical comparisons of the rates of individual items from the family history interview in the parents in the autism and Down syndrome families. However, it is notable that the highest rates of any individual items were found for the autism fathers; 52% (N=12) were found to have few or no adult friendships (versus 3% of the Down syndrome fathers; N=1), and 48% (N=11) were found to be rigid (versus 7% of the Down syndrome fathers; N=2). The item "socially inappropriate" demonstrated the highest specificity for autism of any individual item examined in the parents, occurring in 26% of the autism fathers (N=6) and 0% of the Down syndrome fathers.

DISCUSSION

In this study we have replicated and extended the finding of others (3, 5, 7, 11, 13, 15, 16) that the relatives of autistic probands show familial aggregation of behaviors that are milder than but qualitatively similar to the defining features of autism. Within this study, the findings for the parents in the autism families were replicated in the grandparents and in the aunts and uncles in the autism families. These findings suggest that the social and communication deficits and stereotyped behaviors examined in this study may be expressions of the genetic liability for autism.

To our knowledge, the present study is the first to examine these characteristics in relatives ascertained through sibships with multiple-incidence autism. Families ascertained in this manner are likely to be more etiologically homogeneous than those ascertained through probands from single-incidence families and perhaps may also have a higher genetic liability for autism. An additional strength of this study is the inclusion of an epidemiologically ascertained sample in Iowa. A limitation of this study is the use of the family history method. While this method has been reported to underestimate the rate of psychiatric disorders in families (27), the validity of this method for examining the characteristics measured in this study has been less well established. In addition, it should be noted that while the parents of the probands with Down syndrome were selected to take into account the possible effects of having a handicapped child, the stress of having two autistic children is likely to be substantially greater than that of raising a child with Down syndrome.

While our findings are in general agreement with those of Bolton et al. (16), the rate of deficits detected in the first-degree relatives of autism and Down syndrome probands by Bolton et al. was substantially lower than the rate detected in our study, precluding any comparison of absolute rates across studies. The findings of this study, however, differ from the results obtained in the family history study of Szatmari et al. (10), in which a high rate of either social or communication deficits was not found in the families of probands with pervasive developmental disorder. The critical difference between our results and those of Szatmari et al. (10) may be that we ascertained families that contained two autistic siblings, whereas Szatmari et al. ascertained families that each contained a single proband with pervasive developmental disorder. Pervasive developmental disorder, a more broadly defined condition than autism, is more common in the population and likely to be a more etiologically heterogeneous dis-

order than autism. Selecting families through multiple-incidence autism sibships is likely to result in a more homogeneous group of families with a higher genetic liability for the behaviors we examined.

Our results suggest possible sex-specific differences in the expression of the broader autism phenotype. The absence of a significant difference between the rates of communication deficits in the autism and Down syndrome fathers can not be taken to mean that these deficits do not exist, given the limitations of the family history method. The lack of significance in this comparison may reflect the small size of the samples being compared. However, there may be gender differences in the degree to which parents exhibit communication deficits. The high rate of communication deficits in the autism mothers (20%) was striking, whereas these deficits were completely absent in the Down syndrome mothers. These results warrant examination in an independent sample.

The findings in this study have implications for future genetic studies of autism. Although the genetic basis for autism is well established, the mechanism of genetic transmission has not yet been determined. Future genetic analyses aiming to delineate genetic mechanisms in autism (e.g., segregation analyses) need to consider the inclusion of the broader autism phenotype in their definitions of affected individuals. Similarly, inclusion of the broader autism phenotype in lod score analysis could substantially improve the power to detect genes for autism, over the power of nonparametric methods, by increasing the number of affected individuals available for study and by improving the specificity of diagnosing nonaffected subjects. The issue of power is particularly relevant in genetic linkage studies of autism, given the absence of vertical transmission of the narrow phenotype (i.e., autism) and the often small size of families with autistic children (28). The results of this study and of others suggesting the existence of a genetically related broader autism phenotype indicate the need for further detailed studies, using direct assessment of relatives, to clarify the range of characteristics that define the boundaries of this phenotype. Further, the high rate of deficits found in parents in families with multiple-incidence autism suggests the potential importance of comparing the rate of the broader phenotype in relatives ascertained through two or more autistic probands with the rate for relatives ascertained through a single autistic proband.

REFERENCES

1. Piven J, Folstein S: The genetics of autism, in The Neurobiology of Autism. Edited by Bauman ML, Kemper TL. Baltimore, Johns Hopkins University Press, 1994
2. Ritvo ER, Jorde LB, Mason-Brothers A, Freeman BJ, Pingree C, Jones MB, McMahon WM, Petersen PB, Jensen WR, Mo A: The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counseling. Am J Psychiatry 1989; 146:1032–1036
3. Folstein SE, Rutter ML: Infantile autism: a genetic study of 21 twin pairs. J Child Psychol Psychiatry 1977; 18:297–321
4. Steffenburg S, Gillberg C, Holmgren L: A twin study of autism in Denmark, Finland, Iceland, Norway, and Sweden. J Child Psychol Psychiatry 1989; 30:405–416
5. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M: Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 1995; 25:63–77
6. Piven J, Simon J, Chase GA, Wzorek M, Landa R, Gayle J, Folstein S: The etiology of autism: pre-, peri- and neonatal factors. J Am Acad Child Adolesc Psychiatry 1993; 32:1256–1263
7. August GJ, Stewart MA, Tsai L: The incidence of cognitive disabilities in the siblings of autistic children. Br J Psychiatry 1981; 138:416–422
8. Freeman BJ, Ritvo ER, Mason-Brothers A, Pingree C, Yokota A, Jensen WR, McMahon WM, Petersen PB, Mo A, Schroth P: Psychometric assessment of first-degree relatives of 62 autistic probands in Utah. Am J Psychiatry 1989; 146:361–364
9. Szatmari P, Jones MB, Tuff L, Bartolucci G, Fisman S, Mahoney W: Lack of cognitive impairment in first-degree relatives of pervasive developmental disorder probands. J Am Acad Child Adolesc Psychiatry 1993; 32:1264–1273
10. Szatmari P, Jones MB, Fisman S, Tuff L, Bartolucci G, Mahoney WJ, Bryson SE: Parents and collateral relatives of children with pervasive developmental disorders: a family history study. Am J Med Genet 1995; 60:282–289
11. Wolff S, Narayan S, Moyes B: Personality characteristics of parents of autistic children. J Child Psychol Psychiatry 1988; 29: 143–153
12. Landa R, Folstein SE, Isaacs C: Spontaneous narrative-discourse performance of parents of autistic individuals. J Speech Hear Res 1991; 34:1339–1345
13. Landa R, Piven J, Wzorek M, Gayle J, Chase G, Folstein S: Social language use in parents of autistic individuals. Psychol Med 1992; 22:245–254
14. Gillberg C: Asperger syndrome in 23 Swedish children. Dev Med Child Neurol 1989; 31:520–531
15. Piven J, Wzorek M, Landa R, Lainhart J, Bolton P, Chase GA, Folstein S: Personality characteristics of parents of autistic individuals. Psychol Med 1994; 24:783–795
16. Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, Bailey A, Rutter M: A case-control family study of autism. J Child Psychol Psychiatry 1994; 35:877–900
17. Wechsler D: Wechsler Intelligence Scale for Children—Revised. New York, Psychological Corp, 1974
18. Wechsler D: Wechsler Intelligence Scale for Children, 3rd ed. San Antonio, Tex, Psychological Corp, 1991
19. Wechsler D: Wechsler Adult Intelligence Scale—Revised. New York, Harcourt Brace Jovanovich, 1981
20. Arthur G: The Arthur Adaptation of the Leiter International Performance Scale. Chicago, Psychological Services Press, 1952
21. Stutsman R: Guide for administering the Merrill-Palmer Scale of Mental Tests, in Mental Measurement of Preschool Children. Edited by Terman LM. New York, Harcourt, Brace and World, 1952
22. Le Couteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J: Autism Diagnostic Interview: a standardized investigator-based instrument. J Autism Dev Disord 1989; 19:363–387
23. World Health Organization: ICD-10 Categories F00-F99 Mental and Behavioral Disorders (Including Disorders of Psychological Development): Clinical Descriptions and Guidelines. Geneva, WHO, 1992
24. Lord C, Rutter M, Goode S, Heemsbergen J, Mawhood L, Schopler E: Autism Diagnostic Observation Schedule: a standardized observation of communicative and social behavior. J Autism Dev Disord 1989; 19:185–212
25. Piven J, Landa R, Gayle J, Cloud D, Chase G, Folstein SE: Psychiatric disorders in the parents of autistic individuals. J Am Acad Child Adolesc Psychiatry 1991; 30:471–478
26. British Manual of the Classification of Occupations. London, Office of Population Censuses and Surveys, 1980
27. Andreasen NC, Endicott J, Spitzer RL, Winokur G: The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 1977; 34:1229–1235
28. Szatmari P, Jones MB: IQ and the genetics of autism. J Child Psychol Psychiatry 1991; 32:897–908