Development and validation of a measure of dysmorphology: Useful for autism subgroup classification

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Editor's Note

The ensuing paper by Miles and colleagues raises several timely themes important for the field: 1) the reliability of our physical examinations for phenotypic features, in particular minor anomalies; 2) the possible training of clinicians not skilled in "dysmorphology" to perform such exams reliably; and 3) the definitions of phenotypic features, most especially these minor anomalies. (Of note an international group is currently working on consensus definitions of such phenotypic features.)

While the authors focus their approach on the evaluation of individuals with the autism spectrum disorders, the principles and issues discussed herein can be generalized to the medical genetics evaluation of patents with any clinical presentation.

John C. Carey
Editor-in-Chief

Development and Validation of a Measure of Dysmorphology: Useful for Autism Subgroup Classification

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Autism spectrum disorders (ASD) comprise a class of neurodevelopmental disorders that can originate from a variety of genetic and environmental causes. To delineate autism's heterogeneity we have looked for biologically-based phenotypes found in consistent proportions of ASD individuals. One informative phenotype is that of generalized dysmorphology, based on whole body examinations by medical geneticists trained in the nuances of anomalous embryologic development. We identified a need for a dysmorphology measure that could be completed by medical clinicians not extensively trained in dysmorphology that would still retain the level of sensitivity and specificity of the comprehensive dysmorphology examination. Based on expert-derived consensus dysmorphology designation of 222 autism patients and a classification validation study of 30 subjects by four dysmorphologists, we determined that dysmorphology designations based on body areas provided superior inter-rater reliability. Using 34 body area designations, we performed a classification and regression tree (CART) analysis to construct a scoring algorithm. Compared to the consensus classification, the model performed with 81% sensitivity and 99% specificity, and classification of a replication dataset of 31 ASD individuals performed well, with 82% sensitivity and 95% specificity. The autism dysmorphology measure (ADM) directs the clinician to score 12 body areas sequentially to arrive at a determination of "dysmorphic" or "nondysmorphic." We anticipate the ADM will permit clinicians to differentiate accurately between dysmorphic and nondysmorphic individuals—allowing better diagnostic classification, prognostication, recurrence risk assessment, and laboratory analysis decisions—and research scientists to better define more homogeneous autism subtypes.

Key words: autism; dysmorphology; congenital anomalies; screening; CART; complex autism

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INTRODUCTION

The autism spectrum disorders (ASD) represent a broad category of neurodevelopmental disorders with three inexplicably intertwined areas of deficit: social responsiveness, communication in its broadest sense, and a need for sameness that manifests itself through both repetitive behaviors and interests. Despite significant variability in the manifestation of these symptoms, it is clear in both individuals and families that autism is caused by factors that simultaneously disrupt these disparate faculties. Furthermore, evidence is compelling that the autism behavioral phenotype may originate from a variety of genetic and environmental causes [Arndt et al., 2005; Freitag, 2007; Geschwind and Levitt, 2007]. We posit that there are common biochemical, structural or developmental pathways that may be impacted at different places and by different agents—genetic, environmental, or epigenetic—to cause the autism phenotype. To solve the autism puzzle, there are many levels of inquiry that must be pursued. Our approach has been to identify phenotypic variables that occur in a significant percentage of individuals with autism and can be used to separate the ASDs into etiologically discrete disorders.

It is well recognized that many physical anomalies are indicators of some insult, genetic or environmental, occurring in the first trimester [Smalley et al., 1988; Rodier et al., 1996; Chambers et al., 2001; Rodier, 2004; Miller et al., 2005; Jones, 2006], and their presence or absence at birth can be used as an indirect measure of what was happening during embryonic and fetal development. The full import of this has been used by medical geneticists and dysmorphologists, starting in the 1960s, to define hundreds of both genetic and environmental syndromes which leave characteristic morphologic footprints [Smith and Bostian, 1964; Winter and Baraitser, 1993; Jones, 2006; OMIM, 2007]. Congenital anomalies may be divided into major malformations, such as facial clefts and structural heart malformations, that are relatively easy to identify and minor abnormalities, such as a single transverse palmar crease, posteriorly rotated ears, or a small chin, which are much more difficult to recognize, classify, or quantify [Merks et al., 2003, 2006]. It is, however, accepted that the presence of multiple minor anomalies distinguishes children who are at increased risk for both major malformations [Marden et al., 1964; Méhes et al., 1973; Méhes, 1985; Leppig et al., 1987] and behavioral disorders including autism [Waldrop and Halverson, 1971; Mnukhin and Isaev, 1975; Steg and Rapoport, 1975; Walker, 1977; Campbell et al., 1978; Links, 1980; Links et al., 1980; Gualtieri et al., 1982; Wier et al., 2006].

To illustrate, Walker studied 74 autistic and non-autistic children matched for age, sex and socio-economic group, using the Waldrop weighted scoring scale [Waldrop and Halverson, 1971] for 16 anomalies. This study 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. They concluded that this shift to a greater number of anomalies in the autistic children 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, and had less frequent family histories of psychiatric illness or of 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. 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 concluded that environmental teratogens, such as valproic acid and thalidomide, may produce teratogenic phenocopies by influencing the same early developmental pathways.

In 2000, we proposed that a subset of children with autism can be identified with physical features indicative of abnormal processes occuring during embyrogenesis [Miles and Hillman, 2000]. Subsequently, we defined complex autism as a subset of individuals with evidence of an abnormality in early morphogenesis, manifested by either significant anomalies (dysmorphology) or microcephaly [Miles et al., 2005]. The complex autism subgroup comprised about 20% of the total autism poulation studied, and individuals with complex autism had poorer outcomes with lower IQs, more seizures, more abnormal EEGs (46% vs. 30%) and more brain abnormalities on MRI (28% vs. 13%). The remainder had essential autism, which was the more heritable group, with a higher sib recurrence (4% vs. 0%), more relatives with autism (20% vs. 9%) and a higher male to female ratio (6.5:1 vs. 3.2:1). These group differences between individuals with complex and essential autism were predicated on the developmental principle that individuals for whom there is evidence of an insult to morphogenesis will be etiologically distinct from those whose development proceeded normally and who will probably differ in outcome and genetic measures.

Reliable phenotyping for anomalies is dependent on having a standardized measurement system and development of a protocol that can be used consistently by a variety of autism clinicians and researchers. We report here on a proposed autism dysmorphology measure (ADM) which employs a semi-structured physical morphology examination to classify individuals into two groups, those whose physical features are considered within the normal range and those who exhibit generalized dysmorphology not observed in their parents or other unaffected family members. Development of this measure began by compiling expert-derived consensus dysmorphology designations for 222 autism patients. These examinations were carried out by the Autism Center geneticists using the system first described in 2000 [Miles and Hillman, 2000], and validated in a study by four dysmorphologists. This body of data was used as the training set to develop a statistical model for defining phenotypically distinct subgroups of individuals with autism.

Our goal was to produce a dysmorphology measure that could be completed by clinicians who are not extensively trained in dysmorphology, and still retain the level of sensitivity and specificity of the comprehensive dysmorphology examination. Other objectives were to develop a measure that did not require disrobing the patient and to develop a protocol that would provide a springboard for further research, including the use of computerized anthropometrics [Bichtsmeier et al., 2000; Aldridge et al., 2005] and the delineation of additional dysmorphology syndromes which are associated with autism. The ADM algorithm depends on the assessment of 12 body structures and results in classification as either "dysmorphic" or "nondysmorphic."

METHODS

Study Participants

The study sample consisted of 222 consecutive, unrelated patients diagnosed with autistic disorder at the Autism Center of the University of Missouri-Columbia Hospitals and Clinics between 1995 and 2001. 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 with no recognizable ascertainment bias toward more or less phenotypically abnormal, mentally retarded, or multiplex participants. Of 425 consecutive patients evaluated over this time, 81% (344/425) met DSM-IV [American Psychiatric Association, 2000] criteria for the diagnosis of a pervasive developmental disorder, 231 with autistic disorder, 24 with Asperger syndrome, 60 with PDD-NOS, and 29 with near-autism. For the purpose of model development, only patients with clearly diagnosed autistic disorder were included in the analyses, excluding those with Asperger syndrome, PDD-NOS, and broad autism phenotype [Piven and Palmer, 1999; Geschwind et al., 2001]. This study sample is designated our expert determined consensus group. Nine individuals with autistic disorder were excluded who also were diagnosed with a recognized syndrome due to chromosome aneuploidy, gene mutation, or teratogen exposure.

Procedures

Autism spectrum diagnostic evaluation. The ASD diagnosis was made by the Autism Center directors using DSM-IV criteria, CARS scores [Schopler et al., 1986], and a center-based short form of the Autism Diagnostic Interview-Revised scoring protocol (ADI-R) [Lord et al., 1994]. Independent diagnostic evaluations were conducted by the autism center clinicians (JHM, REH), and either a child psychiatrist or a neuropsychologist. The results were compared, and in any case where there was a disparity, the individual was discussed jointly to reach a conclusion. The complete ADI-R was done for patients whose diagnosis was in question; in all cases the full ADI-R confirmed the previous diagnosis.

Clinical evaluation. The Autism Center evaluation utilized a standard data set for the collection of prenatal, perinatal, developmental, language, behavior, neurologic, dietary, health, and family history. Parent/caregiver occupation and education were used to calculate socio-economic status [Hollingshead, 1975]. Standard laboratory tests included G-banded karyotype, DNA for fragile X, urine metabolic screen, quantitative urine organic acids, urine amino acids, short chain fatty acids, thyroid profile, comprehensive metabolic panel, and hematologic profile with differential and lead level. Brain MRIs were obtained in 69% of the subjects and EEGs in 65%. Additional diagnostic tests were obtained as clinically indicated.

Head circumference measurement. The method used for determination of microcephaly and macrocephaly has been previously described [Miles et al., 2000]. The occipital-frontal circumference is measured, and microcephaly is defined as a measurement number of $\leq$2nd centile and macrocephaly as $\geq$98th centile. Intra-and inter-rater reliability ranged from 0.92 to 0.95 as measured by intraclass correlations.

Dysmorphology assessments and standardized recording. Physical examinations were performed for each subject including standard morphologic measurements of the head, face, hands, feet, body proportions, and dermatoglyphic analysis [Hall et al., 1989; Aase, 1990; Farkas, 1994; Jones, 2006]. The skin was examined with a Woods lamp.

Parents and other available relatives were examined, and family photographs were reviewed. Each of the measurements was converted to age and, when available, sex specific centiles from standard dysmorphology tables. Description of each physical feature was standardized using the London dysmorphology database (LDDB) codes [Winter and Baraitser, 1993], which enumerates over 2,200 separate feature codes. This standard terminology has been used for the last two decades by medical geneticists and provides an unambiguous list of feature definitions. For our purpose of describing physical dysmorphology, we selected the 556 LDDB features which (1) describe altered morphogenesis, (2) are measurable by a noninvasive physical examination, (3) are relatively easy to define or measure, (4) are present from birth or infancy, and (5) are relatively stable over time. Biochemical, physiological, hormonal, and other nonmorphological features including body habitus were not used.

The LDDB classification is organized into a portfolio of 33 primary or level 1 body areas including cranium, hair, forehead, ears, eyes, nose, face, mouth, teeth, hands, thorax, etc. Height is also considered a level 1 designation. Most body areas are then subdivided into 2–11 subcategories (level 2). Finally, individual descriptive features (level 3) are listed under each subheading. For example, the body area code for hands is 23.00.00. Hand subcategories include carpals, dermatoglyphics, fingers, metacarpals, phalanges, thumbs, and general abnormalities. Fingers are designated 23.04.00, and there are 23 separate ways to describe abnormal fingers including short fingers (23.04.03), clinodactyly (23.04.05), post-axial polydactyly (23.04.12), and tapering fingers (23.04.17). Table I illustrates the LDDB format.

Model Development

Development of consensus determination. To develop the consensus group, each of the 222 ASD participants was examined and designated either dysmorphic, nondysmorphic or equivocal using our previously described dysmorphology coding system [Miles and Hillman, 2000]. That system classified participants as "dysmorphic" based on the number of abnormal physical features (LDDB level 3). These included minor anomalies, measurement abnormalities, and descriptive features recorded for the subject and not present in their nonautistic parents. Individuals with three or fewer features were defined as "nondysmorphic" (n = 172). Those with six or more features were designated dysmorphic (n = 26), with the remainder placed into an equivocal group (n = 24). Each of the study participants was examined by one of two medical geneticists (JHM/REH) who worked in the same clinic and frequently discussed patients to determine dysmorphology classification. Independent interrater reliability studies were carried out on 100 of the children prior to consensus determination and provided a reliability score of 0.88 as measured by intraclass correlations.

To further establish reliability for that coding system, 30 additional study participants were selected for dysmorphology evaluations by four geneticists (JHM/SRB/MEB/RAM). The participants were chosen to provide a breadth of phenotypic features and for willingness to travel to Columbia for the research evaluation. Over a 2-day period, four fellowship-trained medical geneticists/dysmorphologists individually examined each subject and one or both parents for 30 minutes. The examiners were supplied with a photograph of each child, recent height, weight and head circumference measurements, and photographs of siblings and parents who were not present. The dysmorphologists were given minimal instructions but told to perform a thorough dysmorphology examination and to record each dysmorphic feature. Body measurements and abnormal features were scored by the dysmorphologists using the LDDB codes provided. Each subject was classified as dysmorphic, nondysmorphic, or equivocal using the feature-based coding system described above and previously published [Miles and Hillman, 2000]. The results were also analyzed for the consistency with which the four raters classified the features, the body areas, and the participants overall designation as dysmorphic or nondysmorphic. The results were analyzed for interrater reliability and classification validity using Kappa coefficients [Landis and Koch, 1977] and an intra-class correlation coefficient [Shrout and Fleiss, 1979].

Selection of the most informative dysmorphology designations. To determine which dysmorphology designations would be most helpful in the development of the dysmorphology model, the number of times each body area (LDDB levels 1 & 2) and each feature code (LDDB level 3) were rated abnormal in the consensus sample was tabulated for the study group of 222 participants and the validity group of 30 participants. To determine the utility of the individual features and body areas for distinguishing between dysmorphic and nondysmorphic individuals, their frequency in each group was calculated.

Development of the scoring algorithm. In order to develop a scoring algorithm that would capture the difference between the two designations (dysmorphic vs. nondysmorphic) in the most parsimonious manner with the best sensitivity and specificity, three statistical approaches were investigated; cluster analysis, logistic regression analysis, and classification and regression tree (CART) analysis. Cluster analysis was performed to see if the data naturally broke into groups without considering the

TABLE I. Body Regions and Features Classified as Dysmorphic in Study Group of 222 Individuals With Autistic Disorder Using the London Dysmorphology Database Format

Body regions/LDDB codes[a]	Dysmorphic features	Times cited in consensus study (222 subjects)
1. Stature***		7
02.01.00	Short stature (≤10%)	7
2. Cranial shape***		12
03.01.02	Brachycephaly	4
03.01.03	Dolichocephaly/scaphocephaly	5
03.01.04	Macrocephaly	31
03.01.05	Microcephaly	9
03.01.06	Plagiocephaly/asymmetrical skull	3
3. Cranial structure*		5
03.06.01	Cutis gyrata of scalp	1
03.06.02	Scalp defects, cutis aplasia	1
03.07.04	Fontanelles, large	1
03.07.07	Cranial sutures, wide	2
4. Hair texture*		2
04.02.05	Coarse hair	2
5. Hair growth pattern***		67
04.04.03	Unusual hair whorl/pattern	46
04.04.04	Widow's peak	2
04.04.05	Frontal upsweep/cowlick	19
6. Forehead***		20
05.01.02	High frontal hairline	5
05.01.03	Prominent forehead/frontal bossing	2
05.01.06	Wide forehead	5
05.02.01	Low frontal hairline	6
05.02.03	Narrow forehead/temporal narrowing	2
7. Ear structure***		28
06.01.02	Asymmetric ears	1
06.01.06	Dysplastic ears	4
06.01.10	Auricular pits/fistulas	1
06.01.12	Prominent ears	2
06.01.14	Simple ears	3
06.07.01	Crumpled ear helix	1
06.07.03	Over-folded ear helix, lop ear	12
06.07.05	Prominent ear helix	3
06.08.02	Attached ear lobule	1
8. Ear size*		14
06.01.07	Large ears	11
06.01.15	Small ears/microtia	3
9. Ear placement*		5
06.01.08	Low-set ears	1
06.01.09	Posteriorly rotated ears	4
10. Eye structure and size*		6
07.01.01	Asymmetric eyes	1
07.01.07	Prominent eyes/proptosis	1
07.05.05	Microophthalmia	1
07.12.01	Blue sclera	3
11. Eye placement***		49
07.01.03	Deep-set eyes	35
07.01.05	Hypertelorism	11
07.01.06	Hypotelorism	2
07.01.07	Prominent eyes/proptosis	1
12. Eyebrows***		15
08.01.03	Sparse/decreased eyebrows	1
08.01.07	Medial eyebrow flare	6
08.01.08	Synophrys	6
08.01.09	Thick eyebrows	2
13. Eyelids, palpebral fissures***		43
08.03.06	Nodular eyelids	1
08.03.07	Ptosis of eyelids	2
08.05.03	Short palpebral fissures	5
08.05.04	Palpebral fissures slant up	1
08.05.05	Palpebral fissures slant down	11
08.05.06	Wide/long palpebral fissures	1
08.06.00	Periorbital skin, general abnormalities	1

(*Continued*)

TABLE I. (*Continued*)

Body regions/LDDB codes[a]	Dysmorphic features	Times cited in consensus study (222 subjects)
08.06.02	Epicanthic folds	20
08.06.03	Fullness of peri-orbital region	1
14. Nose structure***		39
09.00.00	Nose, other	3
09.01.01	Broad base to nose	3
09.01.05	Pinched nose	1
09.01.08	Flat nose	1
09.01.10	Upturned nose	1
09.03.01	Depressed/flat nasal bridge	3
09.03.02	High/prominent nasal bridge	6
09.03.04	Wide nasal bridge	19
09.06.05	Short nasal septum	1
09.07.02	Broad nasal tip	1
15.Nose size***		11
09.01.04	Large/long nose	6
09.01.09	Small/short nose	5
16. Face size and structure***		34
10.01.01	Asymmetric face	5
10.01.04	Coarse facial features	1
10.01.07	Flat face	1
10.01.10	Mid-face hypoplasia	2
10.01.13	Small face	1
10.01.15	Thin/long face	3
10.01.16	Triangular face	2
10.03.02	Pointed chin	3
10.05.04	Prominent mandible/prognathism	1
10.05.05	Small mandible/micrognathia	15
17. Mouth and lips***		16
11.01.02	Down-turned corners of the mouth	2
11.01.03	Cupid bow shape of mouth	1
11.01.04	Macrostomia	2
11.01.05	Microstomia	2
11.01.06	Open mouth appearance	2
11.02.04	Prominent/everted lower lip	1
11.04.01	Cleft upper lip (nonmidline)	2
11.04.05	Thin upper lip	4
18. Philtrum***		28
11.03.01	Long philtrum	9
11.03.03	Short philtrum	14
11.03.04	Simple/absent philtrum	5
11.03.05	Wide philtrum	0
19. Oral cavity***		33
12.02.02	Thick/wide alveolar ridges	5
12.04.01	Cleft palate	2
12.04.03	High palate	17
12.04.04	Narrow palate	1
12.05.07	Long/large tongue	3
12.04.08	Cleft uvula	4
12.05.10	Smooth tongue	1
20. Teeth**		15
13.01.06	Enamel abnormalities	1
13.01.07	Irregular or crowded teeth	4
13.01.13	Abnormally shaped teeth	2
13.01.14	Small teeth	2
13.01.16	Wide-spaced teeth	6
21. Neck**		11
15.01.03	Low posterior/trident hairline	7
15.01.05	Short neck	3
15.01.10	Thick/broad neck	1
22. Back and spine**		10
16.01.03	Lordosis	3
16.01.06	Scoliosis	2
16.02.04	Sacral dimple/sinus	5
23. Thorax and shoulders**		10
17.01.03	Pectus carinatum	1
17.01.04	Pectus excavatum	1

TABLE I. (*Continued*)

Body regions/LDDB codes[a]	Dysmorphic features	Times cited in consensus study (222 subjects)
17.02.01	Absent or hypoplastic breasts	1
17.07.01	Hypoplastic/inverted/absent nipples	1
17.07.02	Supernumerary nipples	2
17.11.00	Shoulder shape abnormal	1
17.11.02	Narrow shoulders	2
17.11.03	Sloping shoulders	1
24. Abdomen***		6
18.01.04	Diastasis recti	1
18.01.09	Inguinal hernia	2
18.01.10	Umbilical hernia	1
18.01.15	Protuberant abdomen	1
18.02.01	Anal atresia/stenosis	1
25. Genitalia***		10
20.02.05	Abnormal labia	1
20.03.03	Hydrocele	1
20.03.04	Hypospadias 1°, 2°, 3°	3
20.03.05	Large penis	1
20.03.10	Overriding/shawl scrotum	2
20.03.12	Cryptorchid testes	2
26. Upper limbs*		13
22.01.03	Asymmetric arms	1
22.04.01	Cubitus valgus	8
22.04.03	Limited movement/flexion deformity elbow	2
22.05.04	Restriction of supination/pronation	2
27. Hands***		
23.01.05	Large hands	2
23.01.07	Small hands	2
28. Dermatoglyphics*		26
23.03.01	Abnormal dermatoglyphic patterns	15
23.03.03	Abnormal palmar creases	8
23.03.04	Single palmar crease	3
29. Fingers, thumbs***		47
23.04.04	Camptodactyly	2
23.04.05	Clinodactyly	16
23.04.17	Tapering fingers	16
23.05.05	Short/hypoplastic metacarpals	3
23.06.07	Short phalanges	2
23.06.09	Wide phalanges	1
23.06.10	Long phalanges	5
23.07.03	Broad thumbs	2
30. Nails***		21
24.01.06	Hyperplastic, includes ridged nails	5
24.01.07	Hyperconvex/clubbed nails	6
24.01.09	Small/hypoplastic/deepset nails	9
24.01.10	Short nails	1
31. Lower limbs*		5
25.01.03	Asymmetric lower limbs	1
25.05.03	Genu valgum	4
32. Feet***		54
26.01.01	Pes planus	16
26.01.09	Club foot, varus	1
26.01.11	Large feet	2
26.01.16	Small feet	2
26.01.17	Wide feet	2
26.02.07	Hallux valgus	3
26.05.00	Toes, other	3
26.05.02	Broad toes	4
26.05.05	Over-riding toes (includes clinodactyly)	12
26.05.09	Syndactyly 2-3 of toes	3
26.05.10	Syndactyly of toes (not 2-3)	3
26.05.11	Wide-spaced toes	3
26.05.13	Camptodactyly/hammer toes	1
33. Joints*		31
31.01.01	Joint contractures	1
31.01.04	Joint laxity	30

(*Continued*)

TABLE I. (*Continued*)

Body regions/LDDB codes[a]	Dysmorphic features	Times cited in consensus study (222 subjects)
34. Skin*		72
34.01.05	Hypohydrotic or dry skin	6
34.01.09	Hyperelastic skin	3
34.01.19	Soft skin	14
34.02.02	Patchy hypoplasia (Shagreen patch)	1
34.03.02	Patchy depigmentation of skin	10
34.03.04	Patchy pigment of skin/cafe au lait spots	37
34.05.01	Adenoma sebaceum	1

*No significant difference between dysmorphic and nondysmorphic subjects.
**Significant difference between dysmorphic and nondysmorphic subjects ($P = 0.04$ to 0.01).
***Highly significant difference between dysmorphic and nondysmorphic subjects ($P = 0.007$ to 0.7×10^{-8}).
[a]London dysmorphology database dysmorphology codes.

dysmorphic classification, and we did not find any underlying groups corresponding to the dysmorphology. Logistic regression analysis was conducted with the binary logic option in SAS; adding variables using a step-wise regression procedure resulted in the nonexistence of maximum likelihood estimates because some factors have extremely high sensitivity or specificity [Flies et al., 2003]. These two approaches were rejected.

CART analysis was investigated because the data were binary and the objective was to create an algorithm which classified participants into two groups, either dysmorphic or nondysmorphic [Brieman et al., 1984]. The frequency of each of the previously selected body area LDDB codes was determined for the 222 subjects in the experimental data set and analyzed using the CART statistical approach. The CART analysis considers each variable to see which will better classify the data as dysmorphic or nondysmorphic. The variable with the highest frequency of correct classification is chosen as the first node. Two branches are formed at each node, subdividing the participants into those with the dysmorphic feature and those without. The CART algorithm then proceeds with the participants in each branch separately as it did in the beginning. That is, it starts with two "new" data sets, one being the data set from the group of participants that fell into the dysmorphic category and the second being the data set that fell into the nondysmorphic category. The CART algorithm continues to break down the data until further division would create a single participant in a grouping.

A number of variations of the CART model were analyzed using S-plus CART software. One variation classified the participants as dysmorphic, equivocal, or nondysmorphic as in the original protocol. Other variations folded the group classified as equivocal by the expert dysmorphologists into either the dysmorphic or nondysmorphic groups. Also, separate model variations were developed which either placed no restrictions on the body areas selected or forced specific body areas into the model. This was done for features which did not appear in the unrestricted model but were considered by the expert dysmorphologists to be critical for a comprehensive assessment of generalized dysmorphology. Each model was analyzed to determine the most parsimonious determination of dysmorphology while retaining good validity scores and replication scores in analysis of the test data set. Once developed, the model was then tested with a separate group of 31 individuals with autistic disorder to determine whether its sensitivity and specificity could be replicated in an independent sample.

Additional Statistics

Inter-rater reliability for head circumference was established by calculating intraclass correlation coefficients [Shrout and Fleiss, 1979]. Reliability studies for dysmorphology coding by the four dysmorphologists was established using Kappa coefficients [Landis and Koch, 1977] and an intraclass correlation coefficient [Shrout and Fleiss, 1979]. Agreement of the four dysmorphologists, using the original feature counting system, with the prior consensus determination of dysmorphic versus nondysmorphic established classification validity. Predictive validity could not be tested because the group was too small. Table II provides summary data comparing nondysmorphic and dysmorphic study subjects. Continuous random variables were summarized by their mean, standard deviation, and range. For categorical random variables, separately for the nondysmorphic and dysmorphic cases, the proportion of cases in each category is given. For the categorical random variables, univariate comparisons of nondysmorphic and dysmorphic subjects were made using chi square tests. Age and sex ratio comparisons were made using Students *t*-test. The Wilcoxon Rank Sum test was used to verify that there were no significant differences between the age distribution of the study group and the group lost to follow-up.

TABLE II. Demographic Characteristics of 222 Study Subjects Separated by Dysmorphology Status

	Nondysmorphic,[a] N = 196		Dysmorphic, N = 26		*P*-value
Mean age (SD)	8.1 (7.1)		13.4 (9.8)		NS
Range	1.4–55.9		2.1–41.2		
Sex ratio	5.3:1	165:31	2.7:1	19:7	NS
Ethnicity					
White	83%	163/196	96%	25/26	NS
Black	6%	12/196	0%	0/26	
Asian	2%	4/196	0%	0/26	
Bi-racial/multi-racial	9%	17/196	4%	1/26	
Socio-economic status (SES)[b]					
Groups I and II	43%	66/152	34%	5/16	0.03
Group III	31%	47/152	21%	2/16	
Groups IV and V	26%	39/152	45%	9/16	

[a]Includes 24 equivocal.
[b]SES highest for Group I and lowest for Group V.

RESULTS

Participant Characteristics

Demographic characteristics of the consensus group are provided in Table II. Participants whose dysmorphology status was previously classified as equivocal [Miles and Hillman, 2000] are included in the nondysmorphic category. No significant differences in age or ethnicity were noted between the dysmorphic and nondysmorphic participants. Socioeconomic status was slightly lower in dysmorphic group. As reported previously, individuals with autistic disorder who are nondysmorphic have a higher male to female ratio than the dysmorphic cohort and a slightly later age at autism diagnosis [Miles et al., 2005].

Development of Consensus Determination

The validity of the dysmorphology classification system was established through a separate study of 31 ASD children by four fellowship-trained medical geneticists/dysmorphologists (JHM/SRB/MEB/RAM). Each subject was classified as dysmorphic, nondysmorphic, or equivocal using the coding system described above. Equivocal ratings were folded into the nondysmorphic classification. Dysmorphology designations made by the four dysmorphologists were based on their clinical impression of the patient, the dysmorphology score calculated by counting the number of dysmorphic features codes (LDDB level 3 features) and by a dysmorphology score based on the number of body areas rated as dysmorphic (LDDB level 1&2). When the designation was based on their clinical judgment, the four dysmorphologists agreed with the consensus rating 90% of the time (Kappa = 0.62). When dysmorphic features were counted the agreement was 79% (Kappa = 0.57), and when determination was based on the number of body areas rated as dysmorphic the agreement was 85% (Kappa = 0.55). Tests of agreement among the four dysmorphologists indicated moderate agreement for determinations based on clinical judgment (Kappa = 0.55), fair agreement based on designation by individual features (Kappa = 0.26), and somewhat better agreement when dysmorphology designation was based on body areas (Kappa = 0.38). Intra-class correlation, which was calculated to assess the consistency among the four raters in the number of body areas judged dysmorphic, was 0.65. These results verify the validity of the classification system and support the use of the expert-determined dysmorphology designations as the basis for the development of a dysmorphology measure.

The Most Informative Dysmorphology Designations

Table I provides information on the features and body areas most likely to be utilized by medical geneticists/dysmorphologists to describe physical dysmorphology in an autism population comprising both dysmorphic and nondysmorphic individuals. The list of features coded for the 31 subjects during the validation study was similar (data not shown), even though the validity study was smaller (31 vs. 222 participants) and the group was selected to contain more children designated dysmorphic. In order to determine the most informative designations for dysmorphology classification, comparisons were made among the number of times each feature and each body area was coded for the groups of dysmorphic, nondysmorphic and equivocal participants.

A graph of 20 representative feature codes is presented (Fig. 1). Inspection of the graph is informative, illustrating features that occurred preferentially in the dysmorphic subjects with highly significant frequency. For instance, deep-set nails were noted in 23% of dysmorphic subjects and only 1% of nondysmorphic ($P = 0.000002$), tapered fingers occurred in 27% of the dysmorphic subjects but

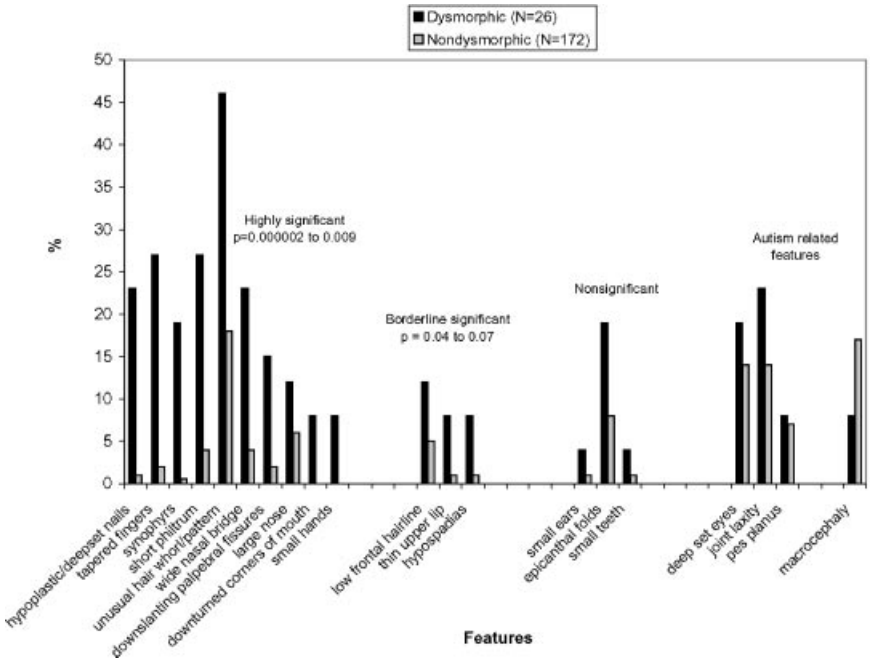

FIG. 1. Selected dysmorphic features in dysmorphic versus nondysmorphic autism subgroups.

only in 2% of the nondysmorphic group ($P = 0.000004$), and a wide nasal bridge was noted in 23% of the dysmorphic group but only in 4% of the nondysmorphic ($P = 0.001$). Another group of features occurred more often in the dysmorphic group but with less variance; for instance, low anterior hair line was noted in 12% of the dysmorphic group and 2% in the nondysmorphic ($P = 0.04$), and a thin upper lip was 8% for the dysmorphic group and 0.6% in the nondysmorphic ($P = 0.06$). Other features, including small ears and a triangular face, though more common in children who were dysmorphic, were infrequently encountered in either group, indicating their use in a classification system would be limited by low sensitivity. Three features—deep set eyes, ligamentous laxity and pes planus—occurred roughly equally in the dysmorphic and nondysmorphic participants. Ligamentous laxity was noted in 23% of dysmorphic participants versus 14% of nondysmorphic, pes planus in 8% dysmorphic and 7% nondysmorphic, and deep set eyes in 19% dysmorphic and14% nondysmorphic. Finally, we identified macrocephaly twice as often in the nondysmorphic subjects (17% vs. 8%). Macrocephaly and ligamentous laxity, which includes pes planus, have previously been noted to occur commonly in autism [Gillberg and Coleman, 1992; Miles et al., 2000]. These data add deep-set eyes to the list of physical features commonly observed in autism generally.

Inspection of the original consensus data set revealed that the descriptive features used to label a structure "dysmorphic" were not exclusive, and different features were often coded by the two geneticists to describe the same body area or region. Also, we found poor reliability in the designation of specific features by the four geneticists. They recorded 226 different level 3 features as abnormal in at least one of the 31 subjects. But 144 of the designations were only noted by one rater, 82 features were recorded by more than one rater, and only 12 features were recorded by all four geneticists. In many cases the four geneticists chose different terms to describe the same dysmorphic structure. For instance, the same nose was described as broad, bulbous nasal tip and as broad based. The same ears were described as crumpled helix, dysplastic ear, and asymmetric. Because of the poor coding reliability for specific descriptive features, we analyzed agreement when dysmorphology designations were based on body area designations. This increased the agreement among the four dysmorphologists from 79% to 85%, indicating that a system which assesses dysmorphology by body regions would be more reliable.

Of the 34 body regions listed in Table I, 25 significantly differentiated dysmorphic from nondysmorphic subjects (Fig. 2). Statistical analyses indicated that for 20 body regions there was a highly significant difference ($P = 0.007$ to 0.7×10^{-8}) between the number of times the region was coded in dysmorphic versus nondysmorphic participants. For example, abnormalities of the fingers and thumbs were observed almost exclusively in the dysmorphic participants, occurring in 77%, but only in 9% of nondysmorphic participants. Abnormalities of the nails were noted in 50% of the dysmorphic group and 3% of the nondysmorphic. Highly

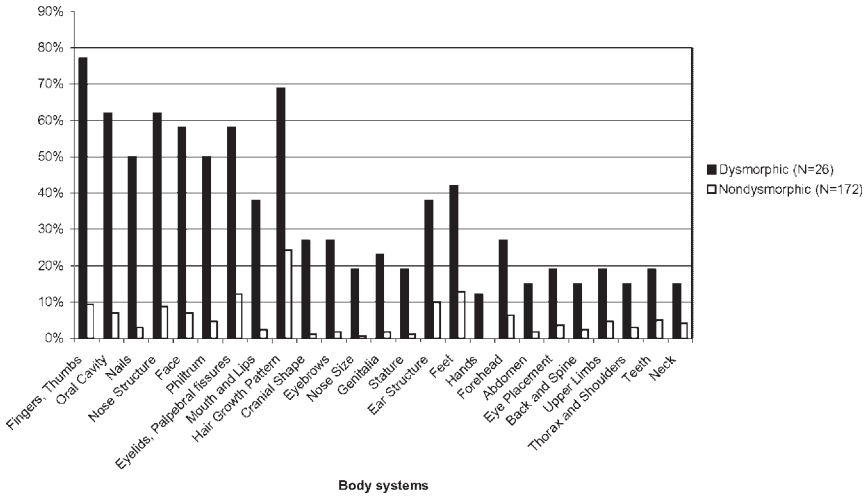

FIG. 2. Body systems with significant differences ($P < 0.05$) in dysmorphic versus nondysmorphic autism subgroups.

significant differences also occurred for abnormalities of the oral cavity, nose structure, face size and structure, philtrum, eyelids and palpebral fissures, mouth and lips, hair growth pattern, cranial shape, eyebrows, nose size, genitalia, short stature, ear structure, feet, hands, forehead, abdomen and eye placement. A second tier of structures which were significantly different ($P = 0.04$ to 0.01) included back/spine, upper limbs, thorax/shoulders, teeth and neck. Ear size, ear placement, eye size, lower limbs, dermatoglyphics, hair texture, skin, eye structure, neck and cranial structure did not separate the two groups. This noninformative group included body regions frequently cited as abnormal in both groups, such as the skin and abnormal dermatoglyphics, and structures that were infrequently cited in either group, such as lower limbs and eye structure. Abnormal ear placement, which occurred exclusively in the dysmorphic group, did not reach significance because it only occurred in 4% of the dysmorphic participants. Likewise, abnormal ear size occurred in 12% of the dysmorphic participants and 5% of the nondysmorphic. Because both ear placement and size are highly specific and classically important markers of dysmorphology, they were folded in with ear structure; analysis for the combined ear group was highly significant ($P = 0.0003$).

ADM Scoring Algorithm

The CART model selected as the basis for the ADM was forced to include ears and classified the subjects in the original equivocal group as nondysmorphic. The model produced an algorithm which used 12 body regions coded as normal or abnormal (Table III). The statistical data for this model, presented in Table IV, indicate that when compared with the consensus classification of 222 participants, the model performed with 81% sensitivity and 99% specificity. Finally, the CART algorithm was used to classify a test dataset of 31 additional individuals with autistic disorder; compared with the consensus classification, the CART algorithm performed well with 82% sensitivity and 95% specificity in this replication sample (Table IV). It was rather surprising that sensitivity and specificity remained so high in the test dataset since we allowed the CART algorithm to continue until further division would create a single participant in each grouping. It can be said that we didn't "trim the tree." More reliability is expected in the earlier selection of predictive variables than in later ones. So the very slight degradation of performance in the small training dataset is very encouraging.

To allow straightforward and efficient use, the CART algorithm is presented in the tree form (Fig. 3) which directs the clinician to score the 12 body areas sequentially to arrive at a determination of dysmorphology or nondysmorphology. Each of the 12 scoring nodes is defined in Table III. For each node, we have listed all of the specific descriptive dysmorphic features noted by the authors in both the consensus and validity studies. This does not preclude using additional descriptive features that can be subsumed under the nodal body area. For instance, 16 separate descriptions of ear dysmorphology are listed; additional features, including abnormalities of the anti-helix, absent ear, deficient ear cartilage, auricular pits, fistulas or tags as well as others found in the LDDB, could also be used to describe a dysmorphic ear. However, to preserve the specificity and sensitivity of the measure, it will be imperative that coding of each node conform faithfully to the definitions provided in Table III and the LDDB. We are currently developing a training manual which will include photographic examples.

TABLE III. Autism Dysmorphology Measure (ADM) Brief Descriptions of Coded Features

Body regions/LDDB codes	Dysmorphic features	Brief description[a]
Stature		
02.01.00	Short stature	Stature <10%
Hair growth pattern		
04.04.03	Unusual hair whorl/pattern	A double or very eccentrically placed whorl. Hair grows in "wrong" direction
04.04.04	Widow's peak	Accentuation of the normal V-shaped insertion of the frontal hair which extends onto the forehead
04.04.05	Frontal upsweep/cowlick	Literally as if a cow had licked the frontal hair and it stayed in an upward sweep from the forehead
Ear structure, size and placement		
06.01.02	Asymmetric ears	Difference in size
06.01.06	Dysplastic ears	Malformed ear
06.01.07	Large ears	Measure from top to bottom; >97th centile on chart
06.01.08	Low-set ears	The topmost insertion of the ear is below a line drawn horizontally between the canthi of the eyes. Must assess with head upright
06.01.09	Posteriorly rotated ears	Measure with head upright, ears rotated posteriorly >30°
06.01.10	Auricular pits/fistulas	Pits, sinuses or fistulae on ear or in front of the ear
06.01.12	Prominent ears	Most ears that appear prominent are large and rotated forwards. By judgment or measurement
06.01.14	Simple ears	Ears without the normal "geography" especially in the triangular fossa between the helix and the crus of the anti-helix. Often cup shaped and smooth
06.01.15	Small ears/microtia	Small normal looking ears, or small dysplastic ears
06.02.02	Prominent anti-helix	Anti-helix is larger than normal and stands out
06.07.02	Notched ear helix	Notches (V-shaped) or slits (focal deficiencies)
06.07.01	Crumpled ear helix	As if someone had crunched it between their thumb and fingers and the folds had stayed in place
06.07.03	Over-folded ear helix, lop ear	Lop ear is a limp, droopy often anteverted ear, sometimes cup shaped. May be an exaggeration of the normal fold
06.07.04	Pits of ear helix	Deep or shallow indentations on front, top or back
06.07.05	Prominent ear helix	Similar to prominent ears
06.08.02	Attached ear lobule	Lobule is attached posteriorly to skin behind the ear
Nose size		
09.01.04	Large/long nose	Subjective code based on age and family pattern
09.01.09	Small/short nose	Short from top to bottom. Can measure from nasion to sub-nasion
Face size and structure		
10.01.01	Asymmetric face	One side of face is smaller or larger than the other
10.01.04	Coarse facial features	Heavy look to the face because of sagging cheeks, thick lips, heavy brow
10.01.07	Flat face	Subjective and overlaps with mid-face hypoplasia and flat malar region
10.01.10	Mid-face hypoplasia	Overlaps with flat malar area but more medial
10.01.13	Small face	Small, but not triangular.
10.01.15	Thin/long face	Thin from side to side and long from top to bottom
10.01.16	Triangular face	Broad forehead and small chin gives a small delicate face
10.03.01	Dimpled or grooved chin	A mid-line groove as in Kirk Douglas
10.03.02	Pointed chin	Pronounced and different from family
10.04.01	Flat malar region	Overlaps with flat mid-face, more lateral
10.05.04	Prominent mandible/prognathism	Prognathism. A jutting jaw
10.05.05	Small mandible/micrognathia	Subjective impression must be related to age and family pattern. Jaw grows preferentially with age
Philtrum		
11.03.01	Long philtrum	Long area between columella of nose and lip margin
11.03.02	Prominent/deep philtrum	Deep groove between the pillars or prominent pillars
11.03.03	Short philtrum	Short area between columella and upper lip margin
11.03.04	Simple/flat/absent philtrum	Smooth, featureless philtrum
11.03.05	Wide philtrum	Widely spaced philtral pillars and intervening groove
Mouth and lips		
11.01.02	Down-turned corners	Corners of mouth normally end in horizontal position
11.01.03	Cupid bow shape of mouth	Tented or cupid's/hunter's bow with a pronounced upward curve and smaller concave curve in the middle
11.01.04	Macrostomia	Large opening, including a wide mouth
11.01.05	Microstomia	Small mouth opening
11.01.06	Open mouth appearance	Mouth droops open
11.02.04	Prominent/everted lower lip	Lower lip is prominent and rolls downwards
11.02.05	Thick lower lip	Thick and usually prominent
11.04.01	Cleft upper lip (nonmidline)	As in cleft lip and palate
11.04.03	Prominent upper lip	Projecting often thick upper lip

TABLE III. (*Continued*)

Body regions/LDDB codes	Dysmorphic features	Brief description[a]
11.04.05	Thin upper lip	Pencil-line thin upper lip
Teeth		
13.01.06	Enamel abnormalities	Enamel covers the crown and abnormality may result in excessive wear and erosion down to gum level
13.01.07	Irregular or crowded teeth	Distorted symmetry of tooth eruption with irregular positioning and crowding. May be due to jaw structure
13.01.13	Abnormally shaped teeth	Peg-shaped, conical, screwdriver shaped teeth, etc.
13.01.14	Small teeth	Small for age
13.01.16	Wide-spaced teeth	May be with small teeth or abnormal jaw. Wide gap between central incisors is a diastema
Hands		
23.01.05	Large hands	Large, hypertrophied hands
23.01.07	Small hands	Tiny, delicate or thin hands
Fingers, thumbs		
23.04.04	Camptodactyly	Inability to straighten the fingers
23.04.05	Clinodactyly	Incurving—often seen in 5th finger
23.04.16	Skin syndactyly of fingers	Viewed from palm excess skin between fingers. Ranges from minor which pushes rings to knuckle to complete fusion
23.04.17	Tapering fingers	Exaggeration of normal finger taper
23.04.19	Thin fingers	Often with long fingers
23.05.05	Short/hypoplastic metacarpals	Short and sometimes "stubby." View dorsum of clenched fist to see irregular shortening, often with dimples
23.06.07	Short phalanges	View relative to palm and other fingers. Rule out short metacarpal(s)
23.06.09	Wide phalanges	Often shaped like a bullet, especially if wide and short
23.06.10	Long phalanges	Long and usually slender as in arachnodactyly
23.07.03	Broad thumbs	A broad, spatulate, and sometimes deviated thumb
Nails		
24.01.06	Dystrophic, inc. ridged nails	May be congenital; rule out degenerative condition
24.01.07	Hyperconvex/clubbed nails	Accentuation of normal convexity
24.01.09	Small/hypoplastic/deep-set nails	Small, underdeveloped nails
24.01.10	Short nails	Small, underdeveloped nails
Feet		
26.01.09	Club foot, varus	Foot in-turned from the ankle downwards
26.01.11	Large feet	Feet >2SD for age
26.01.16	Small feet	Feet <2SD for age
26.01.17	Wide feet	Wide from side to side
26.02.07	Hallux valgus	Lateral deviation of the big toe
26.05.02	Broad toes	Mostly broad, spatulate ends
26.05.05	Over-riding toes	Bent, incurved or overlapping toes, inc clinodactyly
26.05.08	Short toes	Subjective relative to foot and age
26.05.09	Syndactyly 2-3 of toes	May be partial or complete. Common in families
26.05.10	Syndactyly of toes (not 2–3)	Webbing with skin or bone of other toes
26.05.11	Wide-spaced toes	Increased spaces between all of the toes
26.05.13	Camptodactyly/hammer toes	Inability to extend the toes

[a]Adapted from the London dysmorphology database.

DISCUSSION

The autism dymorphology measure (ADM) is a new measure of generalized dysmorphology with the potential to be used by researchers and clinicians to identify phenotypically distinct subgroups of autism. This measure resulted from our recognition that designating specific physical features as dysmorphic depended to a high degree on clinical judgement and experience. In fact, our four medical geneticists, despite training and extensive experience in dysmorphology, often used different codes to describe the same body area, and each preferentially used certain codes. We had initially classified individuals as dysmorphic if they had six or more dysmorphic features [Miles and Hillman, 2000; Miles et al., 2005]. This relied on performing a complete, unclothed examination, scoring more than 500 single features. This technique, though valuable for the medical geneticist, was deemed inefficient for most clinicians working with children with autism.

In addition, we recognized that developing a measure of general dysmorphology is quite different from describing the specific dysmorphic features that define a discrete disorder, such as Down syndrome. In that case, cluster analyses are helpful in defining the most informative associated diagnostic features. By listing the dysmorphic features and calculating sensitivity and specificity, it is straightforward to develop a diagnostic algorithm based on specific

TABLE IV. Classification Statistics

	Training dataset, n = 222			Test dataset, n = 31		
	Consensus/expert classification			Consensus/expert classification		
	Dysmorphic	Nondysmorphic	Total	Dysmorphic	Nondysmorphic	Total
CART algorithm predicted classification						
Dysmorphic	21	2	23	9	1	10
Nondysmorphic[a]	5	194	199	2	19	21
Total	26	196	222	11	20	31
	Sensitivity	21/26 = 0.81		Sensitivity	9/11 = 0.82	
	Specificity	194/196 = 0.99		Specificity	19/20 = 0.95	

[a]Includes 24 equivocal.

features, such as ligamentous laxity, wispy hair, short fifth finger with clinodactyly, etc [Preus, 1977]. Autism, however, is an etiologically heterogeneous behavioral disorder for which more than 50 well described, discrete causes, in addition to an even larger number of reported chromosome abnormalities, are known [Smith et al., 2000; Miles and McCathren, 2005; Freitag, 2007; OMIM, 2007]. Defining a dysmorphology scoring measure for autism is analogous to defining a measure of dysmorphology

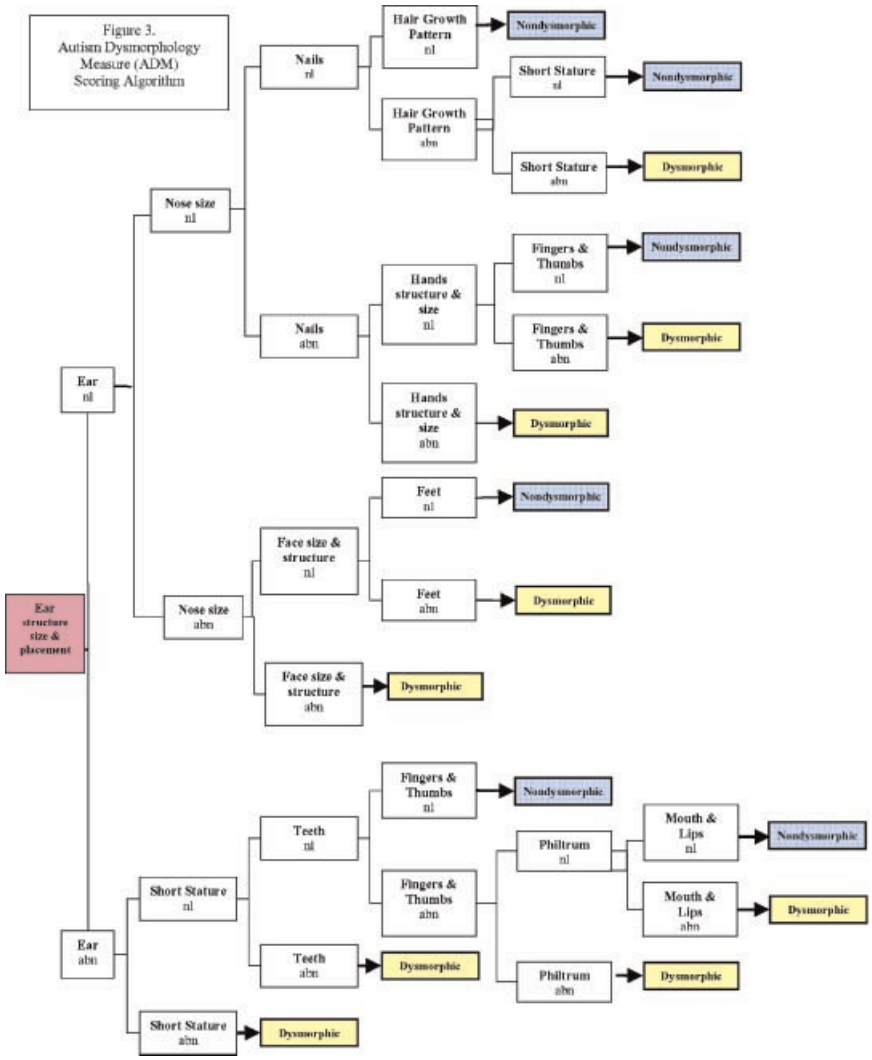

FIG. 3. Autism dysmorphology measure (ADM) scoring algorithm. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

for mental retardation, where throwing out any specific feature is difficult to justify. Based on these considerations and the fact that we achieved better validity when dysmorphology was coded by body regions rather than specific dysmorphic features, we shifted our attention to a system that allows the clinician to code body regions as dysmorphic or nondysmorphic.

We recognize a number of caveats in reducing the complex process of the full dysmorphology examination, based on solid knowledge of embryology, to a relatively simple algorithm. For clinicians, the most difficult aspect of the ADM will be to distinguish truly abnormal structures from normal, including recognition of normal variants. Three strategies should be useful. The first is experience in the field of medical genetics and dysmorphology. This, however, comes from years of experience and is difficult and perhaps impossible to teach quickly. The second is to use one of the major dysmorphology references [Aase, 1990; Winter and Baraitser, 1993; Jones, 2006]. We are currently preparing a picture guide to the 12 nodal body regions used in the algorithm. These descriptions and pictures will provide examples that can be compared with the study subject. The third strategy, and often easiest and most important, is to compare the child to his or her parents. For instance, a large nose in a family with familial large noses does not indicate a significant breach of normal morphologic development. The second caution is that we do not yet know how the measure will perform when used by clinicians, not trained in dysmorphology. Currently, we are engaged in a multisite validity and reliability study, sponsored by the Simons Foundation, in children from 12 centers and of different ethnic backgrounds. The study will initially target pediatricans and child psychiatrists who currently provide medical examinations for children with autism. Following a training period we will compare the clinicians' performance with medical geneticists for the ADM and for each node in the algorithm. This will establish the usefulness of the measure and determine the type and extent of instruction needed for a range of clinicians and scientists to use the measure successfully. Third, is the concern that some individuals may have dysmorphology limited to areas not assessed by the algorithm. The ADM is not intended to replace the general medical examination meant to detect known causes of autism, such as tuberous sclerosis, fragile X syndrome, Timothy syndrome and PTEN disorders. A Woods lamp exam is always recommended to diagnose tuberous sclerosis and genital exams are needed to assess for macro-orchidism associated with fragile X and penile freckles in some PTEN disorders. When evidence of dysmorphology is noted, a comprehensive examination by a trained and experienced dysmorphologist will continue to be the gold standard and should guide decisions on diagnostic laboratory tests.

In our hands, the ADM can separate individuals into two groups based on the presence of general physical dysmorpology. It was designed to lessen the dependence on "expert" clinical judgment and to allow the clinician to rely more on comparison with normal structures. For example, the scorer does not have to specify that an ear crus is horizontal; only that the ear is abnormal. Furthermore, scoring body regions prevents counting different features in the same developmental sequence twice, such as a short philtrum and a pulled-up upper lip. We intend this measure to provide clinicians a practical way to distinguish individuals with complex autism from essential autism, which in turn will lead to more accurate prognoses, recurrence risk assessment, and treatment direction. The ability to obtain this information from a clothed exam will be more practical, especially with children who are fearful and anxious.

Research benefits will come from identifying the more heritable subgroup (essential autism) and should improve power for linkage and sib pair analyses. Since virtually all the identified autism syndrome diagnoses are made in individuals with complex autism, it will be important to determine whether other emerging technologies like chromosomal microarrays are more often diagnostic for this group. Replication studies in different autism populations will be crucial to assessing the ultimate utility of the ADM, including analyses of 3D facial imaging, which promises a more quantitative assessment. Finally, extending the analyses to other behaviorally defined disorders like ADHD [Ogdie et al., 2006] and schizophrenia [Gelowitz et al., 2002; Schiffman et al., 2002] may provide information on heterogeneity in those disorders.

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