American Journal of Medical Genetics 113:231–237 (2002)

Autism, Regression, and the Broader Autism Phenotype

Janet E. Lainhart,[1]* Sally Ozonoff,[2] Hilary Coon,[1] Lori Krasny,[1] Elena Dinh,[1] Julie Nice,[1] and William McMahon[1]

[1]*Department of Psychiatry, University of Utah, Salt Lake City, Utah*
[2]*Department of Psychiatry, M.I.N.D. Institute, University of California-Davis, Sacramento, California*

The broader autism phenotype (BAP) is a subclinical set of personality and other features that is thought to index familiality and/or genetic liability to autism. Eighteen parents of autistic probands with a history of language regression and 70 parents of autistic probands without regression were assessed for features of the BAP and compared with published rates in parents of nonautistic subjects. Parents of probands with regressive and nonregressive autism demonstrated similar rates of the BAP (27.8% vs. 32.9%; $P = 0.33$). The rate of the BAP was significantly higher in both groups of autism parents than in parents of nonautistic subjects ($P \leq 0.01$). Thus, this measure of genetic liability is increased equally in families with both forms of autism when compared with controls. Environmental events are therefore unlikely to be the sole cause of regressive autism in our sample. Environmental events, however, may act in an additive or "second-hit" fashion in individuals with a genetic vulnerability to autism.

KEY WORDS: autism; broader autism phenotype; regression; environment

INTRODUCTION

About 20% of children with autism appear to have relatively normal development during the first 12–24 months of life. This period of relative normalcy gradually or suddenly ends and is followed by a period of regression, characterized most prominently by a significant loss of language skills. Then the full autism "syndrome" soon becomes evident [Kurita, 1985; Hoshino et al., 1987; Rogers and DiLalla, 1990; Tuchman et al., 1991; Tuchman and Rapin, 1997; Kobayashi and Murata, 1998]. Some investigators have hypothesized that regressive autism is caused by adverse reactions to vaccines [Wakefield et al., 1998]. Some parents are now reluctant to have their children vaccinated because they believe it may cause their children to develop autism [Pareek and Pattison, 2000; Halsey and Hyman, 2001; Smeeth et al., 2001]. This is despite epidemiologic evidence showing no association between vaccination and the rates of autism [Fombonne and Chakrabarti, 2001; Taylor et al., 2002] and Institute of Medicine and Center for Disease Control statements denying such an association [Institute of Medicine, 2001; Center for Disease Control, 2002].

Twin and family studies have shown that the liability to autism extends beyond the full autism syndrome and includes qualitatively similar, albeit milder, deficits. These include social and language-based cognitive difficulties, repetitive interests and behaviors, and personality and language characteristics that affect social interactions [Bolton et al., 1994; LeCouteur et al., 1996; Piven et al., 1997a, 1997b; Bailey et al., 1998]. The milder social and language deficits seen in nonautistic relatives are conceptualized as the broader autism phenotype (BAP) [LeCouteur et al., 1996; Piven et al., 1997a, 1997b; Bailey et al., 1998; Santangelo and Folstein, 1999]. Clinical evidence of the liability to autism is found in 12–50% of relatives of individuals with autism, depending on the measures used and relatives studied [Bolton et al., 1994; Piven et al., 1997a, 1997b].

If regressive autism is solely caused by environmental events, such as adverse reactions to vaccines, rates of the BAP in the relatives of children with regressive autism should be no greater than in the general

Additional financial and in-kind support was provided by the Utah Autism Foundation and by Valley Mental Health.

Grant sponsor: National Institutes of Health; Grant number: NICHD PO1 HD35476-05; Grant sponsor: Public Health Services, National Center for Research Resources; Grant number: MO1-RR00064.

*Correspondence to: Dr. Janet E. Lainhart, Utah Neurodevelopmental Genetics Program, 546 Chipeta Way, Suite 441, Salt Lake City, UT 84108-1236. E-mail: janet.lainhart@hsc.utah.edu

Received 17 August 2001; Accepted 6 April 2002

DOI 10.1002/ajmg.10615

population. If environmental events do not independently cause regressive autism, or if they act as "second-hit" phenomena in children who already have the genetic liability to autism, rates of the BAP should be similar in relatives of autistic children with and without regression. We carried out the following study to test these predictions. In addition, we explored several other potentially important phenotypes of interest in the autism probands with and without regression and their parents.

MATERIALS AND METHODS

Participants

Forty-seven probands with idiopathic autism and their parents were studied. Thirteen percent of the autistic subjects were not community ascertained (e.g., recruited from previous studies or clinics). The probands and parents were participants in a program project study of partial and intermediate phenotypes of autism. The project included a magnetic resonance imaging (MRI) study of high-functioning males with autism with and without macrocephaly. Thus, when compared with epidemiologic and other community samples, almost all of the probands in this sample were male, their mean IQ was higher than typical autism samples, a smaller proportion of the probands were nonverbal, and more had macrocephaly [Lord and Rutter, 1994; Lainhart et al., 1997; Folstein et al., 1999; Chakrabarti and Fombonne, 2001]. Every effort was made to include all families who inquired about and met criteria for the study. All parents gave informed consent, and this study was approved by the University of Utah Health Sciences Institutional Review Board.

Autism Assessment

All autistic probands met Autism Diagnostic Interview-Revised [Lord et al., 1994], Autism Diagnostic Observation Schedule-Generic [Lord et al., 2000], and DSM-IV criteria for autism. Known medical causes of autism were excluded by history, karyotype, fragile X DNA testing, and neurocutaneous and dysmorphology examination. Twenty-one percent ($n = 10$) of the autistic probands had a history of regression, as measured by the Autism Diagnostic Interview-Revised (ADI-R). Regression is defined as a loss of communicative language after the acquisition of language skills [Lord et al., 1994]. This resulted in a sample size of 18 parents in the regression group (2 parents with missing data) and 70 parents in the nonregression group (4 parents with missing data).

All probands had a standardized clinical dysmorphology examination, performed by a physician (W.M., a clinical geneticist, or J.E.L., with special training in dysmorphology examination). In addition to head circumference, the examination included 11 measurements and 17 minor anomalies of interest of the head, face, hands, and feet, and qualitative assessment. The methods and reference data of Farkas were used for most of the features examined [Farkas, 1994; Farkas et al., 1994]. The method of Hall et al. [1989] and reference data of Feingold and Bossert [1974] were used for interpupillary distance. Though we did not examine as many features as Miles and Hillman [2000], we scored and categorized dysmorphology in our probands using methods similar to theirs. Probands with three or fewer minor anomalies and/or measurement abnormalities ($\geq$2 SD above or below the mean for age and sex) were categorized as "nondysmorphic." Probands with four or five minor anomalies and/or measurement abnormalities were categorized as "equivocal." Probands with six or more minor anomalies and/or measurement abnormalities were categorized as "dysmorphic." Abnormalities of head size were analyzed separately and were not included in the dysmorphology score.

BAP Assessment

Signs of the BAP in parents were measured using instruments specifically developed for this purpose: the Modified Personality Assessment Schedule-Revised (MPAS-R) [Piven et al., 1997a], the Pragmatic Rating Scale (PRS) [Landa et al., 1992], and the Friendship Interview [Santangelo and Folstein, 1995, 1999]. BAP assessment of parents was done blind to type of onset of autism in the probands (regressive vs. nonregressive). A published operational definition of the BAP was used to determine the affected status of parents [Piven et al., 1997a]. Parents were characterized as having the BAP if they met at least two of the following criteria: a tendency toward rigidity (little interest in and or difficulty adjusting to change) and/or hypersensitivity (excessive distress at comments or behavior of others that is felt to be critical or insensitive), speech abnormalities, and qualitatively impaired friendships. The rate of the BAP in the autism parents was compared with the published rate in parents of nonautistic comparison subjects [Piven et al., 1997a].

Parents also had their head circumference measured. Eighty-nine percent of the parents of both the regressive and nonregressive probands were assessed for lifetime mood and anxiety disorders using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version, Modified for the Study of Anxiety Disorders [Fyer et al., 1995]. Information about history of attention-deficit hyperactivity disorder (ADHD) and substance abuse was collected from 94% of the parents of regressive probands and 97% of the parents of nonregressive probands using the psychiatric disorder section of the 1995 version of the Family History Interview for Developmental Disorders of Cognition and Social Functioning by [Bolton et al., 1994; Piven et al., 1997b; Folstein et al., 1999; Pickles et al., 2000].

IQ was measured in parents using the Wechsler Adult Intelligence Scale-III (WAIS-III) and in probands using the Wechsler Intelligence Scale for Children-III (WISC-III) or the WAIS-III.

RESULTS

Characteristics of the Autism Probands and Parents

Table I shows the characteristics of the probands. There were no significant differences between the characteristics listed for the two groups.

TABLE I. Characteristics of Autism Probands With and Without Regression

	Regressive autism	Nonregressive autism
N	10	37
Mean age (SD)	10.2 (4.4)	11.2 (5.1)
Sex M:F	10:0	35:2
Mean performance IQ (SD)	79.2 (22.2)	86.3 (25.7)
% performance IQ < 70	40.0%	32.4%
% nonverbal	10%	13%
% with probable or definite seizures	10%	13%
% multiplex	20%	22%

There are no significant group differences.

Table II shows the characteristics of the parents. There were no significant differences in the demographics, verbal IQ (VIQ), or performance IQ (PIQ) between the parents of probands with and without regression. The parents were well educated, and many of them were professionals. Compared with the already published data from comparison parents of nonautistic probands [Piven and Palmer, 1997], the mean VIQ of the parents of nonregressive and regressive autistic probands was 4.7 and 7.8 points higher, and PIQ was 5.5 and 7.8 points higher, respectively. The VIQ and PIQ of the regression and nonregression autism parents were significantly higher than those of the comparison parents (all $P < .05$). In addition, significantly more parents of the regressive and nonregressive autistic probands were college graduates and professionals than were the parents of nonautistic subjects (both $P < .0002$).

Rate of the BAP in the Parents

Of the parents of autistic probands with regression, 5/18 (27.8%) met criteria for the BAP. Of the parents of autistic probands without regression, 20 met the criteria for the broader phenotype and 3 had a diagnosis of autism. The overall rate (23/70 = 32.9%) was not significantly different from the rate in the parents of autistic probands with regression ($P = 0.33$). Rates in both groups of parents of autistic probands were significantly higher than the published rate in parents of comparison subjects, 3.6% (regressive autism vs. comparison, $P = 0.01$; nonregressive autism vs. comparison, $P < 0.0001$) [Piven et al., 1997a] (see Table III).

TABLE II. Characteristics of Parents of Autism Probands With and Without Regression

	Parents of probands with regression	Parents of probands without regression
N	18	70
Mean age (SD)	39.9 (5.8)	42.1 (7.0)
Sex M:F	8:10	34:36
Mean verbal IQ (SD)	119.2 (9.5)	116.1 (11.1)
Mean performance IQ (SD)	119.8 (11.4)	117.5 (12.4)
Occupation		
% professional or intermediate	77.8%	62.3%
Education		
% college education	77.8%	68.1%

There are no significant group differences.

In our sample of 88 parents of autistic probands, neither VIQ nor PIQ was significantly correlated with BAP score (autism fathers: VIQ, r = .105, $P = .507$; PIQ, r = .009, $P = .956$; autism mothers: VIQ, r = .059, $P = .721$; PIQ, r = .270, $P = .097$). Similarly, there was no significant association between level of education and BAP score in autism mothers or fathers. However, in autism fathers, BAP score had a significant negative correlation with occupational level (r = −.306, $P = .046$). The higher the BAP score, i.e., the more affected the father, the lower his occupational level.

Additional Findings Among Probands

There were two interesting differences between the regressive and nonregressive autistic probands. The first difference was in head size. In the nonregression group, there were 10 probands with macrocephaly and 1 proband with microcephaly. All probands in the regression group were normocephalic. Mean standardized head circumference (zHC) was significantly larger in the nonregression probands ($P = .029$). There was a trend toward the nonregression subjects having increased rates of macrocephaly and decreased rates of normocephaly ($P = .091$ and .088, respectively). See Table IV.

The second interesting difference between the regressive and nonregressive autism probands was in dysmorphology. All of the regression subjects were classified as nondysmorphic. A significantly larger proportion of nonregression subjects (35.1%) were classified as equivocally or definitely dysmorphic (Fisher's exact test, two-sided, $P = .019$). Because the rates of macrocephaly and dysmorphology were both increased in the nonregression group, we explored the relationship between them. The rate of autistic subjects who were equivocally or definitely dysmorphic was not significantly different in the subjects with macrocephaly, compared with the subjects who were normocephalic. In addition, there was no significant correlation between zHC and the dysmorphology score. However, abnormalities of three dysmorphic measurements (head width, head length, and biocular width) were significantly associated with macrocephaly. We therefore repeated the analysis after removing these measurements from the dysmorphology score. There was still a significantly increased rate of being equivocally or definitely dysmorphic in the nonregression group (27% compared with the regression group (0%) (Fisher's exact test, two-tailed $P = .043$).

Additional Findings Among Parents

Table V shows the rates of the component phenotypes of the BAP, as defined in this study, and the rates of other phenotypes of interest, macrocephaly and psychiatric disorders, in the parents of regressive and nonregressive probands. There were no significant differences between the combined groups of mothers and fathers of the regression and nonregression probands on any of the variables. Mothers of autistic

TABLE III. Evidence of the Liability to Autism in Parents of Autistic Probands With and Without Regression

	Parents of autistic probands with regression (n = 18)	Parents of autistic probands without regression (n = 70)	Parents of nonautistic subjects [Piven et al., 1997a] (n = 55)
Broader autism Phenotype (%)	27.8%	32.9%	3.6%

probands without regression had a significantly increased mean zHC ($P = .04$), compared with mothers of probands with regression. The rate of macrocephaly in the mothers of nonregressive probands was increased, but the difference was not significant.

DISCUSSION

Etiologic heterogeneity has been demonstrated in autism with known causes and is likely in the 90% of autism cases that are idiopathic [Bailey et al., 1998; Szatmari, 1999]. Although data have shown that genetic factors are extremely important in idiopathic autism [Bailey et al., 1995; Santangelo and Folstein, 1999; Szatmari, 1999], there has been recent concern that some cases of idiopathic autism, particularly autism with a regressive onset, may be caused independently by environmental events. Autism with regression may be an important neurobiologic subtype of autism, with different genetic and/or environmental risk factors than nonregressive autism. Alternatively, regression in autism may represent variable expression of the same group of genes that cause nonregressive autism, with or without environmental effects. This appears to be the case for other clinical features of autism. For example, in monozygotic twins concordant for autism, there can be wide variations in the severity of the core features of autism and IQ [LeCouteur et al., 1996]. Whether regressive autism fundamentally differs from nonregressive autism in genetic and nongenetic risk factors and in clinical characteristics other than type of onset is not yet known and awaits testing in an epidemiologic sample.

TABLE IV. Head Circumference and Dysmorphology in Autistic Probands With and Without Regression

	Regressive autism	Nonregressive autism
N	10	37
Mean zHC[a] (SD)	−.071 (.705)	.735[b](1.67)
% macrocephalic	0	27.0[c]
% normocephalic	100	70.3[d]
% microcephalic	0	2.7
% nondysmorphic	100%	64.9%
% equivocally or definitely dysmorphic	0	35.1%[e]
% equivocally dysmorphic	0	24.3%[f]
% definitely dysmorphic	0	10.8%

[a]zHC = head circumference standardized for age and sex, in standard deviations from the reference mean.
[b]$t = 2.281$, $P = .029$.
[c]Fisher's exact test, two-sided $P = .091$.
[d]Fisher's exact test, two-sided $P = .088$.
[e]Fisher's exact test, two-sided $P = .019$.
[f]Fisher's exact test, two-sided $P = .091$.

Our data show that liability to autism is significantly higher in parents of children with regressive autism than in parents of nonautistic subjects. Further, liability to autism, as measured by the BAP, is increased to the same degree in parents of children with regressive and nonregressive autism. Environmental events are therefore unlikely to be a sole cause of regressive autism in our sample. Our data cannot rule out that environmental events may act in an additive or "second-hit" fashion in individuals with a genetic vulnerability to autism.

The increased liability to autism in the parents of regressive and nonregressive individuals with autism did not appear to be due to their higher IQs and educational and professional levels. The BAP score was not significantly related to IQ or educational level in the autism parents. In autism fathers, the BAP score was significantly negatively correlated with professional level: higher BAP scores were associated with lower professional levels. This finding is consistent with our clinical experience. We have observed that the BAP is often associated with functional impairment, particularly affecting social relationships with others at home and at work. Though our clinical observation needs to be further systematically tested, it seems that when features of the BAP, as measured in this study, occur in combination, they may make it difficult for at least some individuals to achieve a professional level commensurate with their IQ. This is certainly the case in high-functioning autism and many cases of Asperger disorder. If rates of the BAP were related to occupational level independent of autism, the parents of autistic probands in our study would be expected to have lower rather than higher rates of the BAP than the comparison parents. In addition, past studies have shown that parents of autistic probands, as a group, have not only increased rates of the BAP, but also mildly but significantly lower PIQs than comparison parents and no differences in VIQ [Piven and Palmer, 1997; Folstein et al., 1999]. If the BAP is related to PIQ independent of autism, the parents of autistic probands in our study should have lower rates of the BAP than the comparison parents. We found the opposite effect.

To our knowledge, this is the first study to examine the liability to autism in regressive vs. nonregressive autism. However, the relatively small sample sizes in our study and the large proportion of high-functioning males with autism may affect the extent to which the results can be generalized. The BAP needs to be studied in larger samples of parents of autistic probands with and without regression to further understand the relationship between type of onset and liability to autism. In addition, study of concordance for regressive onset in monozygotic twins and affected sibling pairs with autism will help clarify to what extent variations in

TABLE V. Additional Findings Among Parents of Autism Probands With and Without Regression

	Parents of probands with regression	Parents of probands without regression
N	18	70
BAP component variables		
% rigidity	33.3%	42.8%
Mothers (%)	22.2	26.7
Fathers (%)	44.4	58.3
% hypersensitivity	50.0%	47.1%
Mothers (%)	66.7	50.0
Fathers (%)	33.3	44.4
% speech abnormalities	0	2.8%
Mothers (%)	0	0
Fathers (%)	0	5.6
% impaired friendships	22.2%	20.3%
Mothers (%)	0	3.0
Fathers (%)	44.4	36.1
Head size		
Mean zHC (SD)	−.106 (1.82)	.487 (1.27)
Mothers	−.349	.686[a]
Fathers	.137	.299
% macrocephalic	5.56%	12.12%
Mothers (%)	0	12.5[b]
Fathers (%)	11.1	11.8
Psychiatric disorders		
Major depression	37.5%[c]	50.0%[d]
Mothers	50.0	62.1
Fathers	25.0	39.4
Social phobia	35.7%[c]	37.1%[d]
Mothers	37.5	37.9
Fathers	37.5	36.4
Obsessive compulsive disorder	0[e]	4.6%[f]
Mothers	0	10.5
Fathers	0	0
Panic disorder	6.25%[c]	9.7%[d]
Mothers	0	13.8
Fathers	12.5	6.1
Specific phobia	18.7%[c]	24.2%[d]
Mothers	25.0	37.9
Fathers	12.5	25.7
Generalized anxiety disorder	0[c]	4.8%[c]
Mothers	0	3.4
Fathers	0	6.1
History of ADHD	0[e]	4.4%[g]
Mothers	0	5.7
Fathers	0	3.0
History of alcohol abuse	0[h]	0[g]
Mothers	0	0
Fathers	0	0
History of drug abuse	5.9%[h]	1.5%[g]
Mothers	11.1	0
Fathers	0	3.0

[a] $t = -2.123$, $P = .04$.
[b] Fisher's exact test, two-sided, $P = .559$, one-sided, $P = .355$.
[c] $n = 16$.
[d] $n = 62$.
[e] $n = 8$.
[f] $n = 43$.
[g] $n = 68$.
[h] $n = 17$.

type of onset in autism are explained by genetic variation. Most important will be the identification of specific genetic loci associated with autism and their relationship to pattern of onset.

In this study, we also explored several other potentially important phenotypes in probands with regressive and nonregressive autism and their parents. The significantly lower mean head circumference, trend toward lower rates of macrocephaly, and possibly less dysmorphology in autism probands with regression vs. without regression, and a similar pattern for zHC in the mothers, are intriguing and merit further investigation. To our knowledge, associations between smaller mean zHC, lower rates of macrocephaly, and regression have not been reported in the past, and the issue has been examined only by one other researcher [Miles et al.,

2000]. In her study, which used different methods from ours, the data show similar rates of macrocephaly in autistic probands with and without regression [Miles et al., 2000].

Our data suggest that although familial liability is elevated to the same extent in regressive and nonregressive autism, there may be other fundamental differences between individuals with autism with these different types of onset. If our findings of increased mean zHC, a trend toward an increased rate of macrocephaly, and increased rates of dysmorphology not related to head size are replicated in nonregressive vs. regressive autism, they will have important implications. The increased number of minor congenital anomalies, which are measures of fetal maldevelopment, in our nonregression probands may indicate that the fetal development of autistic individuals without regression is different from those with regression. Because macrocephaly in autism usually develops after birth [Lainhart et al., 1997; Stevenson et al., 1997], the increased head size and trend toward an increased rate of macrocephaly in our nonregressive probands may indicate that aspects of postnatal development are also different in regressive and nonregressive individuals with autism, in addition to type of onset.

Compared with other studies of component phenotypes of the BAP, the percent of parents with the individual features varied somewhat from that of past studies using similar methods [Piven et al., 1997a; Santangelo and Folstein, 1999; Murphy et al., 2000]. Variations in the rate of component phenotypes of the BAP in different samples have been shown [Piven et al., 1997a; Santangelo and Folstein, 1999; Murphy et al., 2000]. The variations may be due to regional differences in the combination of genes and environmental factors that interact to cause autism and their expression in different populations. The rates of the composite BAP in our regression and nonregression parent samples, which included parents of simplex and multiplex autism probands, were between the approximately 20–25% rate of the BAP reported in parents of simplex probands [Santangelo and Folstein, 1999] and the 56% rate reported in the parents of multiplex families [Piven et al., 1997a]. There were no significant differences in the rates of components of the BAP and psychiatric disorders in the parents of probands with and without regression. This finding suggests that the components of the BAP and the psychiatric disorders measured in this study do not differentiate the liability to autism in regressive vs. nonregressive autism parents.

Assuming that features of the BAP represent genetic liability to autism [LeCouteur et al., 1996; Santangelo and Folstein, 1999], our data suggest that genetic factors may be just as important in regressive autism as they are in nonregressive autism. Environmental factors, if involved in the pathogenesis of autism, do not appear to be preferentially involved in regressive vs. nonregressive autism in our sample. The coordinated study of potential prenatal and postnatal environmental risk factors, along with markers of genetic liability, may result in the most thorough understanding of the role of environmental factors in both regressive and nonregressive autism. Even if genetic risk factors are most important in autism, the wide variations in the autism and broader autism phenotypes and associated features still warrant a thorough search for environmental factors that may affect severity of the disorder. Though there is no cure for autism, lessening the burden of illness and impairment for individuals with autism and their families would be a major and far-reaching contribution.

ACKNOWLEDGMENTS

The authors thank Barbara Young, Jubel Morgan, and other staff of the Utah Autism Project for their assistance. The authors express their sincere gratitude to the children and adults with autism and their parents who participated in this study.

REFERENCES

Bailey A, LeCouteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. 1995. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 25:63–77.

Bailey A, Palferman S, Heavey L, LeCouteur A. 1998. Autism: the phenotype in relatives. J Autism Dev Disord 28:369–392.

Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, Bailey A, Rutter M. 1994. A case-control family history study of autism. J Child Psychol Psychiatry 35:877–900.

Center for Disease Control, National Immunization Program. 2002. MMR-autism theory and the CDC's conclusion based on several studies. www.cdc.gov/nip/vacsafe/concerns/autism/vaccines&autism.htm.

Chakrabarti S, Fombonne E. 2001. Pervasive developmental disorders in preschool children. JAMA 285:3093–3099.

Farkas LG. 1994. Examination In: Farkas LG, editor. Anthopometry of the head and face, 2nd edition. New York: Raven Press. p 3–56.

Farkas LG, Hreczko TA, Katic MJ. 1994. Craniofacial norms in North American Caucasians from birth to young adulthood. In: Farkas LG, editor. Anthopometry of the head and face, 2nd edition. New York: Raven Press. p 241–335.

Feingold M, Bossert WH. 1974. Normal values for selected physical parameters: an aid to syndrome delineation. Birth Defects Orig Artic Ser X(13):1–15.

Folstein SE, Santangelo SL, Gilman SE, Piven J, Landa R, Lainhart J, Hein J, Wzorek M. 1999. Predictors of cognitive test patterns in autism families. J Child Psychol Psychiatry 40:1117–1128.

Fombonne E, Chakrabarti S. 2001. No evidence for a new variant of measles-mumps-rubella-induced autism. Pediatrics 108:E58.

Fyer AJ, Endicott J, Mannuzza S, Klein DF. 1995. Schedule for affective disorders and schizophrenia-lifetime version, modified for the study of anxiety disorders, 1985. Updated for DSM IV (SADS-LA IV). Anxiety Family Genetic Unit, New York: New York State Psychiatric Institute.

Hall JG, Froster-Iskenius UG, Allanson JE. 1989. Handbook of normal physical measurements. Oxford: Oxford University Press. p 142–144.

Halsey NA, Hyman SL. 2001. Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12–13, 2000. Pediatrics 107:E84.

Hoshino Y, Kaneko M, Yashima Y, Kumashiro H, Volkmar FR, Cohen DL. 1987. Clinical features of autistic children with setback course in their infancy. Jpn J Psychiatry Neurol 41:237–246.

Institute of Medicine Immunization Safety Reviews. 2001. Measles-mumps-rubella vaccine and autism. Washington DC: National Academy Press. p 13–69.

Kobayashi R, Murata T. 1998. Setback phenomenon in autism and long-term prognosis. Acta Psychiatr Scand 98:296–303.

Kurita H. 1985. Infantile autism with speech loss before the age of thirty months. J Am Acad Child Psychiatry 24:191–196.

Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo S, Coon H, Folstein SE. 1997. Macrocephaly in children and adults with autism. J Am Acad Child Adolesc Psychiatry 36:282–290.

Landa R, Piven J, Wzorek MM, Gayle JO, Chase GA, Folstein SE. 1992. Social language use in parents of autistic children. Psychol Med 22: 245–254.

LeCouteur A, Bailey A, Goode S, Pickles A, Robertson S, Gottesman I, Rutter M. 1996. A broader phenotype of autism: the clinical spectrum in twins. J Child Psychol Psychiatry 37:785–801.

Lord C, Rutter M. 1994. Autism and pervasive developmental disorders In: Rutter M, Taylor E, Hersov L, editors. Child and adolescent psychiatry. London: Blackwell Scientific Publications. p 569–593.

Lord C, Rutter M, LeCouteur A. 1994. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, Rutter M. 2000. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30:205–223.

Miles JH, Hillman RE. 2000. Value of a clinical morphology examination in autism. Am J Med Genet 91:245–253.

Miles JH, Hadden LL, Takahashi TN, Hillman RE. 2000. Head circumference is an independent clinical finding associated with autism. Am J Med Genet 95:339–350.

Murphy M, Bolton PF, Pickles A, Fombonne E, Piven J, Rutter M. 2000. Personality traits of the relatives of autistic probands. Psychol Med 30:1411–1424.

Pareek M, Pattison HM. 2000. The two-dose measles, mumps, and rubella (MMR) immunization schedule: factors affecting maternal intention to vaccinate. Br J Gen Pract 50:969–971.

Pickles A, Starr E, Kazak S, Bolton P, Papanikolaou K, Bailey A, Goodman R, Rutter M. 2000. Variable expression of the autism broader phenotype-findings from extended pedigrees. J Child Psychol Psychiatry 41:491–502.

Piven J, Palmer P. 1997. Cognitive deficits in parents from multiple-incidence autism families. J Child Psychol Psychiatry 38:1011–1021.

Piven J, Palmer P, Landa R, Santangelo S, Jacobi D, Childress D. 1997a. Personality and language characteristics in parents from multiple-incidence autism families. Am J Med Genet 74:398–411.

Piven J, Palmer P, Jacobi D, Childress D, Arndt S. 1997b. The broader autism phenotype: evidence from a family study of multiple incidence autism families. Am J Psychiatry 154:185–190.

Rogers SJ, DiLalla DL. 1990. Age of symptom onset in young children with pervasive developmental disorders. J Am Acad Child Adolesc Psychiatry 29:863–872.

Santangelo SL, Folstein SE. 1995. Social deficits in the families of autistic probands. Am J Med Genet 57:89.

Santangelo SL, Folstein SE. 1999. Autism: a genetic perspective. In: Tager-Flusber H, editor. Neurodevelopmental disorders: contributions to a new framework from the cognitive neurosciences. Cambridge, MA: MIT Press. p. 431–447.

Smeeth L, Hall AJ, Fombonne E, Rodrigues LC, Huang X, Smith PG. 2001. A case-control study of autism and mumps-measles-rubella vaccination using the general practice research database: design and methodology. BMC Public Health 1:2.

Stevenson RE, Schroer RJ, Skinner C, Fender D, Simensen RJ. 1997. Autism and macrocephaly. Lancet 349:1744–1745.

Szatmari P. 1999. Heterogeneity and the genetics of autism. J Psychiatry Neurosci 24:159–165.

Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. 2002. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. Br J Med 16:393–396.

Tuchman RF, Rapin I. 1997. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. Pediatrics 99:560–566.

Tuchman RF, Rapin I, Shinnar S. 1991. Autistic and dysphasic children. I: Clinical characteristics. Pediatrics 88:1211–1218.

Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. 1998. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 351:637–641.