

Personality and Language Characteristics in Parents From Multiple-Incidence Autism Families

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Several studies have suggested that the genetic liability for autism may be expressed in non-autistic relatives of autistic probands, in behavioral characteristics that are milder but qualitatively similar to the defining features of autism. We employ a variety of direct assessment approaches to examine both personality and language in parents ascertained through having two autistic children (multiple-incidence autism parents) and parents of Down syndrome probands. Multiple-incidence autism parents had higher rates of particular personality characteristics (rigidity, aloofness, hypersensitivity to criticism, and anxiousness), speech and pragmatic language deficits, and more limited friendships than parents in the comparison group. The implications of these findings for future genetic studies of autism are discussed. *Am. J. Med. Genet.* 74:398–411, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

There is now considerable evidence supporting the importance of genetic factors in the etiology of autism. The recurrence risk for autism following the birth of an autistic child is approximately 100 times the population base rate [Smalley et al., 1988] and three epidemiologically based twin studies have reported concordance rates for autism among monozygotic (MZ) twins which range from 36% to 91%, as compared to zero

concordance among dizygotic (DZ) twins [Bailey et al., 1995; Folstein and Rutter, 1977; Steffenburg et al., 1989]. These MZ concordance rates suggest that the heritability of autism may be over 90% [Bailey et al., 1995]. Finally, there is little evidence that observable pre- and perinatal factors have a substantial role in the etiology of autism in most individuals with this disorder [Lord et al., 1991; Piven et al., 1993].

Of potential importance in understanding the genetics of autism is the emerging evidence indicating that, in addition to causing autism, the genetic liability for this disorder may also be expressed in non-autistic relatives of autistic probands, in behavioral and cognitive characteristics that are milder but qualitatively similar to the defining features of autism. Folstein and Rutter [1977] were the first to propose this idea, based on finding a high rate of cognitive deficits (e.g., reading and spelling deficits and language delay) in the non-autistic MZ co-twins they examined in their twin study. This proposal echoed the earlier observations of Kanner and Eisenberg [1957], who noted that a number of parents of autistic children they described were "serious minded," perfectionist individuals, with an intense interest in abstract ideas and who appeared to lack a genuine interest in developing relationships with others. Unfortunately, these early observations were misinterpreted to mean that, somehow, parental personality and child-rearing practices resulted in the occurrence of autism. Subsequent studies examining parent-child interactions have consistently failed to support this hypothesis [summarized by Cantwell et al., 1976]. However, while the notion that family environment plays a role in the etiology of autism has clearly been laid to rest, there is mounting evidence suggesting that particular behavioral characteristics may occur more commonly in the family members of autistic individuals than in the general population.

In the first large-scale systematic assessment of the family members of autistic children, Bolton et al. [1994], using the family history method, demonstrated higher rates of social and communication deficits and stereotyped behaviors in the parents and siblings of 99 autistic probands, compared to the parents and siblings of 36 Down syndrome (DS) probands. They referred to the occurrence of these characteristics in fam-

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ily members as evidence of a "broader autism phenotype (BAP)." Similarly, in the twin study by Bailey et al. [1995] concordance for the BAP was detected in 92% of MZ twin pairs, whereas only 10% concordance for these more broadly defined characteristics was noted in DZ pairs. Recently, the findings by Bolton et al. [1994] have been replicated and extended in a sample of 25 multiple-incidence autism and 30 DS families [Piven et al., 1997], showing significantly higher rates of social and communication deficits and stereotyped-repetitive behaviors in parents, aunts and uncles, and grandparents in the autism families. Earlier family history studies of autism by Piven et al. [1990], DeLong and Dwyer [1988], and Gillberg [1989] are consistent with the results of these studies. However, a family history study by Szatmari et al. [1995], examining parents of 52 probands with pervasive developmental disorder and controls, failed to find evidence of differences in personality characteristics, speech, or conversation.

While the results of these family history studies strongly suggest the existence of a broader autism phenotype, the family history method is probably not sufficient for fully defining the boundaries of this extended phenotype. To accomplish this, studies employing direct assessment of relatives using a variety of behavioral, cognitive, and possibly biological approaches are necessary. Clarification of the boundaries of the BAP will allow more accurate identification of affected relatives, potentially increasing our understanding of genetic mechanisms, as well as increasing the number of affected individuals available for genetic linkage studies in this disorder.

Several studies employing direct assessment of a variety of behavioral characteristics in relatives of autistic probands have been undertaken [Landa et al., 1992; Piven et al., 1994; Wolff et al., 1988]. These studies support the early observations of Kanner and Eisenberg [1957] and others and are in general agreement with the results of family history studies. However, as with most first attempts, conclusions from these studies have been limited by several methodological shortcomings. Wolff et al. [1988], blind to proband diagnosis, employed a clinical interview to assess the parents of 21 autistic children and the parents of 21 non-autistic mentally retarded controls. Parents of autistic children were more often judged to have 'schizoid' personality traits, based on the presence of a lack of emotional responsiveness and empathy, impaired rapport with the examiner, a history of and preference for being alone, over-sensitivity to experience, special interest patterns and oddities of social communication. While the results of this study offer a much richer picture of the range of personality characteristics that might make up the broader autism phenotype than afforded by the family history data, a significant limitation of this study was the failure to employ a standardized interview that would facilitate replication of these results. Piven et al. [1994] undertook a preliminary analysis of a subset of families from the Baltimore Autism Family Study (BAFS), using best-estimate ratings derived from a standardized personality interview of subjects and informants (the modified Personality Assessment Schedule, M-PAS). Parents of 38 autistic pro-

bands were rated as aloof, untactful, and undemonstrative, more commonly than the parents of 20 Down syndrome (DS) controls. The personality interview employed in this study was developed jointly for use in the BAFS, conducted at Johns Hopkins, under the direction of Susan Folstein, in parallel with a family study conducted at the Institute of Psychiatry, under the direction of Michael Rutter. As part of the first systematic and comprehensive study of the broader phenotype in relatives of autistic probands, the intent of this instrument was to cast a broad net for all potentially relevant personality characteristics of the BAP that could be reliably assessed by direct interview of a subject and informant. While the exploratory results of the study by Piven et al. [1994] suggested that social deficits were present in autism parents more commonly than in controls, only weak to moderate effects were detected in 3 of 18 characteristics examined and the results were not corrected for multiple comparisons. In addition, as a result of the lengthy assessment protocol parents could not be rated blind to case-control status. The results from the study by Piven et al. [1994] suggested that further direct study of personality characteristics in relatives of autistic probands is warranted, employing more focused hypotheses regarding the components of the BAP, blind ratings, and a sample with greater power to detect existing differences.

Finally, in another preliminary analysis of a subset from the BAFS, a complementary approach to the assessment of personality characteristics through a semi-structured interview was taken by Landa et al. [1992], who blindly examined the social use of language in parents of autistic probands and controls during conversations with the interviewers. Using the sum of 19 items from the Pragmatic Rating Scale (PRS), autism parents were found to demonstrate pragmatic language deficits significantly more commonly than controls. While these results were obtained using blind ratings and a standardized assessment instrument, they were focused on only a narrow aspect of the BAP (i.e., social use of language), and require replication in an independent sample.

In the present study, we employ a variety of direct assessment approaches to examine both personality and language in parents ascertained through having two autistic children (multiple-incidence autism parents) and controls. Direct assessments of personality and language characteristics have not been previously reported in multiple-incidence autism families. These families offer several advantages over families ascertained through a single autistic proband. Probands in multiple-incidence autism families are less likely than single-incidence probands to have autism as a result of non-genetic causes [see review by Piven and Folstein, 1994] and therefore are likely to represent a more etiologically-homogeneous sample 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 BAP) than relatives ascertained through families of single-incidence autistic or PDD probands. For these reasons, relatives in multiple-incidence au-

tism families provide a potentially important study group for exploring the boundaries of the phenotype in autism. In addition, in this study we employ blind ratings using modified versions of instruments we previously employed in the study of parents from single-incidence families and focus more narrowly on hypotheses generated from previous work by our group and others.

METHODS

Sample Selection

Autism families. Families with at least two autistic children were ascertained for this study through a systematic ascertainment of 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 (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) on medical record review, neither proband had evidence of a significant co-occurring medical condition thought to possibly be etiologically related to autism, such as tuberous sclerosis, neurofibromatosis, phenylketonuria, a chromosomal anomaly identified on karyotype or Fragile X screening or significant CNS injury [Piven and Folstein, 1994]. 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.

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 re-contacted 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 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 review of medical records which revealed that a diagnosis of autism was unlikely. One adopted sibship met diagnostic criteria for the study but was excluded on the basis of the biological parents unavailability to participate, and five families either refused or could not be located, leaving six potential multiple-incidence sibships 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 schools in their districts to learn of potential multiple-incidence autism sibships. Sixteen sibships were identified. Fourteen were already known to us and one refused further contact, leaving one potential multiple-incidence autism sibship.

Twenty-five potential multiple-incidence autism sibships were identified in Iowa at this level of screening. On direct evaluation (see below) seven families were excluded as both probands did not meet study criteria for autism, leaving 18 families. On physical examination, no proband was found to have evidence of a significant co-occurring medical condition. Of the 36 identified probands, at least one proband in each of the 18 multiple-incidence sibships had been or was subsequently tested cytogenetically upon entry into our study for Fragile X. All subjects were negative for the Fragile X anomaly.

Non-Iowa families At the start of this study, five multiple-incidence autism families 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 multiple-incidence autism families ascertained from outside of Iowa. On direct examination (see below) all met study criteria for autism and none were excluded for having a significant medical condition or cytogenetic evidence of Fragile X syndrome.

Final sample of multiple-incidence autism families The sample of 25 multiplex autism families included 42 male and 8 female autistic probands ranging from 4 to 28 years of age. Adequate performance IQ (pIQ) estimates were available on 45 of 50 probands from the medical record. The following IQ measures, if obtained by a psychologist, were considered adequate for estimation of pIQ: the Wechsler Intelligence Scale for Children-Revised [Wechsler, 1974], the Wechsler Intelligence Scale for Children-III [Wechsler, 1991], the Wechsler Adult Intelligence Scale-R [Wechsler, 1981], the Leiter International Performance Scales [Arthur, 1952], or the Merrill-Palmer Scales [Stussman, 1952]. When multiple tests were available, the test (in the order of priority listed above) obtained closest to 12 years of age was used for estimating pIQ. Fifty-one percent of subjects had pIQs in the 70+ range, 22% were in the 50–69 range, 27% were in the 30–49 range, and none of those tested were less than 30. Five were felt to not have had adequate testing at the time this study was undertaken, due either to the test employed or their inability to cooperate with testing. Resources were not available to attempt further testing of these five individuals.

Comparison families. Thirty families with a child with Down syndrome (DS), secondary to a nondysjunction of chromosome 21, constituted the comparison group in this study. The rationale for choosing this group was based on 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 DS child would not be expected to

have an increased genetic liability, over 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 2–12, 13–18, and 18+ years. Initially, a letter was sent home to parents of DS children in the public schools in eastern Iowa. Nine families, all in the lower proband age group, were recruited from this source. Using a second strategy, the remaining 21 families (70%) were recruited randomly from a list of families of newborns diagnosed with DS at the University of Iowa who lived within a 150-mile radius of the university. To obtain a comparable number of families in each DS proband age group, families were preferentially recruited who had probands in the middle and oldest age group first. Specifically, 49 DS probands were identified through a random search of the medical record as being in the appropriate age group and living within 150 miles of the university. Letters were sent to these families asking them to write or call our research team if they did not wish to be called regarding a research project involving families with a DS child. Twelve families had either moved from their listed address and were unavailable or indicated they were not interested in receiving a telephone call. Of the 37 remaining families who were called, 11 declined participation in the study. Of the remaining 26 families who agreed to enter the study (i.e., 70% response rate), three were excluded (two had translocation of chromosome 21; one had an autistic relative) and two dropped out because of deaths in the nuclear family, leaving 21 families ascertained through this approach. The final sample of DS families included 13 male and 17 female DS probands. Proband's ranged from 2–27 years of age.

Assessment of Autistic Proband's

Diagnosis Parental informants for all subjects were interviewed regarding the subject's diagnosis with a standardized interview, the Autism Diagnostic Interview (ADI) [LeCouteur et al., 1989]. An algorithm constructed for use with the ADI (using ICD-10 criteria for autism) has been shown to adequately discriminate autistic and non-autistic IQ-matched controls [LeCouteur et al., 1989]. Adequate interrater agreement ($Kappa < .90$) on the ADI-algorithm (using ten videotaped interviews) for a diagnosis of autism was established by all raters prior to the start of data collection. In addition, proband's were directly assessed using the Autism Diagnostic Observation Schedule (ADOS) [Lord et al., 1989], a structured observation and interview schedule developed to aid in the diagnosis and assessment of autistic individuals. The information from the ADOS functioned as a check on the proband's current behavior as reported by the parents on the ADI.

Physical examination. All subjects were evaluated by a screening neurodevelopmental examination for evidence of significant neurological impairment or medical conditions thought to be etiologically related to autism (see above). Almost all subjects had been previously screened through a medical evaluation at a ter-

tiary 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.

Assessment of Parents

Modified Personality Assessment Schedule, Revised (M-PAS-R) Subjects and informants were interviewed by one of two interviewers (P.P., D.J.) with the subject and informant versions of the Modified-Personality Assessment Schedule, Revised (M-PAS-R). The M-PAS-R was part of a 3-hour interview that included a semi-structured interview to elicit the subject's life story (i.e., nodal life events, social life, and school and work history), the Friendship Interview, and a standardized psychiatric interview. A subset of subjects were also administered a semi-structured interview for diagnosing DSM-III-R personality disorder. Only the results of the M-PAS-R and Friendship Interview are reported here.

The M-PAS-R was originally adapted from the Personality Assessment Schedule [Tyrer, 1988; Tyrer and Alexander, 1979; Tyrer et al., 1979], a semi-structured interview for the assessment of personality disorder. A modified version of this instrument (the M-PAS), for the assessment of a subset of 18 personality characteristics that were thought to possibly be components of the broader autism phenotype, was described in detail in a previous report on parents of autistic and DS proband's examined as part of the BAFS (see Piven et al. [1994] for details on the development of the M-PAS). For the present study, the content of the M-PAS was revised (the revised version of which is referred to as the M-PAS-R) in the following ways: (1) ten items that either were infrequently endorsed in the previous study (i.e., eccentricity, self-consciousness, hypochondriasis, and magical thinking) or, based on either analyses from the previous study or anecdotal experiences by the first author, were thought to be unlikely to reflect the broader autism phenotype (i.e., impulsiveness, shyness, suspiciousness, irritability, aggressiveness, and submissiveness) were deleted from the interview schedule. This allowed us to focus our efforts more narrowly on fewer (i.e., eight) characteristics, reducing the resources required and potentially improving the reliability of our assessments. (2) The definition of one characteristic, rigidity, was expanded substantially. In addition to the original intent of this item, to focus on difficulties the subject had in adjustment to change we coded rigidity as present if a subject (or informant) indicated a striking lack of interest in seeking change. The rationale for this change came after discussions with Paul Costa, who suggested that adjustment to change was more likely to represent an aspect of anxiety (already included in our assessment), whereas diminished interest in seeking change reflected a different personality factor, "openness to experience," and seemed to be more in line with the original intent of the item. "Openness to experience" is one of the principal factors making up the five-factor model of personality structure [Costa and McCrae, 1985]. (3) The M-PAS was supplemented with additional optional probes, de-

rived from the first author's previous experience in eliciting characteristics in the interview, and examples of ratings of present and absent. (4) Finally, the language used in the definition of several characteristics was modified in an attempt to make it clearer without changing the intent of the original item. Definitions employed for the eight characteristics of the M-PAS-R appear in Appendix 1.

In the previous study by Piven et al. [1994] of personality characteristics in parents of autistic probands, the 18 characteristics of the M-PAS were defined by ratings on a 0–7 point scale of intensity. Adequate interrater reliability was demonstrated in that study for the presence (0, 1) or absence (2–7) of the characteristics on the M-PAS (i.e., mean pairwise kappa of 0.91, with only one characteristic, submissive, having a kappa value of <0.70). Although intra-class correlations on all 18 characteristics were greater than 0.7 for all but two characteristics (irritable and impulsive) in the BAFS, in our training sessions for the present study we did not feel we could adequately distinguish behaviors on this 8-point scale. In order to reduce potential concerns about interrater reliability of this measure, in the present study characteristics were therefore rated as either present or absent only. With the exception of one item with only moderate interrater reliability (undemonstrative, Kappa = .48); interrater agreement for the presence or absence of the characteristics on the M-PAS-R was found to be good to excellent (mean Kappa = 0.87; range 0.73–1.0; $n = 16$) across three raters (J.P., P.P., and D.J.).

For each characteristic, a set of both mandatory and optional questions was employed to elicit a discussion about that characteristic. During the discussion, subjects (and informants interviewed separately) were asked to give specific examples illustrating the presence or absence of these characteristics. Subjects were asked not to focus on periods when they may have suffered from an episodic psychiatric disorder but instead to give examples of personality traits that were most indicative of their general style of functioning. Ratings were based only on behavioral examples given by the subject (or informant) and were not determined on the basis of observations or interpretations made by the interviewer. Observations about the subject's behavior were made using a separate instrument, i.e., the Pragmatic Rating Scale [Landa et al., 1992].

As noted, the interview included both subject and informant (usually a spouse) versions. Previous reports have documented a lack of subject–informant agreement on ratings of personality disorder [Zimmerman et al., 1986, 1988] and a number of personality traits [McCrae, 1982; Tyrer et al., 1979]. Subject–informant differences were also noted in our previous study using the M-PAS, where analyses were done separately on subject and informant data. Since the goal of this study was not to explore subject–informant differences, but rather to code the most valid estimate of several specific personality traits, we devised a method for combining data from subjects and informants into a "best estimate," and only best estimate ratings were entered into our computer database for analysis in this study.

Rules used for determining best-estimate ratings have been described previously [Piven et al., 1994].

All interviews were videotaped and subsequently edited for any information which could possibly identify the subject or informant as an autism or a DS parent. Subsequently, videotapes were blindly rated (by J.P., P.P., D.J., or D.C.). Over the course of the study some subjects inadvertently became known to all the raters (19% of autism and 3% of DS parents) and could not therefore be rated blindly. In order to be consistent with the videotaped rating employed in the blind ratings, ratings made from videotaped interviews (as opposed to field ratings) were used for subjects where blind ratings were not available for some of the analyses.

Pragmatic Rating Scale (PRS). The PRS was employed to provide an assessment of pragmatic and speech behaviors observed during the subject interview. A detailed description of the PRS, including its development, is included in a previous report which examined social language use in the parents of autistic individuals [Landa et al., 1992]. In brief, based on theoretical and clinical reports, and pilot work, 19 pragmatic behaviors which make up the PRS were selected to reflect abnormalities in social language use that might be present in relatives of autistic individuals and therefore reflect aspects of the broader autism phenotype. Pragmatic behaviors examined covered such things as social judgment (e.g., did the individual reveal personal information that was inappropriate in the context of the interview), clarity and relevance of the message (e.g., were accounts vague and difficult to follow), or judgments about the listener's informational needs (e.g., did the individual provide excessive detail). In addition to these 19 pragmatic items, six items assessing speech behavior were developed as part of the PRS (although they were not described in the previous publication by Landa et al. [1992]) to measure such things as pronunciation; rate, volume, rhythm, and intonation of speech; and timing and reformulation of responses. The 25 items of the PRS (including the 19 pragmatic and six speech items) appear in Table III.

The PRS ratings were based on conversational behavior observed throughout the interview session, including a 15-minute conversation held midway through the session. During this 15-minute period, the interviewer initiated new topics in conversation and attempted to make inquiries about comments from the subject in much the same way as one would in any social exchange. Several times during the conversation, the interviewer created opportunities for subjects to demonstrate pragmatic deficits, for example by occasionally indicating that they misunderstood the subject and observing whether adequate revisions were made.

After first editing out information which might distinguish cases from controls, the videotaped interviews (described above and including the M-PAS-R and informal conversation) were rated. Where possible, these ratings were performed blind to case-control status of the subject. The 25 behaviors of the PRS were 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. Ratings of 1 or 2 required the examiner to provide at least one example. The threshold for a rating of 1 or 2 was high and excluded the isolated errors that occur normally in conversation. When the appropriateness of a behavior was questionable due to insufficient sampling, that behavior was rated as normal. For the purposes of analysis, ratings were collapsed into present (1 or 2) and absent (0). Since only the 19 pragmatic behaviors were studied in the initial report, we examined pragmatic and speech behaviors separately in the present study. For each subject, the 19 pragmatic items and the six speech items were summed (one point was assigned for each item rated as present) to produce a total pragmatic and total speech score. Interrater reliability for the total pragmatic score has been previously shown to be high (intra-class correlation coefficient = 0.95) and 3-month test-retest reliability was shown to be adequate (i.e., mean scores did not significantly differ) [Landa et al., 1992]. However, interrater reliability for the total speech score has not yet been examined.

Friendship scale. The Friendship Interview is a semi-structured interview, designed jointly by research groups at Johns Hopkins and the Institute of Psychiatry (under the direction of Susan Folstein and Michael Rutter) for use in the Baltimore and British Autism Family Studies. The Friendship Interview is aimed at assessing the number and quality of an individual's friendships. Subjects are asked a number of questions about the quality of what they consider their three closest friendships. A previous report on data from the BAFS revealed significant differences in an overall friendship score between parents of autistic and DS probands [Santangelo and Folstein, 1995]. Based on the experience of the first author with this interview, in the present study we restricted our analyses to two items from the Friendship Interview: the extent to which the friendship was characterized by mutual emotional support (ratings of 0, 1, 2, or 3) and the extent to which the subject is able to confide in their friend(s) about private worries and hopes (ratings 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 (intra-class correlation = .97) for two raters across ten subjects. This instrument is available on request from the first author.

NEO-Personality Inventory (NEO-PI). The NEO-PI is a 181-item questionnaire developed through rational and factor analytic methods to measure the dimensions of the five-factor model of personality structure [Costa and McCrae, 1985]. Subjects answer items on a 5-point Likert scale ranging from strongly disagree to strongly agree. Internal consistency for the five domain scales—Neuroticism (N), Extroversion (E), Openness (O), Agreeableness (A), and Conscientiousness (C) ranges from .76 to .93, and scores for adults

are quite stable, with 3- to 6-year test-retest correlations ranging from .63 to .83. Both specific broader domain and facet scales (i.e., six per domain) are scored for the dimensions of N, E, and O; only domain scales are available with this version of the instrument for A and C. Gender-specific adult norms are available for the derivation of T scores for each subject. The NEO-PI was employed in this study specifically to assess the validity (i.e., meaning) of the eight characteristics on the M-PAS-R through examination of intercorrelations between items on both instruments.

Analysis

Sample characteristics (e.g., parental age, education level), rates of M-PAS-R personality characteristics, total pragmatic and speech scores on the PRS and friendship scores, in cases and controls, were compared using simple statistics (chi square and t-test statistics). For the major outcome variables of interest to this study (eight personality characteristics of the M-PAS-R, total speech and pragmatic language scores of the PRS, and the friendship score), tests were considered significant if they passed the $P < .005$ level of significance (two-tailed; i.e., corrected for multiple comparisons). The effect size (for continuous variables) and odds ratio (for categorical variables) were also determined for the major outcome variables. The relationship between the facets and dimensions of the NEO-PI and the M-PAS-R personality characteristics, as well as the relationship between the pragmatic language, speech, and friendship scores with the eight M-PAS-R characteristics, were examined using Pearson Product Moment Correlations. The possible interrelationships of the eight M-PAS-R items were examined using the contingency coefficient C, which is uniquely useful when only categorical information is available for both sets of attributes [Siegel, 1956]. To determine the best equation for predicting case control status, the 11 personality and language variables of interest were entered into a logistic regression using a forward stepwise variable selection procedure, with an alpha of .05 employed for entry and 0.9 for removal from the model.

RESULTS

Twenty-five mothers and 23 fathers from 25 multiple-incidence autism families and 30 mothers and 30 fathers from 30 Down syndrome families were eligible to participate in this study. Autism parents were only included in the analysis if they were the parent of two autistic children. Two mothers had autistic children with two different fathers, resulting in only 23 autism fathers being included in this analysis. Neither father's age ($t = 0.76$; $df = 51$; $P > .45$) or level of education ($\chi^2 = 1.39$; $df = 4$; $P = .85$) nor mother's age ($t = .29$; $df = 53$; $P = .77$) or level of education ($\chi^2 = 6.95$; $df = 4$; $P = .14$) differed significantly between cases and controls. Father's occupational level, as specified by the British Manual of the Classification of Occupations [1980], also did not differ significantly between the two groups ($\chi^2 = 6.2$; $df = 4$; $P = .18$).

Personality, Language, and Friendship Ratings

Best-estimate ratings on the M-PAS-R were made on 48 autism and 60 DS parents on the basis of both subject and informant interviews (in 46 autism and 54 DS parents), subject interviews only (in one autism and one DS parent), and informant interviews only (in one autism and four DS parents). Informant-only data were available on one autism parent whose whereabouts were unknown to the family and four DS parents, one deceased and three who refused to participate. Blind ratings were available on 39 autism and 58 DS parents (81% and 97%, respectively). Several autism parents were known to all the members of the research team, usually as a result of their frequent attendance at the University of Iowa Child Psychiatry Clinic, and therefore blind ratings could not be accomplished on these individuals. Because of possible rater bias in subjects where blind ratings were not possible, and because those for whom blindness could not be established often seemed to be some of the most severely affected individuals, the blind ratings in this study are considered a more conservative estimate than analyses performed using both blind and unblind ratings, where blind ratings were not available.

The frequencies of blind, best-estimate ratings of the eight personality characteristics examined on the M-PAS-R appear in Table I. After Bonferroni correction for multiple comparisons, the characteristics “aloof,” “hypersensitive to criticism,” “anxious,” and “rigid” were the four characteristics that appeared to be present significantly more often in parents of autistic probands than in controls. For these four characteristics, the relative odds (RO) (including the 95% confidence intervals, CI) of being rated as affected if the subject was an autism parent were: aloof, RO = 8.4 (CI: 1.71, 41.31); hypersensitive to criticism, RO = 11.0 (CI: 2.28, 53.0); anxious, RO = 6.32 (CI: 1.62; 24.65); and rigid, RO = 10.07 (CI: 3.31, 30.61). Three characteristics—aloof, hypersensitive, and anxious—were present in approximately 25% of autism parents, whereas the characteristic rigidity was present in almost 50%. The pattern of findings on gender-specific analyses, performed on the total sample (i.e., using non-blind ratings to maintain a larger sample size when blind ratings were not available), were consistent with analysis of the total sample (i.e., there was no evidence of sex-specific

TABLE I. A Comparison of Blind, Best-Estimate Ratings on the M-PAS-R in Autism and DS Parents

	Autism	DS	χ^2 (df)	P
	(N = 39)	(N = 58)		
	N (%)	N (%)		
Aloof	9 (23)	2 (3)	9.06 (1)	.003*
Hypersensitive	11 (28)	2 (3)	12.63 (1)	.0004*
Anxious	10 (26)	3 (5)	8.41 (1)	.004*
Rigid	19 (49)	5 (5)	20.43 (1)	.00001*
Unresponsive	9 (23)	4 (7)	5.18 (1)	.02
Untactful	10 (26)	4 (7)	6.56 (1)	.01
Undemonstrative	9 (23)	5 (9)	3.87 (1)	.049
Overly conscientious	10 (26)	6 (10)	3.89 (1)	.049

N = number rated as having the characteristic present.
*Significant after correction for multiple comparisons ($P < .005$).

differences), except for the characteristic anxious. Autism fathers were rated as anxious significantly more frequently than DS fathers (35% vs. 0%; $\chi^2 = 15.26$, $df = 1$, $P < .0009$), whereas significant differences on this characteristic were not detected in a comparison of mothers (28% in autism mothers vs. 10% in DS mothers; $\chi^2 = 3.0$, $df = 1$; $P = .09$).

Total pragmatic language and total speech scores were computed for each subject by summing scores on each of the 19 pragmatic language and six speech items, respectively, on the PRS. Ratings of 0, 1, and 2 were collapsed into ratings of present (1 or 2) or absent (0). Autism parents ($n = 38$) had significantly more pragmatic language (mean (SD)_{autism} = 3.9 (5.5); mean (SD)_{DS} = 0.8 (2.3); $t = 3.27$, $df = 46$, $P = .002$) and speech abnormalities (mean (SD)_{autism} = 1.2 (2.2); mean (SD)_{DS} = 0.04 (0.3); $t = 3.19$, $df = 38$, $p = .003$) than DS parents ($n = 53$), after correction for multiple comparisons ($P < .005$), as evidenced by their significantly higher mean composite scores on the PRS and speech measures. Effect size was 0.80 (CI: 0.38, 1.22) for the pragmatic language score and 0.93 (CI: 0.51, 1.35) for the total speech score. The frequency of pragmatic language and speech abnormalities, in the total sample (i.e., including the 90% with blind and 10% with non-blind ratings), are displayed in Table II. Because of the relative low frequency of ratings on the 25 PRS items, the results from the total sample (blind + non-blind) are presented. The greatest differences in frequency between autism and DS parents on the pres-

TABLE II. Frequency of Pragmatic Language and Speech Abnormalities* on the PRS in all Autism and DS Parents

	Autistic	DS
	(n = 46)	(n = 55)
	N (%)	N (%)
Pragmatic Language		
Too detailed	11 (23.9)	3 (5.5)
Failure to reference	8 (17.4)	0
Vague accounts	9 (19.6)	2 (3.6)
Accounts disorganized	11 (23.9)	1 (1.8)
Failure to clarify	12 (26.0)	0
Out of sync	12 (26.0)	0
Overly frank	6 (13.0)	1 (1.8)
Overly direct	5 (11.0)	1 (1.8)
Too informal	6 (13.0)	5 (9.1)
Overtalkative	9 (19.6)	4 (7.3)
Fails to reciprocate	9 (19.6)	5 (9.1)
Fails to greet**	0	0
Odd humor	6 (13.0)	2 (3.6)
No sense	2 (4.3)	2 (3.6)
Topic preoccupations	3 (6.5)	1 (1.8)
Switches topics	0	0
Inappropriate	4 (8.7)	0
Unclear intent	2 (4.3)	0
Rare initiation	6 (13.0)	3 (5.5)
Speech		
Unusual timing	11 (23.9)	0
Volume (too loud/soft)	9 (19.6)	1 (1.8)
Mispronounces	7 (15.2)	0
Abnormal intonation	6 (13.0)	0
Rate (too fast/slow)	3 (6.5)	0
Unusual rhythm	0	0

*0, 1, and 2 ratings are collapsed into present (1 or 2) or absent (0).
**“Fails to greet” was a rating made in the field but was not observed on videotaped ratings.

ence of the 19 pragmatic language items were observed on six items—too detailed, failure to reference, vague accounts, accounts disorganized, failure to clarify, and out of sync; all rated more abnormal in autism parents. The frequency of these characteristics in autism parents ranged between 18% and 25%, whereas the frequency in DS parents ranged from 0% to 6%. For the speech items, the greatest differences in frequency of abnormality occurred in four items—mispronunciation, abnormal intonation, abnormal volume, and unusual timing; again, these speech characteristics were more commonly noted in autism parents. In controls, the base rate of these abnormalities was zero (except for one item occurring in one DS parent), whereas the frequency in autism parents ranged between 13% and 24%. Although the sample size was very small for analysis of differences by gender, in general the frequency of PRS characteristics rated abnormal appeared to be similar in fathers and mothers.

Ratings on two items of the friendship interview (emotional support and confiding) were summed across three potential friendships for each subject to produce a single score which characterized the number and quality of an individual's friendships. Ratings on this interview were not made blind to case-control status. Mean score for the autism parents (mean = 9.2, SD = 5.4) was significantly higher than the DS parents (mean = 3.6, SD = 4.4) ($t = 5.76, df = 100, P = .0001$) with an effect size of 1.14 (CI: 0.72, 1.56). Results were consistent with non-parametric (Mann-Whitney) analysis ($Z = 5.2, P = .00001$). Forty-six percent of autism parents scored ≥ 1.5 SD beyond the mean of the controls; 37% of autism parents and 4% of DS parents scored the maximum of 15, indicating that they did not report having a single friendship (characterized by mutual emotional support and confiding). Again, gender-specific analyses similarly revealed significantly higher scores (i.e., fewer quality friendships) in both autism fathers and mothers compared to DS fathers and mothers, respectively. Autism fathers did, however, appear to have somewhat higher friendship scores (i.e., fewer friendships) than autism mothers (10.65 vs. 7.87, respectively), whereas the absolute difference between scores for DS fathers and mothers (4.33 and 3.00, respectively) was somewhat smaller.

Significant intercorrelations of the eight M-PAS-R

items and the speech, pragmatic language, and friendship scores are given in Table III. As expected, there were significant intercorrelations between items relating to the domain of social behavior (friendship score, pragmatic language score, and four characteristics from the M-PAS-R: aloof, undemonstrative, untactful, and unresponsive). In addition, both measures of aspects of communication (i.e., pragmatic language and speech) were highly intercorrelated. Anxiety and hypersensitivity were two items that did not correlate significantly with any of the 11 items assessed. The M-PAS-R characteristic "rigid" correlated significantly with a number of items measuring social aspects of behavior (undemonstrative and friendship score) and communication (pragmatic language and speech), as well as showing a significant correlation to the personality characteristic "conscientious."

Validity of the M-PAS-R

In order to examine the validity of the M-PAS-R and gain insight into the nature of the personality characteristics we measured, we examined the relationship between the NEO-PI facets and the eight personality characteristics assessed on the M-PAS-R. Table IV presents the intercorrelations of the NEO-PI facets and M-PAS-R characteristics from 87 subjects (47 autism and 40 DS parents) who were administered both instruments. As expected, the M-PAS-R items "anxious" and "hypersensitive" were significantly correlated with several facets of neuroticism. Both anxious and hypersensitive were correlated significantly with N1 and N3 (anxiety and depression, respectively). In addition, hypersensitive showed significant correlations to N2 (hostility), N4 (self-consciousness), and N4 (vulnerability). Also as expected, significant negative correlations occurred between aloof and two facets of extroversion, warmth (E1) and gregariousness (E2). Finally, rigid, the other characteristic of the M-PAS-R to appear significantly more commonly in autism parents than DS parents (see Table I), was significantly negatively correlated with 04 of the openness dimension. Individuals who score high on this facet are characterized by a preference for routine and familiar experiences. Rigid was also significantly negatively correlated with agreeableness. The presence of high ratings on both (nega-

TABLE III. Intercorrelation of M-PAS-R Characteristics, Pragmatic Language, Speech, and Friendship Scores

	Anx	Hypers	Aloof	Undemonst	Untact	Unrespons	Rigid	Conscienc	Pragmat lang	Speech	Friends
Anxious											
Hypersensitive											
Aloof											
Undemonstrative			.65*								
Untactful											
Unresponsive			.54*	.58*	.54*						
Rigid				.46*		.37					
Conscientious							.46*				
Pragmatic language			.38*	.32	.35*	.35*	.31				
Speech			.31		.32		.26		.80*		
Friendship			.43*	.44*	.37*	.41*	.41*		.57*	.39*	

Only correlations significant at $P < .01$ are noted on the table.
*Correlation significant at $P < .001$.

TABLE IV. Correlations Between M-PAS-R Characteristics and Facet Scores From the NEO-PI

NEO-PI facets	M-PAS-R characteristics							
	Anx	Hypersens	Aloof	Undemonst	Untact	Unrespons	Rigid	Conscienc
N1	.40*	.39*						
N2	.35	.40*			.33			
N3		.41*						
N4		.33						
N5								
N6		.34						
E1			-.32	-.35*				
E2			-.32	-.41*				-.28
E3								
E4								
E5		-.38*						
E6				-.29				
O1								
O2								
O3								
O4								-.30
O5								
O6								
A								-.32
C								

Only correlations significant at the $P < .01$ level are noted on this table.
 *Correlation significant at $P < .001$.

tive) openness and (negative) agreeableness is thought to describe an individual who is more than just closed to changes in experience, but who in addition displays what has been referred to as an “interpersonal stubbornness” [Paul Costa, personal communication]. Together, the significant correlations with neuroticism, (negative) extroversion, (negative) openness, and (negative) agreeableness lend validity to the four personality characteristics—hypersensitive to criticism, anxious, aloof, and rigid—found on univariate analysis to characterize some autism parents.

The NEO-PI was developed for the assessment of the dimensions of normal personality and was not developed for the assessment of the particular personality characteristics we hypothesized to be present in autism relatives. Therefore, we did not specifically set out to use the NEO-PI to examine case-control differences in this sample. However, because this instrument is a self-report measure, eliminating the possibility of rater bias, and because of the extensive psychometric data supporting its validity and reliability, we further examined the NEO-PI factor scores for differences between autism and DS parents. For this analysis, raw scores were converted into gender-specific t-scores, based on normative data referenced in the manual (Costa and McCrae, 1985). The results of this analysis revealed that autism parents were rated significantly higher than DS parents on the neuroticism domain ($t = 3.61$; $df = 85$; $P = .001$), with an effect size of 0.79 (CI: 0.31, 1.22). No group differences were detected in mean scores on the other four domains.

Toward a More Comprehensive Definition of the Personality and Language Characteristics of the Broader Autism Phenotype

In order to explore which items from the list of 11 we have identified (eight M-PAS-R items, pragmatic language, speech, and friendship score), were most useful

in distinguishing autism parents from DS parents, we entered all 11 variables, along with a 12th, gender, into a logistic regression analysis to predict case vs. control status. The final equation produced included four items: rigid ($B = 1.37$; $df = 1$; $P = .034$) and hypersensitive to criticism, from the M-PAS-R ($B = 2.13$; $df = 1$; $P = .02$), the total speech score, from the PRS ($B = 1.86$; $df = 1$; $P = .006$), and the friendship score, from the Friendship Interview ($B = 0.14$; $df = 1$; $P = .01$), and correctly classified 82% of the 101 subjects entered into this analysis (model $\chi^2 = 60.05$, $df = 4$, $P = .0000$; goodness of fit: $\chi^2 = 80.13$, $df = 96$, $P = .88$).

While the results of the univariate analyses we report lend further support to the existence of a BAP and begin to define the range and severity of characteristics which make up the broader autism phenotype, exactly how these characteristics should be combined for future genetic analyses remains a major question. Although very preliminary, we thought it would be useful from both a clinical and research perspective to propose an example of one simple algorithm that could potentially be employed for defining autism relatives affected with the broader autism phenotype. To accomplish this, we constructed an equation whereby each of the four items identified in the logistic regression analysis were assigned one point if present in an individual and no points if absent. Scores on the four items were then summed to produce a “BAP score” that could be used to estimate the degree to which an individual displayed characteristics consistent with the BAP (e.g., $BAP\ score = rigid + hypersensitive\ to\ criticism + friendship + speech$), with the range of possible scores being 0 to 4. For the items rigid and hypersensitive to criticism, presence or absence was based on the rating of present or absent on the M-PAS-R. The items friendship and speech were determined to be present if an autism parent scored ≥ 1.5 SD beyond the mean for DS controls on that item. The frequencies of the BAP

scores for autism and DS parents appear in Table V. To maximize specificity, without severely limiting sensitivity, we arbitrarily set a threshold for affected at a BAP score of ≥ 2 . At this cutoff, 26/46 autism parents vs. 2/55 DS parents were affected for a sensitivity of 56% (26/46) and a specificity of 96% (53/55). Similar results were obtained using either the equation produced by the logistic regression, which classified subjects as either affected or unaffected (i.e., sensitivity and specificity were 71% and 90%, respectively) or employing a modified version of our simplified equation, using gender-specific cutoffs for ratings of present or absent on the friendship and speech scores (i.e., sensitivity and specificity were 52% and 95%, respectively).

We then employed the above algorithm (i.e., rigid + hypersensitive + speech + friendship ≥ 2) to estimate the frequency of the BAP in spousal pairs. By this definition, in 43% of the autism families only one parent was classified as affected, whereas in 38% of autism families both parents had a BAP score of two or more. In addition, the rate of the BAP in mothers and fathers was roughly equal, occurring in 65% of fathers and 52% of mothers.

DISCUSSION

The results of our comparison of personality characteristics from the M-PAS-R, in autism and DS parents, conservatively (i.e., employing blind ratings and correction for multiple comparisons) suggest that four characteristics—aloof, rigid, hypersensitive to criticism, and anxious, occur more commonly in parents from autism families than controls. These results are in agreement with recent analyses from the BAFS, where significantly higher rates of two personality characteristics—aloof and anxious—were detected in 178 parents ascertained through a single autistic proband compared to 78 parents ascertained through a DS proband [Santangelo and Folstein, 1996]. In that study, an earlier version of the M-PAS-R was used, which employed a somewhat different definition of the characteristic rigidity. This difference may account for the failure to detect significantly higher rates of this characteristic in autism parents in the BAFS. Using identical instruments (scoring on the Friendship Interview differed between the two studies) the differences we detected in pragmatic language, as well as in the number and quality of friendships, also replicate the findings from the BAFS, showing both pragmatic language abnormalities and

decreased number and quality of friendships in autism parents. Finally, abnormalities in speech production, while not previously reported, occurred more commonly in parents from multiple-incidence autism families compared to controls.

Strengths and Limitations

This study has several strengths that should be noted. First, in contrast to previous family history and family interview studies, direct, blind assessments were employed using standardized instruments. Case-control differences detected on the M-PAS-R interview were also detected on a self-report personality measure, lending further support to these differences not being the result of rater bias. Second, in this study we examined a sample of parents ascertained systematically through two autistic probands. 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 sample of multiple-incidence autism families as opposed to a sample ascertained through a single autistic proband theoretically increased the etiologic homogeneity of our sample, as well as possibly increasing the genetic liability for both autism and the BAP in relatives.

Several possible limitations of this study should also be considered. First, while we made efforts to systematically ascertain and retain control families in this study, the extent to which our controls accurately estimate the rate of the personality and language characteristics we examined in this study in a population sample of non-dysjunction DS 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 paper but also added to the contributions required by participants. It is possible that the demands and motivation for participation in this study, aimed at understanding issues primarily of relevance to the genetics of autism, may have resulted in systematic ascertainment of a control group which was more compliant and which 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. Second, while we largely interpret our data in terms of its genetic implications, the possibility that our findings are the result of an environmental effect must also be considered. Clearly, most people would consider the burden of having two children with autism to be substantially more than having a single autistic child. Against this was our attempt to base personality ratings on the M-PAS-R on life-long characteristics as well as on the findings from the twin study by Bailey et al. [1995] where social deficits were detected in all five of the non-autistic co-twins vs. none of the seven DZ co-twins. However, it is also easy to imagine how the stress of having two autistic children might influence the parent's ability to make close friendships. The final answer to this issue will require evaluation of a larger twin sample with direct testing or possibly the assessment of adoptive parents of multiple-incidence autistic children, both very difficult

TABLE V. Frequency of Broader Autism Phenotype Score in Autism and DS Parents*

BAP Score	Frequency	
	Autism (n = 46)	DS (n = 55)
0	N (%) 8 (17)	N (%) 42 (76)
1	12 (26)	11 (20)
2	14 (30)	2 (4)
3	9 (20)	0
4	3 (7)	0

*BAP score = rigid + hypersensitive to criticism + friendship score + speech score, with one point assigned for each characteristic present in a subject.

studies to conduct. Third, personality and language ratings on individual subjects were made at the same time by the same rater, and therefore were not independent. While this is a standard practice in epidemiologic studies, where data is gathered at one or several interviews using standardized instruments, the possibility of multi-collinearity (vs. a true correlation of some items measured) may have affected our results. In this regard it is reassuring to note that the item correlations displayed in Table III generally occur in the directions hypothesized. So, for example, the social personality characteristics (e.g., aloof, undemonstrative, untactful, and unresponsive) are generally significantly intercorrelated and show significant positive correlations with the other measures that presumably tap into social behaviors (e.g., friendship score and pragmatic language). Similarly, significant correlations were expected and observed between the two measures of communication-pragmatic language and speech. Also, to some extent, the pattern of correlations between the M-PAS-R items and the NEO-PI facets suggests that the items we are measuring tap into different personality domains, although the sample is too small to attempt meaningful statistical comparisons of the correlations between items on these two measures.

Defining the Broader Autism Phenotype

The results of this study not only lend further support to the existence of a milder phenotypic expression of the genetic liability for autism in non-autistic relatives of autistic probands, but they provide further detail regarding the definition of this more broadly defined autistic phenotype. To begin with, three of the four variables retained in the logistic regression model are reminiscent of the defining features of the narrow autism phenotype. The characteristics "friendship," from the friendship interview, "speech," from the PRS, and "rigidity," from the M-PAS-R, closely parallel the respective domains of social, communication, and ritualistic-repetitive behaviors which define the current DSM-IV conceptualization of autistic disorder. Similarly, pragmatic language deficits and aloof behavior, also found more commonly in autism parents than controls, are conceptually related to the social and communication deficits seen in autistic individuals.

The inclusion of the M-PAS-R characteristics "anxious" and "hypersensitive to criticism" in a definition of the BAP however, warrant further discussion, as neither is a criteria considered in the diagnosis of autism. However, although the characteristic "anxious," as measured by the M-PAS-R, is not one of the defining characteristics of autism, and autistic individuals do not commonly complain of anxiety, clearly behavioral phenomena that could be interpreted as a possible expression of anxiety are frequently observed in autistic individuals and are often related to some of the more maladaptive aspects of the disorder (e.g., repeated questioning, upset with change, preoccupations). In addition, two previous reports have shown high rates of anxiety disorders in parents of single-incidence autistic probands, supporting the validity of this finding in relatives [Piven et al., 1991; Smalley et al., 1995].

Examining correlations of the M-PAS-R items with the facets of the NEO-PI also provides further insight into the meaning of the M-PAS-R characteristics found more commonly in autism parents. The M-PAS-R characteristic "anxious" was significantly correlated with two facets on the neuroticism domain of the NEO-PI—anxiety (N1) and angry hostility (N2). The only other M-PAS-R characteristic to correlate significantly with neuroticism was "hypersensitivity to criticism"; correlating significantly with the facets of anxiety (N1), angry hostility (N2), depression (N3), self-consciousness (N4), impulsiveness (N5), and vulnerability (N6). This pattern of correlations suggests that both of these characteristics, anxious and hypersensitive to criticism, measure related aspects of personality. Further examination of the patterns of expression in mothers and fathers suggests that "anxious" and "hypersensitivity to criticism" may be alternative aspects of the expression of neuroticism in males and females with the BAP. The M-PAS-R characteristic "anxious" occurred significantly more commonly in autism fathers when compared to DS fathers, whereas significant differences were not detected in autism and DS mothers. "Hypersensitivity," although occurring significantly more commonly in both autism fathers and mothers compared to same-sex controls, occurred at approximately twice the rate in autism mothers (44%) compared to autism fathers (22%). Similar differences in rate were found in DS mothers (7%) versus DS fathers (0%). The significant correlation of both "anxious" and "hypersensitive to criticism" to the neuroticism domain of the NEO-PI, along with a somewhat different pattern observed in males and females, suggests the possibility that these two M-PAS-R characteristics are alternative, gender-specific expressions of the same underlying personality construct, with "anxious" being more commonly expressed in autism fathers and "hypersensitivity" being more commonly expressed in autism mothers. In general, no other significant gender differences were observed.

The finding of significantly higher rates of rigidity in autism parents is not necessarily surprising, given the findings from family history studies showing higher rates of ritualistic-repetitive behaviors in autism relatives [Bolton et al., 1994; Piven et al., 1997], the anecdotal reports describing conceptually-related personality characteristics in parents of autistic children [Eisenberg, 1957], and the overlapping phenomenology between the personality characteristic rigidity and ritualistic-repetitive behaviors in autism. However, it is notable that rigidity, as defined in this study, occurred more commonly in autism parents (49%) than any of the other characteristics that we have suggested may contribute to the BAP. In autism parents rated as affected on the BAP algorithm (i.e., BAP score ≥ 2), rigidity was the most common of the four variables in the BAP algorithm (i.e., rigidity, hypersensitivity to criticism, friendship score, and speech) to be rated as present, occurring in 69% of individuals. In addition, 18 of the 19 autism parents rated as rigid (or 95%), also met criteria on the BAP algorithm we employed.

In attempting to discern which psychological mechanisms may be of primary importance in explaining au-

tistic symptomatology, previous theories have focused mainly on either the social [Fein et al., 1986] or communication [Rutter, 1974] domains. However, these results suggest that it is the ritualistic-repetitive domain that may be of primary importance and, in particular, rigidity, as defined in this study, which may be a *forme fruste* of this disorder. Indeed, in the original paper by Kanner [1943] "insistence on the preservation of sameness" was noted to be one of the two pathognomonic features of the disorder, with the other being autistic social deficits. We also suggested previously that abnormalities in the ritualistic-repetitive domain may be the most enduring features of autism in a retrospective study of the course of behavioral change over time in social, communication, and ritualistic-repetitive behaviors [Piven et al., 1996]. This hypothesis is also consistent with diminished flexibility of thought in autism, as evidenced by abnormalities on tests of executive function in autistic individuals [Ozonoff et al., 1994]. Further insights into the meaning of rigidity in this study can be gleaned from examining the correlations of this characteristic with the items of the NEO-PI. Rigidity correlated significantly with (negative) 04 of the openness-to-experience dimension and negative agreeableness. Low ratings on 04 indicate an individual who is unwilling to try new activities, avoids novelty, and prefers to stick to their routine. The joint occurrence of (negative) 04 and (negative) agreeableness is thought to suggest an "interpersonal rigidity" [P. Costa, personal communication] and thus suggests an additional social aspect of this characteristic that is consistent with our overall conceptualization of the BAP as involving both social deficits and rigidity. Finally, rigidity was also significantly correlated with the pragmatic language, speech, and friendship scores, and, as described below, is conceptually related to the pragmatic language abnormalities we detected in this study.

Closer inspection of the pragmatic language items that showed the greatest difference in frequency between cases and controls (e.g., inability to clarify, accounts disorganized, failure to reference) reveals that the most commonly rated pragmatic language abnormalities seemed to have less direct social significance (e.g., overly direct, overly informal) and have more to do with clarity and relevance of the message being communicated. Based on the results of a factor analysis, Landa et al. [1992] proposed three PRS subscales—*inadequate expression*, *disinhibited social communication*, and *odd verbal interaction*. The most striking pragmatic language abnormalities observed in autism parents in the present study appear to fall mostly into the first factor of "inadequate expression." Landa et al. [1992] speculated that this subscale suggested the use in autism parents of a rigid linguistic rule system that affects expression and comprehension of the message. This linguistic inflexibility is qualitatively similar in concept to but significantly milder than similar deficits seen in autistic individuals [Landa et al., 1995].

In this study, we also detected a significantly higher rate of particular speech abnormalities in autism parents vs. controls. Speech abnormalities as assessed in this study have not previously been reported in rela-

tives and require replication. In that the presence of these characteristics was not specifically part of the hypotheses put forward in designing this study (the assessment of speech items was included merely as part of the PRS assessment), the positive results were surprising. However, as with other aspects of the BAP the speech abnormalities we report are reminiscent of some of the speech abnormalities observed in autistic individuals (e.g., abnormal intonation, volume, or timing), supporting the validity of their inclusion as part of the BAP. While we have not yet examined the interrater reliability of the speech score, rating of these behaviors seems to be somewhat more straightforward than the judgments and inferences involved with rating personality characteristics and pragmatic language, where adequate reliability has been established. We therefore expect the rating of these speech deficits to prove reliable on further study.

Genetic Implications

There are several implications of these findings for genetic studies of autism. First, these results lend further support to the presence of a BAP and suggest possible approaches to assessment and definitions for use in genetic studies. Second, inclusion of the BAP may be particularly useful in studies attempting to tease apart the etiologic heterogeneity of this disorder, through examination of the familial aggregation of related disorders (i.e., autism, pervasive developmental disorder, and the BAP) in proband subgroups defined by different behavioral, cognitive, or biological parameters. Third, previous genetic analytic studies (with the exception of the study by Pickles et al. [1995]) have neglected to consider the BAP as an outcome in their analyses. Segregation analysis and other analytic approaches to examining possible models of transmission, using this more broadly defined phenotype, have the potential to contribute to our understanding of genetic mechanisms in this disorder. Fourth, due to the absence of vertical transmission and the typically small family size [Jones and Szatmari, 1988], pedigrees ascertained through an autistic proband usually contain few individuals affected with autism. Inclusion of the BAP may therefore increase the power of genetic linkage studies to find genes in autism by increasing the number of affected individuals available over several generations. This approach provides an additional strategy which complements non-parametric approaches, which define only individuals with the narrow phenotype as affected. In addition, moderate-size pedigrees with multiple members affected with the BAP may differ etiologically from families without such familial aggregation. Linkage studies performed in this subgroup could also potentially be informative.

A fifth issue to consider based on the results of this study demonstrating the aggregation of personality and language characteristics, and other studies showing the aggregation of cognitive deficits, in families ascertained through an autistic proband [Ozonoff et al., 1993; Piven and Palmer, in press], is whether aspects of the autistic phenotype that may be conceptually distinct (e.g., executive function, speech abnormalities, so-

cial deficits in personality, and rigidity) should be viewed as expressions of different genes contributing to the autistic phenotype. The possibility that autism is the result of multiple interacting genes (i.e., an oligogenic disorder) has been suggested [Pickles et al., 1995]. Examination of the components of the BAP in relatives may allow us to disentangle genetically meaningful but distinct aspects of the autistic phenotype that segregate independently, but together can combine to produce autism. This approach may be more fruitful for genetic analyses than employing syndromic-like definitions, such as the example we have suggested in this paper for the BAP, where an algorithm is proposed which includes a number of conceptually unrelated behaviors which together define the BAP. This approach has traditionally been taken in linkage studies (e.g., schizophrenia, where a spectrum of diagnoses define affected status). Current efforts at detecting genes in dyslexia, where separate linkages have been demonstrated to distinct reading tasks (e.g., phonological awareness and single word reading), suggest that this may be a useful approach to detecting genes of moderate effect in genetically heterogeneous, oligogenic disorders [Grigorenko et al., 1996]. Similarly, research into the genetic basis of personality has suggested that dimensional personality traits such as novelty-seeking (as opposed to personality disorder syndromes which group together a variety of behaviors on the basis of their association in impaired individuals) may be associated with specific genetic loci [Benjamin et al., 1996; Ebstein et al., 1996]. This particular association may also have particular relevance to understanding the genetic basis of the BAP given the qualitative similarities but opposite nature of the personality characteristics seen in novelty seeking and rigidity, as defined in this study.

Sixth, examination of the BAP in parental dyads has enabled us to consider whether the genetic liability for autism is transmitted through one (unilineal transmission) or both (bilineal transmission) parents. In this study, we found evidence that in at least 38% of the cases both parents showed evidence of the BAP. Clearly, this scenario cannot be easily distinguished from the possibility of assortative mating. However, bilineal transmission of interacting genes is also not inconsistent with the hypothesis we have put forth that the genes contributing to the autism phenotype may be associated with conceptually distinct aspects of the phenotype, and produce autism when they occur together in the same individual. Examination of the patterns of transmission of the BAP in this way may add further insights to our understanding of genetic mechanisms in autism.

Finally, in this study we examine a sample of parents ascertained through the presence of two autistic children in the family. Based on the large effect sizes (ranging from 0.80 to 1.14) and odds ratios (ranging from 8.42 to 11.0) that we observed for the variables of interest in this study compared to results from the BAFS, we hypothesize that the genetic liability for the BAP in these families is greater than in families ascertained through a single autistic proband. More definitive comparisons of rates in cases and controls to the

results of the BAFS are problematic, given the different methods employed in the two studies (e.g., use of modified instruments and blind ratings). Possibly the only legitimate comparison that can be made is on the total pragmatic language scores, where blind ratings were obtained on the same instrument in this study and the preliminary report by Landa et al. [1992]. Similar rates were found in the autism parents in both studies (mean = 3.9_{Iowa} vs. 4.0_{BFS}) whereas rates in the Iowa controls were roughly twofold higher than those in the BFS (1.2_{Iowa} versus 0.47_{BFS}). Clearly, testing of this hypothesis requires a comparison of single and multiple-incidence samples, ascertained through comparable methods and assessed using identical measures.

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APPENDIX 1

Definitions of Personality Characteristics on the Modified-Personality Assessment Schedule—Revised

1. **Conscientious:** dependable, steadfast, striving, single-minded (i.e., goal-directed).
2. **Rigidity:** little interest in and/or difficulty adjusting to change (i.e., new situations, ideas, or altered routines).
3. **Aloof:** lack of interest in or enjoyment from being with people.
4. **Undemonstrative:** restricted range (verbal and non-verbal) affective expression.
5. **Anxious:** nervousness or anxiety, not amounting to an anxiety state or phobic disorder.
6. **Hypersensitive to criticism:** excessive distress at comments or behavior of others that is felt to be critical or insensitive.
7. **Unresponsive:** a lack of responsiveness to the emotional cues of others.
8. **Untactful:** behavior that puts others off, upsets or irritates them, or may even lead to their suffering.