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Essential Versus Complex Autism:
Definition of Fundamental Prognostic Subtypes

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Heterogeneity within the autism diagnosis obscures the genetic basis of the disorder and impedes our ability to develop effective treatments. We found that by using two readily available tests, autism can be divided into two subgroups, "essential autism" and "complex autism," with different outcomes and recurrence risks. Complex autism consists of individuals in whom there is evidence of some abnormality of early morphogenesis, manifested by either significant dysmorphology or microcephaly. The remainder have "essential autism." From 1995 to 2001, 260 individuals who met DSM-IV criteria for autistic disorder were examined. Five percent (13/260) were microcephalic and 16% (41/260) had significant physical anomalies. Individually, each trait predicted a poorer outcome. Together they define the "complex autism" subgroup, comprising 20% (46/233) of the total autism population. Individuals with complex autism have lower IQs ($P = 0.006$), more seizures ($P = 0.0008$), more abnormal EEGs (46% vs. 30%), more brain abnormalities by MRI (28% vs. 13%). Everyone with an identifiable syndrome was in the complex group. Essential autism defines the more heritable group with higher sib recurrence (4% vs. 0%), more relatives with autism (20% vs. 9%), and higher male to female ratio (6.5:1 vs. 3.2:1). Their outcome was better with higher IQs ($P = 0.02$) and fewer seizures ($P = 0.0008$). They were more apt to develop autism with a regressive onset (43% vs. 23%, $P = 0.02$). Analysis of the features predictive of poor outcome (IQ < 55, functionally non-verbal) showed that microcephaly was 100% specific but only 14% sensitive; the presence of physical anomalies was 86% specific and 34% sensitive. The two tests combined yielded 87% specificity, 47% sensitivity, and an odds ratio of 4.8:1 for poor outcome. Separating essential from complex autism should be the first diagnostic step for children with autism spectrum disorders as it allows better prognostication and counseling. Definition of more homogeneous populations should increase power of research analyses.

KEY WORDS: autism; essential; dysmorphology; head circumference; outcome

INTRODUCTION

Autism is a neuropsychiatric disorder of early childhood, defined exclusively on the basis of impairments in social interactions and communication, and repetitive or stereotypic behaviors, delineated in the DSM-IV [American Psychiatric Association, 1994]. Clinically, the autism diagnosis is variable with some children having more or fewer symptoms in each of the three domains, very low to above average IQs, and outcomes that range from entering regular school and functioning well in society to requiring lifelong care [Bailey et al., 1998; Spence, 2001; Silverman et al., 2002].

There have long been concerns that autism research is hampered by a lack of diagnostic uniformity, leading to mixed populations which make inter-study comparisons difficult [Links et al., 1980]. In the late 1990s, the adoption of standardized, replicable diagnostic instruments and diagnostic criteria (DSM-IV, ADI-R, ADOS-G, ICD-10, CARS) [Schopler et al., 1986; World Health Organization, 1992; American Psychiatric Association, 1994; Lord et al., 1994, 1998] largely insured that major research studies were conducted with children who satisfy similar neurobehavioral criteria. The constancy of the core manifestations has stood up to intensive scrutiny and clearly separates autism from other behavioral diagnoses such as mental retardation and ADHD. It bears repeating that future autism studies must be grounded on a firm behavioral diagnosis.

Despite this meticulous attention to diagnosis, there remains enormous clinical variability within autism [Folstein et al., 1998; Spiker, 1999; Beglinger and Smith, 2001; Spiker et al., 2002]. Children with autism vary in their presentation, course and outcomes, in the quality and intensity of their core autism symptoms, their adaptive and cognitive levels and responses to therapy [Asperger, 1944; Wing and Gould, 1979; Wing, 1981a; Prizant and Schuler, 1987; Wing and Atwood, 1987; DeLong and Dwyer, 1988; Rutter and Schopler, 1988; Volkmar et al., 1989; Coleman, 1990; Szatmari, 1992; Castelloe and Dawson, 1993; Roux et al., 1997; Bailey et al., 1998; Fein et al., 1999; Spence, 2001; Silverman et al., 2002]. In 1994, the diagnostic term "infantile autism" was replaced by "autistic disorder" [American Psychiatric Association, 1994] implying that the autism phenotype comprises a spectrum of disorders varying in severity, associated symptoms and causality.

Unraveling the genetic heterogeneity in autism and dissecting its correspondence, or lack thereof, with clinical characteristics has proven much more difficult than for the prototypic single gene disorders [reviewed in Fein et al., 1999; Spence, 2001]. Reports of sibs discordant for their autism spectrum disorders led to the disheartening expectation that we would not be able to understand the heterogeneity until we found specific autism genes and we could not find the autism genes

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until we understand the heterogeneity [DeLong and Dwyer, 1988; Silverman et al., 2002].

Most attempts to discover the fundamental genetic bases of autism have focused on cognition and the core diagnostic symptoms. Variance in IQ has garnered the most attention, since between half and three quarters of autistic children have IQ scores below 70 [Lotter, 1966; Rutter, 1983; Steffenburg and Gillberg, 1986; Lincoln et al., 1995; Chakrabarti and Fombonne, 2001] and because cognitive levels measured in early childhood have been a strong predictor of outcome [Cohen et al., 1987; Lord and Schopler, 1989a,b; Kobayashi et al., 1992; Venter et al., 1992; Volkmar, 1992; Fein et al., 1999]. Stevens et al. [2000] reported that children who tested during preschool as low functioning (based on non-verbal IQ, receptive vocabulary and socialization) either remained low functioning or dropped significantly in their level of functioning when retested at school age. They concluded that early normal or near-normal non-verbal IQ was the best predictor of adequate functioning by grade school. In multiplex sibships, non-verbal IQ scores correlated positively [Szatmari et al., 1996; Spiker et al., 2002], indicating that cognitive abilities in autism, as in typically developing populations, were largely genetically determined. Moreover, IQ levels appeared to correlate with a fundamental genetic variable, the male to female ratio; the more severely retarded the population, the lower the male to female ratio [Wing, 1981a,b; Gillberg, 1989; Szatmari et al., 1989]. The greatest male predominance occurred in Asperger syndrome as did the highest IQ scores.

In the young autistic child or in individuals with pockets of intelligence, IQ assessment is difficult [reviewed in Bailey et al., 1996], and IQ and DQ scores measured in early childhood may change over time and with therapy. Lord and Schopler [1989a] reported mean differences greater than 23 points comparing test scores prior to age 4 with those at age 8 and older, findings which have been replicated in other populations [Sigman et al., 1999]. Even without special treatment, children first assessed in early preschool years are likely to show marked increases in IQ score by school age [Lord and Schopler, 1989b]. It is unclear if this reflects limitations of assessment methods in younger children, the natural history of the disorder or, since none of these studies are longitudinal, some bias of ascertainment [Freeman et al., 1991]. Evidence that IQ is not the primary genetic variable in autism, was first presented by Le Couteur et al. [1996] who found that IQ scores can vary widely in identical twins. Jorde et al. [1990] found that dividing the Utah cohort by IQ revealed no significant differences in recurrence risks and gave no indications of inheritance patterns. This is consistent with our data, which show that though individuals with complex autism as a group have lower IQ scores than those with essential autism, it is the essential/complex autism distinction that provides the more fundamental separation. IQ scores did not correlate with sex ratios, recurrence risks, family histories of autism, or type of onset [Miles et al., 2001; Miles, unpublished data].

Numerous studies have focused on language variability to create more homogeneous autism subgroups. Language competence, like cognitive ability, is under significant genetic control, demonstrated by the robust language correlations reported within sibships, twins and/or more distant relatives [Fombonne et al., 1997; Piven and Palmer, 1997; Bailey et al., 1998; Hughes et al., 1999; MacLean et al., 1999; Pickles et al., 2000; Spiker et al., 2002; Silverman et al., 2002]. Silverman et al. [2002] found reduced variance within sibships for speech delays and age at phrase speech. Likewise, in a study of 171 autism sibships, Spiker et al. [2002] found a highly significant association within autism sib pairs for language delay and absence of phrase speech. Pickles et al. [2000] studied over 3,000 relatives from 149 autism families and found that the percent of relatives with an autism phenotype correlated positively with the severity of autism for the verbal probands, but not for probands lacking speech, suggesting a genetic difference between verbal and non-verbal autism probands. The utility of using language to identify genetically distinct subgroups, was demonstrated by Hutcheson et al. [2003], who found higher LOD scores for linkage to the AUT1 region on chromosome arm 7q in the more language-impaired group. This was the first time functional phenotypes were successfully correlated with genetic linkage. Nevertheless, language development does not appear to be the primary autism genetic determinant, since many non-verbal autistic children have parents and/or sibs with high functioning autism or Asperger syndrome [Eisenmajer et al., 1996; Volkmar et al., 1998; Gillberg, 1999; Gillberg and Wing, 1999]. Recently, Miller and Ozonoff [2000] compared individuals with high-functioning autism with impaired language to individuals with Aspergers; with IQ differences controlled, they found no significant group differences in motor, visual spatial, or executive functions, suggesting language development is primarily IQ dependent.

Some investigators have tried to correlate genetic indicators with behavioral symptoms. In a well executed study of 212 multiplex sibships, Silverman et al. [2002] found evidence for familiality for the ADI items which describe preoccupations, compulsive routines, and rituals and deficits in non-verbal communication. We found that autism without repetitive motoric behaviors correlated with a family history of obsessive compulsive disorder [Miles et al., 2000b]. Studying 171 multiplex families, Spiker et al. [2002] found the autistic behavioral symptoms did not identify distinct behavioral phenotypes, but clustered along a continuous severity dimension such that children with the lowest non-verbal IQ scores were more apt to be non-verbal and have more severe impairment in ADI-R scores. Sib comparisons did, however, reveal positive correlations for IQ scores, verbal status, total non-verbal language and rituals scores. Recent efforts by Joseph et al. [2002] to distinguish an autism subtype based on different cognitive profiles found that children with poor verbal skills had more social impairment and this correlated with macrocephaly [Deutsch and Joseph, 2003]. They hypothesized that this could be an autism subtype associated with a greater disturbance in brain development. Taken in total, most studies have shown that in autism, IQ and language differences are clearly heritable, while social features exhibit a lesser degree of heritability. They do not, however, allow us to determine the primary genetic basis of these associations.

In the course of our studies, we noted that a significant subset of children with autism have congenital anomalies which clearly indicate some insult to early embryologic development has occurred [Miles and Hillman, 2000]. We hypothesized that the distinction between the autistic children who suffered an abnormality of morphogenesis and those who did not, would allow us to define fundamentally different subgroups whose autism was due to different causes. This paper describes the subdivision of the autism spectrum disorders into two subgroups, complex and essential autism. Complex autism is defined by the presence of a significant number of physical anomalies and/or microcephaly. The remainder, in whom we find no evidence of abnormal morphogenesis are defined as having essential autism. The essential and complex subgroups are relatively easy to identify clinically, and appear to differ in their outcomes, recurrence risks, sex ratios, and family histories.

MATERIALS AND METHODS

Subjects

The study sample consisted of 260 unrelated patients diagnosed with autistic disorder or Aspergers syndrome at the Autism Center at the University of Missouri-Columbia

Hospitals and Clinics. Of 412 consecutive patients referred to the Autism Center between 1994 and 2001, 77% (316/412) met DSM-IV [American Psychiatric Association, 1994] and CARS (Childhood Autism Rating Scale) [Schopler et al., 1986] criteria for the diagnosis of a pervasive developmental disorder. The autism spectrum diagnoses included 244 with autistic disorder, 16 with Asperger syndrome and 56 with PDD-NOS. The 260 individuals with autistic disorder or Asperger syndrome are included in this study.

Because this was the first dedicated autism clinic in Missouri and was supported by the Missouri Department of Mental Health, patients with a suspected diagnosis of autism were drawn from the entire state for diagnosis, medical management, and guidance on behavioral issues and school placement. There was no recognizable ascertainment bias toward more or less phenotypically abnormal, mentally retarded or multiplex subjects and no exclusion of individuals who met autism diagnostic criteria specified by DSM-IV and CARS criteria. Each patient was evaluated by the Autism Center directors using a center-based version of the ADI scoring protocol and only those meeting criteria were included in the study. Independent diagnostic evaluations were conducted by a child psychiatrist and a neuropsychologist. The results were compared and in any case where there was a disparity, the individual was discussed jointly to reach a conclusion. One third of the patients were evaluated with the complete ADI-R [Lord et al., 1994]; in all cases the ADI-R confirmed the previous diagnosis.

Clinical Evaluation

The Autism Center evaluation utilized a standard data set for the collection of historical information including prenatal, perinatal, development, language, behavior, neurologic, dietary, health and family history. All pertinent records including school, therapy, and IEP reports as well as psychological, developmental, and medical testing were reviewed. A detailed history of the onset of autistic symptoms was obtained including the age of onset of each symptom and whether delays and or losses occurred in language, gross motor, fine motor, activities, or social interactions. Laboratory tests included G banded chromosomes, DNA for fragile X, urine metabolic screen, organic acids, urine amino acids, short chain fatty acids, thyroid profile, CMP, heme profile, and lead level. Brain MRIs were obtained in 65% of the subjects and EEGs in 58%. Physical examinations were performed including standard morphologic measurements of the head, face, hands, feet, body proportions, and dermatoglyphic analysis [Hall et al., 1989; Aase, 1990; Jones, 1997]. The skin was examined with a Woods lamp. Parents and other available relatives were examined and family photographs were reviewed. All study data were entered into a fully searchable relational database.

Morphology Classification

The method used for phenotypic classification has been described previously [Miles and Hillman, 2000]. In this study, we classified children as "dysmorphic" if they had more than six abnormal physical features including minor anomalies, measurement abnormalities, and descriptive features not present in their non-autistic parents. Individuals with less than three features were defined as "non-dysmorphic." Those with between three and six features were placed into an equivocal group. Each of the study individuals were examined by one of two medical geneticists (JHM/REH). Interrater reliability studies were carried out on 100 children and provided a reliability score of 0.88. The interrater reliability for the 30 patients examined independently by four dysmorphologists was 0.83 [Miles et al., 2003]. Of the 260 individuals examined 41 (16%) were dysmorphic, 191 (74%) were non-dysmorphic, and for 27 (10%) individuals the examination was equivocal.

Head Circumference

The method used for determination of microcephaly and macrocephaly has been previously described [Miles et al., 2000a]. The occipital-frontal circumference is measured and microcephaly is defined as a measurement number of the 2nd centile and macrocephaly as $\geq$98th centile. Our intra-and inter-rater reliability ranged from 0.92 to 0.95. Of the 260 subjects, 13 (5%) were microcephalic; the remainder were normocephalic or macrocephalic.

Brain MRI

Brain MRIs were obtained on 65% (170/260) of the subjects using a Siemens 1.5T scanner following our autism brain protocol and interpreted by a CAQ (Certificate of Added Qualifications) neuroradiologist. Patients were anesthetized by a board-certified anesthesiologist using our autism protocol (both protocols available on request). Brains were classified as abnormal if the neuroradiologist determined that the brain structure fell outside the normally accepted range. We recognize that this determination is inexact. For instance, individuals with a mega cisterna magna or an Arnold-Chiari malformation may or may not have developmental concerns. This inexactness, however, reflects the current state of the science and is accepted as such. MRIs that were equivocal were reviewed by a pediatric neurologist and the neuroradiologist and the consensus determination was accepted.

IQ/DQ Assessment

Each patient was assigned an IQ/DQ score based on the most recent and comprehensive neuropsychological evaluation. Children were evaluated by the Autism Center's neuropsychology team (53%) or recent results from the schools or other psychologists were used (47%). When more than one set of test results were available, non-verbal IQ scores were used with the order of preferred testing being the Leiter-R [Roid, 1997], the WISC-III [Wechsler, 1991], and the Stanford Binet [Thorndike et al., 1986]. For younger children, developmental quotients, specifically daily living skills scores from the Vineland [Sparrow et al., 1984] were used. Scores reported in Table II were from the Leiter (76), Vineland (61), Wechsler (30), Stanford Binet (5), Slossen (1), other (2). To be certain that the use of Vineland developmental quotient scores did not distort the data, the IQ score comparisons between essential and complex autism were calculated for the 112 individuals who had available IQ scores. No significant differences were noted. The mean IQ in the essential group was 79 (SD 26.5) and in the complex group was 55.8 (SD 24.1); P value $= 0.0006$. In the essential group, 62% had an IQ > 70; 19% an IQ < 55. In the complex group, 31.5% had an IQ > 70; 47.4% an IQ < 55. Differences between the essential and complex group scores were both significant at $P = 0.01$. Though the use of the Vineland DQ scores did not affect the comparisons, the combined the IQ/DQ scores were slightly lower than the IQ scores alone.

Language Assessment

Children were defined as functionally verbal when they used sentences to convey their wants and needs and produced a range of flexible sentence types. This corresponds to fluent speech defined in the Autism Diagnostic Observation Schedule [Lord et al., 1998, 1999, 2000]. Each individual was designated as either functionally verbal or not based on either formal testing using the ADOS, ADI-R, VABS [Sparrow et al., 1984], or CELF-III [Semel et al., 1995] or by a combination of parental report and clinical observation. Of the 103 subjects who were at least 8 years old, 49/103 (48%) were defined as verbal.

Outcome Assessment

Outcomes were specified for individuals age 8 years or older using an outcome classification based on IQ/DQ scores and verbal ability. Excellent outcome was defined as having an IQ/DQ score over 70 and being functionally verbal. Good outcome included those individuals with IQ/DQ scores between 55 and 70 who had functional verbal abilities. Poor outcome was defined as an IQ/DQ score <55 or being functionally non-verbal by the age of 8 years. Of the 74 individuals included in the analysis, only seven were tested by the Vineland. A similar comparison, limited to individuals with IQ scores produced similar results (data not presented).

Family History

Family histories were obtained by direct semi-structured interviews using the family history method [Orvaschel et al., 1982; Thompson et al., 1982; Andreasen et al., 1986; Rice et al., 1995; Yuan et al., 1996; Davies et al., 1997]. Using our investigator-based family history interview form, an in-depth interview was conducted. The informants were asked about each first, second, and third degree relative individually, inquiring about any medical, psychological/psychiatric, or behavioral problems. Disease specific questions were then used to clarify the diagnosis. A family history of autism was rated as significant if the proband had either (1) an affected first degree relative or (2) a second degree relative affected plus at least two additional affected individuals in the same family branch in a pattern suggesting mendelian inheritance.

Statistical Analysis

Tables I and II give summary data comparing cases of essential and complex autism. Continuous random variables were summarized by their mean, standard deviation, and range. For categorical random variables, separately for the essential and complex cases, the proportion of cases in each category are given. For the categorical random variables, univariate comparisons of essential and complex autism were made using χ^2 tests. For age and sex ratio, comparisons were made using Students t-test. Because the distribution of IQ is skewed, comparisons for IQ were made using the Kolmogorov–Smirnov test and the t-test after log transforming IQ.

We constructed a logistic regression model in order to determine which features best predicted poor outcomes. The following variables were used in the regression model: gender, dysmorphology classification, microcephaly, macrocephaly, seizures, regressive onset. Abnormal MRI, abnormal EEG were excluded from the analysis because of the large number of missing values. In addition to modeling outcome for all cases, outcome was modeled separately for complex and essential cases.

TABLE I. Demographic Characteristics of Essential Versus Complex Autism*

	Essential autism (N = 187)		Complex autism (N = 46)	
Mean age (SD)	8.1 (7.2)		12.6 (9.5)	
Range	1.4–55.9		1.0–41.2	
Ethnicity				
White	81%	152/187	96%	44/46
Black	7%	13/187	2%	1/46
Asian	2%	4/187	0%	0/46
Bi-racial/multi-racial	10%	18/187	2%	1/46
Socio-economic status				
Group I and II	45%	67/148	34%	10/29
Group III	32%	47/148	21%	6/29
Group IV and V	23%	34/148	45%	13/29

*Socio-economic status of birth family was unknown for 56 individuals.

RESULTS

Two hundred sixty consecutive patients evaluated at the University of Missouri Autism Center between 1994 and 2001 met DSM-IV diagnostic criteria for autism (94%) or Aspergers syndrome (6%). The study population was primarily children with a mean age of 9 years; 86% were Caucasian, 7% biracial, 5% African-American, and 1.5% Asian (Table I). No significant differences emerged between individuals with essential and complex autism.

Phenotypic features which we considered potentially useful for the separation of the behavioral autism diagnosis into more homogeneous subgroups were identified. We sought features that were consistently present in a substantial percentage of autistic children, and were discrete, measurable and "replicable." The crucial requirement was that the feature be pathophysiologically relevant with potential to become a genetic marker. Because we wanted to identify features that manifest prior to the onset of autistic symptoms, we looked for features that were stable from birth. The two features identified as the most informative were "dysmorphology," which occurred in 16% of the population, and microcephaly which occurred in 5%.

The presence of significant "dysmorphology" and microcephaly were used to define the complex autism subgroup, providing physical evidence of an insult to early embryological development. The remainder, who were physically non-dysmorphic and non-microcephalic were designated "essential autism." The two groups differ in their genetic features (sex ratio, sibling recurrence risk, family history of autism), measures of outcome (IQ, seizures) and type of onset (regressive). All subjects identified with an autism related syndrome were in the complex group (Table II).

Forty-eight percent of those with essential autism have IQ/DQ scores >70, compared with only 22% of those with complex autism (see Table II). Correspondingly, only 25% of those with essential autism have IQ/DQ scores <55, compared with 52% of those with complex autism. Because the distribution of IQ/DQ scores was found to be highly skewed, the IQs of those with complex autism were compared to those with essential autism using the Kolmogorov–Smirnov test ($P = 003$). Comparisons using a log transformation of the IQ scores gave similar results ($P < 0.003$).

To further elucidate the differences between complex and essential autism we compared outcomes for subjects age 8 years or older, using an outcome classification based on IQ/DQ scores and verbal ability (Table III). Of the 15 individuals with excellent outcomes, 93% had essential autism and only 7% had complex autism. In the good outcome group, 79% had essential autism and 21% complex. However, individuals with a poor outcome were almost evenly divided between those with essential and complex autism, demonstrating that complex autism is a more specific indicator of poor outcome than essential autism is an indicator of an excellent outcome.

Because many features might be associated with outcome, we tested each feature individually to determine which were most predictive of a poor outcome (Table IV) and an excellent outcome (Table V). For poor outcome, microcephaly was most predictive with a positive predictive value of 100%. The dysmorphology classification was the next most predictive single feature. The complex autism designation provided the highest sensitivity with a positive predictive value of 86%. Seizures and a regressive onset appeared somewhat predictive. Gender, abnormal brain MRI, abnormal EEG, and macrocephaly were not. Excellent outcomes were less predictable with only essential autism having a positive predictive value above 50% (Table V).

TABLE II. Essential Versus Complex Autism (Total = 233)*

	Essential autism = 187 (80%)	Complex autism = 46 (20%)	*P* value
Genetic indicators	162:25	33:11	
Sex ratio	6.5:1 (162:25)	3.2:1 (35:11)	0.08
Sib recurrence risk (true autism)	4% (9/231)	0% (0/52)	ns
Sib recurrence (true + traits)	12% (27/231)	6% (3/52)	ns
Latter sib recurrence (true autism)	6% (6/97)	0% (0/18)	ns
Latter sib recurrence (true + traits)	13% (13/97)	5% (1/18)	ns
Family history of autism[a]	20% (32/159)	9% (3/35)	ns
Outcome indicators			
Mean IQ/DQ (SD)	70.4 (25.4)	53.1 (22.8)	0.0009
Range	20–160	20–91	0.003
Score >70	48% (71/145)	22% (6/27)	0.01
Score <55	25% (37/145)	52% (14/27)	0.006
Verbal language (≥8 years)	47% (27/58)	80% (24/30)	0.003
Seizures	17% (31/187)	39% (18/46)	0.0008
Clinical course indicator			
Regressive onset[a]	43% (79/185)	24% (11/45)	0.02
Other associations			
Abnormal EEG[a]	30% (32/107)	46% (12/26)	ns
Abnormal brain MRI[a]	13% (15/122)	28% (8/29)	0.08
Syndrome diagnosis	0% (0/187)	24% (11/46)	<0.0005

*Twenty-seven subjects were not included because their dysmorphology status was equivocal.
[a]Family history, type of onset were not known for all children. Not all children had an EEG or MRI.

To further determine the predictive value of the factors, a logistic regression model was built which compared the physical features, laboratory results, and gender with outcome. When all cases were considered together, only macrocephaly was a significant predictor of poor outcome ($P = 0.02$, score test). When complex cases were considered alone, macrocephaly remained significant ($P = 0.03$, score test). However, when essential cases were analyzed separately, regression (and not macrocephaly) was significant ($P = 0.03$).

To see if it would be possible to detect additional outcome related variables, similar analyses were carried out within the more homogeneous essential autism subgroup (Table VI). Regressive onset correlated most strongly with a poor outcome ($P < 0.05$). Male sex and seizures, also emerged as significant predictive variables of poor outcome. Within the essential subgroup, no strong predictors for an excellent outcome emerged (Table VII).

Eleven individuals, comprising 4.2% of the total population, were identified with either a chromosomal, single gene or teratogenic syndrome which was considered to be the cause of their autistic disorder (Table VIII). All 11 individuals were classified as complex autism and comprised 24% of that group. Both subjects with tuberous sclerosis were identified by hypopigmented macules and shagreen patches identified during the physical examination and therefore were included in the complex group. Exclusion of the individuals with identified syndromes yielded no significant changes in the data (not shown).

DISCUSSION

There has been a renewed interest in physical phenotypic features in autism, with the hope that they might function as biological markers to separate subsets of subjects for genetic studies. Kanner [1943] originally described children with autism as well formed, beautiful, and free of obvious defects. Although this image is entrenched in the autism literature, it is obvious to the dysmorphologist that a significant number of children with autism have multiple physical anomalies. In the 1970s and early 1980s a number of studies documented that taken as a group, autistic children had physical features outside the norm [Mnukhin and Isaev, 1975; Steg and Rapoport, 1975; Walker, 1977; Campbell et al., 1978; Links, 1980; Links et al., 1980; Gualtieri et al., 1982]. Walker, using the Waldrop weighted scoring scale [Waldrop and Halverson, 1971] for 16 anomalies, studied 74 autistic and non-autistic children matched for age, sex, socioeconomic group and geographic domicile, and found that the mean minor anomaly score of 5.76 for the autistic children was significantly higher than the control group score of 3.53. He concluded that this shift to a greater number of anomalies in the autistic subjects proved organicity in autism. Links et al. [1980] recognized that autistic children had more anomalies than their sibs, and that the autistic children with the higher anomaly scores had lower IQs, spent more time in the hospital, had less frequent family histories of psychotic illness, drug, or alcohol abuse. They concluded that the anomalies were the result of some unknown organic factor that played a role in the etiology of autism. Smalley et al. [1988] declared that MPAs result from insults, either genetic or environmental, that occur in the first trimester, and represent an indirect measure of an abnormality in fetal development. Full understanding of these studies was, however, hindered by the prevailing conviction that autism was a homogeneous disorder and the authors did not speculate that there could be

TABLE III. Outcome Levels for Individuals With Essential Versus Complex Autism at ≥8 Years of Age

	Excellent (N = 15)		Good (N = 14)		Poor (N = 52)		Total (N = 81)	*P* value
Essential autism	93%	14/15	79%	11/14	54%	28/52	53	0.009
Complex autism	7%	1/15	21%	3/14	46%	24/52	28	

TABLE IV. Autism*: Predictors of Poor Outcomes (IQ < 55 and Non-Verbal at ≥8 Years) (N = 62)

Feature	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Odds ratio	95% confidence interval
Microcephaly	14	100	100	4	—
Dysmorphology status	34	86	81	5.6	1.5–20.5
Complex autism	47	87	86	4.2	1.4–12.5
Seizures	37	81	77	2.4	0.9–6.5
Regressive onset	40	74	72	1.9	0.8–4.7
Male sex	81	22	64	1.2	0.4–3.3
Female sex	19	78	60	0.8	0.3–2.3
Abnormal brain MRI	21	72	58	0.7	0.2–2.5
Abnormal EEG	35	50	59	0.5	0.2–1.7
Macrocephaly	29	44	47	0.3	0.1–0.8

*All autism, includes individuals with essential and complex subtypes.

etiologically distinct subgroups within the autism behavioral diagnosis.

Awareness over the last decade that the autism spectrum disorders are etiologically heterogeneous was based mainly on the unexpected difficulties in identifying major autism causing genes [reviewed by Spence, 2001]. This in turn generated the quest for genetically predictive phenotypic markers. Rodier et al. [1996] and Rodier [2002] proposed that physical phenotypic features could be used to pick out the children whose autism was due to mutations in the embryologically important homeobox genes that model the development of the brain stem and face. They also surmised that environmental teratogens including valproic acid and thalidomide produce teratogenic phenocopies by influencing the same early developmental pathways. This line of thinking is consistent with our data that a subset of children with autism can be identified with physical features indicative of abnormal processes occurring during embyrogenesis. The corollary is that complex autism is extremely heterogeneous. All of the syndromes that we currently acknowledge as causes of autism fall within the complex group, including all the chromosome disorders, fragile X, Sotos syndrome, fetal valproate, fetal rubella, Möbius syndrome, and tuberous sclerosis. These diagnoses account for about 20% of the complex subgroup; the remaining 80% will undoubtedly prove to be both heterogeneous and scientifically interesting; they may provide clues to the developmental processes that can lead to the development of autistic behaviors. The second corollary is that it is just as important to identify the lack of dysmorphology that defines essential autism.

The group differences we have found between individuals with complex and essential autism could be predicated on the developmental principle that individuals for whom there is evidence of an insult to morphogeneis will be etiologically distinct from those whose development proceeded normally.

The clinical and genetic differences that we identify between complex and essential autism validate our hypothesis that the groups are etiologically distinctive and also provide practical prognostic information. For all outcome measures, individuals with complex autism do less well. They are twice as likely to have IQ/DQ scores less than 55 (52% vs. 25%) and less than half as likely to have IQ/DQ scores in the normal range (22% vs. 46%). They are twice as likely to develop seizures (39% vs. 17%), and twice as likely to have abnormal brain structure (28% vs 13%). Our outcome analyses, based on both the acquisition of functional language and IQ/DQ scores, show that though many features correlate with poor outcomes, the complex designation is the most sensitive test, yielding an 86% positive predictive value of poor outcome. These results are consistent with our retrospective study of 19 children with autism who completed one year of 22 hr/week 1:1 early intensive behavioral intervention [Stoelb et al., 2004]. The most significant predictor of change in performance scores over the year of therapy was the dysmorphology designation ($P = 0.009$); the presence or absence of dysmorphology predicted language acquisition for 90% of the non-verbal participants.

The genetic consequences of the distinction between complex and essential autism are equally informative. Individuals with essential autism are twice as likely to be male (6.5:1 vs. 3.2:1), are more than twice as likely to have a family history of autism (20% vs. 9%) and the sib recurrence risk is 4%–6% compared with no recurrences in the 46 families of children with complex autism. Finding lesser autistic traits in sibs of children with essential autism was twice that for complex autism families (12% vs. 6%). The small number of sibs limits the power of the calculations; however, the very similar magnitude of differences for all sibs, latter born sibs and for classical autism and milder autistic traits illustrates a consistent pattern. The fact we have not observed any recurrence in sibs in the complex

TABLE V. Autism*: Predictors of Excellent Outcome (IQ > 70 and Verbal at ≥8 Years) (N = 18)*

Feature	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Odds ratio	95% confidence interval
Not microcephaly	100	11	20	4	—
Essential autism	98	41	58	9.7	1.2–78.1
Non-dysmorphic	77	46	25	6.9	0.9–54.6
Macrocephaly	56	65	26	2.3	0.8–6.5
Male sex	83	21	19	1.3	0.3–5.2
Normocephaly	44	46	16	0.8	0.3–2.4
Female sex	17	79	15	0.7	0.2–2.9
Normal EEG	57	40	12	0.5	0.1–2.5

*All autism, includes individuals with essential and complex subtypes.

TABLE VI. Essential Autism: Predictors of Poor Outcome (IQ < 55 and/or Non-Verbal) (N = 28)

Feature	Sensitivity for poor outcome (%)	Specificity for poor outcome (%)	Positive predictive value	Odds ratio	95% confidence interval
Regressive onset	61	43	41	4.6	1.4–15.3
Male sex	86	24	56	1.9	0.5–7.7
Seizures	29	80	62	1.6	0.4–5.7
Macrocephaly	50	52	54	1.1	0.4–3.2
Abnormal MRI	17	75	50	0.6	0.1–3.6
Female sex	14	76	40	0.5	0.1–2.1
Abnormal EEG	33	50	53	0.5	0.1–1.9

group is undoubtedly a statistical aberration since children with complex autism may have disorders such as fragile X syndrome and familial chromsome disorders which confer explicit recurrence risks. Notwithstanding, we feel that once chromosome disorders, fragile X syndrome, Sotos syndrome, and tuberous sclerosis have been ruled out, parents of children with complex autism can be counseled that their recurrence risk is lower than the 4%–6% observed with essential autism. This is consistent with the observation Szatmari [1999] who noted that relatives of probands with higher IQs were at greater risk than those of probands with lower IQ.

Taken together the different sex ratios, family histories, and recurrence risks establish that complex autism is genetically distinct from essential autism. The relationship of complex to essential autism resembles the genetic consequences of another complex genetic disorder, cleft lip ± cleft palate (CL ± P). Originally considered a relatively homogeneous, multifactorial disorder [Carter, 1976; Fraser, 1976], CL ± P is now recognized to have many etiologies. About 5% of cases are caused by various single gene mutations and chromosome disorders; the rest are caused by various genes and/or environmental effects [Marazita et al., 2002]. Like autism, about 30% of the children with CL ± P have other minor and major anomalies and those children have a lower sib recurrence risk [Gorlin et al., 1990]. The assumption is that for those children, the etiology was a sporadic environmental insult. This theory is hard to prove since most environmental insults to morphogenesis are difficult to diagnose. Nevertheless, it does provide a rational hypothesis to explain the lower risk of recurrence for families whose child has the complex autism phenotype.

An additional practical consequence of the separation is that all of the individuals with recognizable syndromes fall in the complex autism diagnosis, or in the case of tuberous sclerosis can almost always be recognized by the dysmorphology examination [Roach et al., 1999]. As more children are being diagnosed with autism, and as the demand for diagnostic services increases, our data indicate that the use of extensive laboratory studies can be limited to children with complex autism. We have not identified any children with chromosome disorders, including the 15q duplications who have not declared themselves by the morphology examination.

For research, ramifications of this distinction come from defining the more genetically homogeneous essential subgroup. By analyzing essential autism separately, we have already made a number of significant observations. First, within essential autism, a regressive onset and macrocephaly have emerged as stronger predictors of poor outcomes. A history of regression in language at the onset of the autistic symptoms predicted a poor outcome with 46% sensitivity, 73% specificity, and a positive predictive value of 84%. Recognizing these outcome predictors is a first step toward designing treatments to improve outcomes. Furthermore, since essential autism is the more heritable subgroup, removing complex autism probands from analyses should improve the power of linkage and sib pair analyses.

The proportion of patients with essential versus complex autism in a population is a function of ascertainment. Patients ascertained from clinics that serve children with other developmental disabilities in addition to autism are likely to be weighted toward patients with complex autism while dedicated autism clinics are weighted toward essential autism. Study populations that select for sib pairs are weighted toward essential autism. The sex ratio of a population will provide a rough estimate of the proportion of essential to complex autism patients, since the male to female ratio is higher in essential autism.

The distinction between complex and essential autism represents the first pass at dissecting the etiologic heterogeneity within the autism diagnosis. The tools we have available to render this classification are neither entirely precise or completely accurate. Though the morphology examination has allowed geneticists to delineate hundreds of discrete genetic disorders, it is still impossible to determine for every individual whether certain physical features which straddle the line between normal and abnormal are the consequence of a significant insult to early morphogenesis or rather result from a benign familial predisposition. Ten percent of autistic individuals could not be unequivocally assigned as either dysmorphic or non-dysmorphic. And microcephaly, though a potent predictor of poor developmental outcomes, is defined arbitrarily based on a head circumference measured at 2 SD. We attempted to assess brain dysmorphology as a third factor

TABLE VII. Essential Autism: Predictors of Excellent Outcome (IQ > 70 and Verbal) N = 14

Feature	Sensitivity for excellent outcome (%)	Specificity for excellent outcome (%)	Positive predictive value (%)	Odds ratio	95% confidence interval
Normal brain MRI	87	23	29	2.1	0.2–21.0
Male sex	86	21	28	1.5	0.3–8.3
Macrocephaly	50	51	27	1.0	0.3–3.6
Normocephaly	50	49	26	0.9	0.3–3.2
Female sex	15	79	20	0.6	0.1–3.5
Normal EEG	50	37	13	0.6	0.1–3.5

TABLE VIII. Syndromes Identified in the 260 Autism Probands

		Number (%)
Chromosomal	46,XX,r(8), 46,XY,del(8)(p22.2), isodicentric 15q, der 15t(4;15) (p16;q13) mat, 47, XY,+21, 47,XXY	6 (2.3)
Single gene disorders	Tuberous sclerosis (2), Sotos syndrome, Sotos like syndrome	4 (1.5)
Teratogen	Fetal valproate syndrome	1 (0.4)
Total syndromes	----	11 (4.2)

in the complex/essential distinction. Though dysmorphic individuals are more than twice as likely to have abnormalities on their brain MRI, the range of abnormalities was too broad to be useful. We believe this is due to our relative lack of experience in interpreting brain structure variations by MRI. Once we have accumulated more experience interpreting findings like assymetry of the ventricles and a giant cisterna magna, we suspect that morphogenesis of the brain will be incorporated into the diagnostic algorithm for complex versus essential autism. DeLong [1999] formulated an intriguing hypothesis that two autism subgroups should be distinguishable on the basis of brain damage. The first type is characterized by bilateral brain damage in early life and the second, more common, idiopathic form is not associated with brain damage. His hypothetical idiopathic form closely resembles essential autism. For now, the separation of complex and essential autism can make more of a contribution to studies of brain morphology in autism than vice versa. Limiting studies of brain morphology to individuals with the essential autism should decrease the background noise of structural variation associated with generalized insults to brain morphogenesis and allow analysis of the more uniform population.

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