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Tetrasomy 18p: Report of the Molecular and Clinical Findings of 43 Individuals

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Thus far, the phenotype of tetrasomy 18p has been primarily delineated by published case series and reports. Findings reported in more than 25% of these cases include neonatal feeding problems, growth retardation, microcephaly, strabismus, muscle tone abnormalities, scoliosis/kyphosis, and variants on brain MRI. Developmental delays and cognitive impairment are universally present. The purpose of this study was to more fully describe tetrasomy 18p at both the genotypic and the phenotypic levels. Array CGH was performed on 43 samples from individuals with tetrasomy 18p diagnosed via routine karyotype. The medical records of 42 of these 43 individuals were reviewed. In order to gain additional phenotypic data, 31 individuals with tetrasomy 18p underwent a series of clinical evaluations at the Chromosome 18 Clinical Research Center. Results from the molecular analysis indicated that 42 of 43 samples analyzed had 4 copies of the entire p arm of chromosome 18; one individual was also trisomic for a section of proximal 18q. The results of the medical records review and clinical evaluations expand the phenotypic description of tetrasomy 18p to include neonatal jaundice and respiratory distress; recurrent otitis media; hearing loss; seizures; refractive errors; constipation and gastroesophageal reflux; cryptorchidism; heart defects; and foot anomalies. Additional findings identified in a small number of individuals include hernias, myelomeningocele, kidney defects, short stature, and failure to respond to growth hormone stimulation testing. Additionally, a profile of dysmorphic features is described. Lastly, a series of clinical evaluations to be considered for individuals with tetrasomy 18p is suggested.

Key words: tetrasomy 18p; isochromosome 18p

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INTRODUCTION

Isochromosome 18p appears to be one of the most commonly observed isochromosomes [Kotzot et al., 1996]. The phenotype of tetrasomy 18p has been delineated through multiple case reports and case series. A thorough review of the literature revealed an average birth weight of 2,519 g, which falls between the 3rd and

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10th centile. The average birth length is 50.1 cm, which is at approximately the 50th centile. The findings described in these 65 case reports and series are presented in Table I. The most common findings included neonatal feeding problems, growth retardation, microcephaly, strabismus, abnormalities in muscle tone, scoliosis/kyphosis, and variants on MRI of the brain. Dysmorphic features include low-set, malformed ears; a small, pinched nose; a high-arched palate; a small mouth; and either prognathism or micrognathia [Swingle et al., 2006].

The molecular mechanism of isochromosome 18p formation has been discussed in several publications [Bugge et al., 1996; Eggermann et al., 1996, 1997; Kotzot et al., 1996]. All cases reported thus far have been monocentric, implying that the isochromosome arises as a result of two independent events: nondisjunction and centromeric misdivision. The alternative mechanism of formation of an isochromosome is a U-shaped exchange, which would typically produce a dicentric isochromosome [Kotzot et al., 1996]. Hence, it is suspected that nondisjunction and misdivision are primarily responsible for the formation of isochromosome 18p. The parental origin of the isochromsome has been reported in five different papers and was found to be maternal in 21 of the 22 cases in which origin could be determined [Bugge et al., 1996; Eggermann et al., 1996, 1997, 1999; Kotzot et al., 1996]. It appears that, in the majority of cases, nondisjunction occurs during maternal meiosis II followed by centromeric misdivision, suggesting that maternal age may play a role in the formation of the isochromosome [Bugge et al., 1996; Kotzot et al., 1996; Eggermann et al., 1999].

The goal of this paper is to more fully describe the molecular features and clinical presentation of tetrasomy 18p. A series of clinical evaluations recommended for individuals with tetrasomy 18p is also presented.

METHODS

Study Participants

All study participants are enrolled in a large ongoing research study at the Chromosome 18 Clinical Research Center. Eligibility criteria for this study included a diagnosis of tetrasomy 18p confirmed by a routine karyotype. All components of this study have been approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio (UTHSCSA). All families were and continue to be involved in the informed consent process, which is appropriately documented.

Molecular Analysis

Blood samples were collected from all study participants as well as the biological parents, if available. As routine karyotypes had been completed prior to the participants' enrollment in the study, they were not repeated as part of this project. Instead, DNA was assessed for copy number changes by oligonucleotide microarray comparative genomic hybridization as previously described in Heard et al. [2009]. Custom arrays were designed using the Agilent e-array software (hg18) and were constructed with 32,000 features (60-mers) across chromosome 18 and 12,000 features across the remainder of the genome.

Chart Review

The diagnosis of tetrasomy 18p was confirmed in all individuals by obtaining copies of the original karyotype. Medical records were then obtained from all participants. All available records were reviewed in detail. Following the record review, the families were contacted by one of three investigators (ER, CS, MZ) to confirm the medical history and to provide information that was not included in the records. If new information was obtained during the interview, additional medical records were requested to confirm the parents' report. In the few instances where the information obtained from the family interview differed from the information in the medical records, the information from the medical records was used in data analysis to minimize recall bias. For example, several parents reported birth weights that were slightly different from the weight listed in the newborn records. In these cases, we used the figure provided in the records as it had been recorded at the time of birth and thus not subject to recall bias.

UTHSCSA Evaluations

The gathering of phenotypic data included evaluations by multiple specialties, including neurotology, audiology, ophthalmology, genetics, neurology, orthopedics, and endocrinology. Each specialty used the standard evaluation that is used in a typical new patient visit in clinic. Thus, none of the evaluations are considered experimental in nature. The endocrine evaluation also included bone age studies, IGF1 and IGFBP3 levels, growth hormone provocative testing using arginine and clonidine, total T4 and TSH measurements, and FSH, LH, estradiol and testosterone levels in postpubertal individuals. Participants also had brain MRIs and skeletal surveys. Hearing was assessed using sound booth audiometry and/or an Auditory Brainstem Evoked Response (ABR).

RESULTS

Molecular Findings

We received blood samples from 43 individuals with tetrasomy 18p diagnosed via routine karyotype. In all but one individual, aCGH confirmed the diagnosis of tetrasomy 18p molecularly. In individual 32C, however, there was an additional region of trisomy extending from the centromere to 18,536,308 (18q11.2). In order to keep the sample as genotypically pure as possible, this individual was removed from the phenotypic analysis. The other 42 individuals' region of recombination is located between nucleotides 15,315,187 and 16,793,854. This region spans the centromere and is without sequence data.

Chart Review

The medical charts of 42 individuals with tetrasomy 18p were reviewed in detail. The medical records from one family were written in Finnish and could not be translated. Instead, information was gathered via an e-mail interview conducted in English, as the family was bilingual. All families were interviewed by one of the investigators. Forty-one individuals had an isochromosome 18p in all cells examined. The remaining individual had mosaicism. In this

TABLE I. Tetrasomy 18p Findings

Feature	Literature	UTHSCSA chart review	UTHSCSA clinical assessment	Total
Developmental delay/mental retardation	65/65	42/42	[b]	107/107 (100%)
Neonatal complications	28/65	41/42	[b]	69/107 (64%)
Feeding difficulties	25/65	35/42		60/107 (56%)
Respiratory distress	3/65	13/42		16/107 (15%)
Jaundice	6/65	24/42		30/107 (28%)
Hypoglycemia	1/65	0/42		1/107 (1%)
Bradycardia	1/65	0/42		1/107 (1%)
Growth retardation	23/65	[a]	6/31	29/96 (30%)
Microcephaly	38/65	[a]	13/31	51/96 (53%)
Palatal anomalies	5/65	1/42	[b]	6/107 (6%)
Cleft palate	3/65	0/42		3/107 (3%)
Bifid uvula	2/65	0/42		2/107 (2%)
Submucous cleft palate	0/65	1/42		1/107 (1%)
Ophthalmologic abnormalities				
Strabismus	22/65	[a]	18/24	40/89 (45%)
Refractive errors	13/65	[a]	17/24	30/89 (34%)
ENT abnormalities				
Hearing loss	2/65	[a]	9/28	11/93 (12%)
Recurrent otitis media	13/65	24/42	[b]	37/107 (35%)
Small/narrow ear canals	2/65	[a]	10/31	12/96 (13%)
Neurological abnormalities				
Abnormal muscle tone	37/65	41/42	[b]	78/107 (73%)
Seizures	13/65	10/42[c]	[b]	23/107 (21%)
CNS Abnormalities				
Myelomeningocele	3/65	3/42	[b]	6/107 (6%)
Brain MRI variants	3/4	[a]	7/12	10/16 (63%)
Cardiac defects	8/65	15/32	[b]	23/97 (24%)
Genitourinary abnormalities				
Cryptorchidism	6/27	12/19	[b]	18/46 (39%)
Hypospadias	2/27	0/19	[b]	2/46 (4%)
Congenital malformations	5/65	3/31	[b]	8/96 (8%)
Gastrointestinal abnormalities				
History of constipation	0/65	34/42	[b]	34/107 (32%)
History of gastroesophageal reflux	0/65	15/42	[b]	15/107 (14%)
Hernias	4/65	5/42	[b]	9/107 (8%)
Pyloric stenosis	2/65	2/42	[b]	4/107 (4%)
Orthopedic abnormalities				
Congenital abnormalities	5/65	19/42	[b]	24/107 (22%)
Scoliosis/kyphosis	21/65	[a]	10/19	31/84 (37%)
Other foot anomalies	10/65	[a]	9/19	19/84 (23%)
Laboratory abnormalities				
Thyroid abnormality	0/65	[a]	0/31	0/96 (0%)
Growth hormone deficiency	0/65	[a]	4/31	4/96 (4%)
IgA deficiency	3/65	1/42	[b]	4/107 (4%)
Stillbirth/early death	3/65	1/42	[b]	4/107 (4%)
Additional findings identified in single individuals	Necrotizing enterocolitis Pancreatitis Giant cell hepatitis Hydrocele Celiac sprue disease			

Abeliovich et al. [1993], Back et al. [1994], Bakshi et al. [2006], Balicek et al. [1976], Balkan et al. [2009], Batista et al. [1983], Blennow and Nielson [1991], Blennow et al. [1995], Boyle et al. [2001], Bugge et al. [1996], Callen et al. [1990], Cote et al. [1979], Condron et al. [1974], DeBerardinis et al. [2005], Eggermann et al. [1997], Esmer et al. [1994], Fryns et al. [1985, 1990], Kleckzkowska et al. [1986], Kotzot et al. [1996], Mewar et al. [1993], Nielsen et al. [1978], Ogata et al. [1977], Park et al. [1991], Ramegowda et al. [2006], Rauch et al. [1992], Rivera et al. [1984], Rocchi et al. [1979], Singer et al. [1990], Swingle et al. [2006], Takeda et al. [1989], Tangheroni et al. [1973], Taylor et al. [1975].

[a]These data were not an item scored in the chart review.

[b]These data were not collected during the clinical assessment process.

[c]An additional seven patients had a history of febrile seizures.

individual, lymphocyte analysis revealed 19% of cells with the isochromosome; fibroblast analysis revealed 68% and 94% mosaicism in abdominal skin and foreskin, respectively.

The final sample was composed of 23 females and 19 males. Ages ranged from 23 months to 31 years 7 months with an average age of 11.9 years. Average maternal age at birth was 32.5 years, and average paternal age was 34.1 years. The average birth weight was 2,842 g (6.36 lbs), and the average birth length was 48.7 centimeters (19.2 in.). The clinical findings are generally summarized in Table I.

Neonatal Complications

The large majority of individuals with tetrasomy 18p had some complications in the neonatal period. The most common finding in the neonatal period was feeding difficulty, identified in 83% of newborns. The feeding problems were frequently related to hypotonia, a high-arched palate, or gastroesophageal reflux. Jaundice requiring phototherapy was also present in 57% of individuals. Respiratory distress, though less common than feeding difficulties and jaundice, was another frequent occurrence in this population and was seen in 31% of our study participants.

Congenital Anomalies

Cardiac. A heart defect was the most common congenital anomaly present in this population. Of the 32 individuals that had undergone echocardiograms, 15 had some type of anomaly. The most common findings were patent ductus arteriosus (7); patent foramen ovale (3); ventricular septal defect (5); and atrial septal defect (2). In all but one of these cases, the anomaly closed spontaneously and did not require surgery. Other cardiac findings included mild mitral valve regurgitation; mitral valve prolapse; bicuspid pulmonary valve; hypoplastic transverse aortic arch; tricuspid valve regurgitation; right ventricular hypertrophy; and two individuals with pulmonic stenosis. One individual had "unusual systolic flow."

Abdominal. Genitourinary anomalies were also seen within our population. Of the 19 males, 12 were diagnosed with cryptorchidism. Six of these individuals required surgical intervention. No abnormalities of external genitalia were noted in the females. Of the 31 patients who had undergone abdominal ultrasounds, 2 had horseshoe kidneys and 1 had bladder diverticuli requiring surgical correction. The only structural anomaly noted in the gastrointestinal tract was pyloric stenosis, which was identified in two individuals. Hernias were diagnosed in five individuals. Four had inguinal hernias while one had an umbilical hernia.

Orthopedic. Six (14%) had clubfoot; two (5%) had vertical talus; two (5%) had metatarsus adductus; and two (5%) had rockerbottom feet. Seven (17%) had congenital hip dysplasia.

Central nervous system. Three of the 42 study participants had myelomeningocele.

ENT

Twenty-four of the 42 participants (57%) had recurrent otitis media and required the placement of PE tubes.

Gastrointestinal

Chronic constipation was a frequent finding and affected 81% of our population. Gastrointestinal reflux was another frequent occurrence and affected 36%.

Neurologic

Muscle tone abnormalities were the most common neurologic anomaly noted. Forty-one of 42 patients had an abnormality of muscle tone. Twenty-one had hypotonia; 8 had hypertonia; and 12 had mixed muscle tone. Approximately one in four had a seizure disorder. An additional seven individuals had febrile seizures.

All study participants had developmental delays as well as some degree of cognitive impairment. Estimates of cognitive functioning were within the mild to moderate range of mental retardation. Table II presents the age range at which key gross motor and expressive language developmental milestones were reached within the study population compared with typically developing peers. Data regarding degree of cognitive impairment and other developmental parameters will be presented in a separate publication (in preparation).

TABLE II. Age of Attainment of Developmental Milestones

	Study children average age of acquisition (months)		
Developmental milestone	Mean	SD	Age of acquisition for typically developing children[a] (months)
Rolls from side to back N = 31	8	4	3
Sat independently N = 34	16	8	6
Crawled N = 29	22	12	7
Walked alone N = 33	33	14	12
Single words N = 28	28	16	12
2–3 word phrases N = 19	66	28	18

[a]The age of acquisition listed for typically developing children indicates the age at which approximately 50% of the Bayley Scales of Infant Development-Second Edition [Bayley, 1993] normative sample of infants and children demonstrated the skill.

Early Death

Of note, within the UTHSCSA population, one female study participant died suddenly at 13 years of age. She presented to the ER with a 1-day history of nausea, vomiting, and lethargy, culminating in asystolic cardiac arrest. Resuscitation efforts were initiated, but the patient developed multiorgan failure and passed away. On autopsy, it was revealed that the patient had a massively distended colon with a large fecal mass measuring 22 cm in diameter. The etiology of the cardiac arrest remains unclear, though an untreated seizure disorder and sepsis have both been suggested as potential causes.

Parental Chromosomes

In 30 of the 42 cases, both parents had had karyotypes completed. In all instances, both parents had normal results. In four of the remaining 12 families, only the mother had had chromosome analysis, the results of which were normal. Two were adopted; thus, birth parents were not available for chromosome analysis. In the remaining six families, neither parent had undergone chromosome analysis.

Clinical Evaluations. All participants were invited to San Antonio to receive a series of clinical evaluations. Thirty-one were evaluated at the Chromosome 18 Clinical Research Center at the University of Texas Health Science Center at San Antonio. This sample included 14 males and 17 females. The average age at evaluation was 9 years 8 months.

ENT

All 31 individuals were evaluated by a neurotologist. Although 10 had small ear canals, no other structural anomalies were noted.

Growth Parameters

Height, weight, and head circumference were obtained on all participants. In general, individuals with tetrasomy 18p were short with 16 (52%) being less than the 25th centile for height and 6 (19%) being less than the 3rd centile for height. Six (19%) were at or below the 3rd centile for weight (three of whom were also below the 3rd centile for height). Thirteen (42%) were at or below the 3rd centile for head circumference.

Orthopedic Evaluation

Nineteen individuals were evaluated by an orthopedist. Kyphosis was diagnosed in three participants, and scoliosis was identified in seven individuals. Seven had pes planus. Two individuals had varus deformity and pes cavus. Two had contractures of the fingers; two had femoral anteversion; one had a slight Erlenmeyer flask deformity; and 1 had a contraction of the left elbow, possibly indicating a hemiparesis.

Audiology Evaluation

Twenty-eight underwent behavioral audiometry. Fourteen had ABR evaluations as well. Hearing loss was identified in nine individuals. Two had sensorineural hearing loss; three had conductive hearing loss; three had mixed hearing loss. One had an unspecified type of hearing loss. Five had mild to moderate hearing loss, two had moderate hearing loss, and the remaining two individuals had a mild or moderate hearing loss in the left ear and a severe hearing loss in the right ear.

Ophthalmology Evaluation

Twenty-four underwent ophthalmologic evaluation. Eighteen subjects showed evidence of strabismus, with 16 subjects demonstrating esotropia (7 accommodative, 5 infantile, 2 acquired non-accommodative, 2 intermittent) 1 subject displaying an esophoria, and 1 subject diagnosed with intermittent exotropia. Seventeen subjects were noted to have some type of refractive error. Four had myopia; eight had hyperopia; and six had astigmatism. Four were diagnosed with anisometropia.

Endocrine Evaluation

Thirty-one participants underwent the endocrine clinical evaluation. Six participants (19%) failed both growth hormone provocative tests (peak growth hormone value <10 ng/mL for children, <5 ng/mL for adults) using arginine and clonidine. Height percentiles of those who failed growth hormone stimulation testing ranged from the 9th–70th percentile. Two of the six individuals were children who fulfilled more traditional growth hormone deficiency criteria with height in the lowest quartile for age and had low IGF-1 levels. It was recommended that these children seek growth hormone treatment. Another individual was an obese adult with height at the 10th percentile and low IGF-1 levels. Given the controversy surrounding treatment of adult growth hormone deficiency, it was recommended that this family discuss growth hormone treatment with the patient's physicians. Of the remaining three individuals who failed both growth hormone provocative tests, one was an adult with height at the 40th percentile and normal IGF-1 level. The last two were children with normal IGF-1 levels, but one was growing along the 70th percentile for height while the other had been drifiting down from the 50th to the 10th percentile over the past several years. For these individuals, close monitoring of growth was recommended. All thyroid hormone and gonadotropin evaluations were normal.

Brain MRI

Twenty-four families consented to have a sedated brain MRI. However, only 8 of the 24 responded to the sedative used in our protocol: chloral hydrate. Four additional individuals had MRIs without sedation. Among the 12 patients that were scanned, three had enlargement of the lateral ventricles, and three had a thin or small corpus callosum. Two had minor signal abnormalities. One individual had a lipoma of the ambient cistern. Some individuals had more than one abnormality noted on brain MRI.

Genetics Evaluation

All 31 participants were evaluated by a board-certified clinical geneticist (ER). Features noted in more than 25% of individuals are listed in Table III.

TABLE III. Features Noted During Genetics Evaluation

Feature	Prevalence
Ptosis or hooded eyes	10/31
Posteriorly rotated ears	10/31
Unraveled helices	9/31
Small ears (at or below 3rd centile)	16/31
Abnormal columella (broad, or extends below alae nasi)	15/31
Small nares	7/31
Smooth philtrum	27/31
Small mouth	17/31
Thin upper lip vermilion	11/31
Abnormal Cupid's bow (smooth, ill-defined, narrow)	12/31
Palatal abnormalities (high, arched, narrow)	25/31
Dental crowding	6/31
Prominent and/or pointed chin	17/31
Sloping shoulders/trapezius	16/31
Mild/partial syndactyly of the toes	12/31
Narrow feet	12/31
Clinodactyly	19/31
Prominent finger tip pads	10/31
Camptodactyly/finger contractures	18/31
Gap between 1st and 2nd toes	12/31
Proximally placed anus	4/14[a]
Shawl scrotum	3/9[a]

[a]This part of the exam was deferred in some patients.

Photographs of individuals exhibiting the typical facial features of tetrasomy 18p are included in Figure 1.

DISCUSSION

In this report, we present the largest series of individuals with tetrasomy 18p described to date. A thorough review of the literature identified the characteristic features of tetrasomy 18p. They include growth retardation, microcephaly, strabismus, abnormalities in muscle tone, scoliosis/kyphosis, and variants on brain MRI. Developmental delays and cognitive impairment are also universally present. A thorough chart review of 42 patients and clinical evaluations of 31 of these patients allows us to expand the phenotypic spectrum of tetrasomy 18p to include neonatal jaundice, recurrent otitis media, hearing loss, seizures, refractive errors, a history of constipation and gastroesophageal reflux, heart defects, and pes planus. Less frequently, kidney defects, hernias, and myelomeningocele as well as short stature and failure to respond to growth hormone stimulation testing are diagnosed in individuals with tetrasomy 18p. Some individuals who did not respond to growth hormone stimulation testing and who also had low IGF-1 values still had normal growth for unknown reasons. Based on our data as well as the reports in the literature, guidelines for the evaluation of individuals with tetrasomy 18p are suggested in Figure 2.

Of interest, one of the UTHSCSA cases had mosaicism. Reports of mosaic tetrasomy 18p in the literature are uncommon. There are several reports of a prenatal diagnosis of mosaic tetrasomy 18p followed by termination of the pregnancy [Gocke et al., 1986; Verschraegen-Spae et al., 1993; Blennow et al., 1995; Pinto et al., 1998]. Thus, these reports do not provide useful information regarding the clinical features of individuals with mosaic tetrasomy 18p. Pfeiffer and Schulze [1994] reported three cases of presumed mosaic tetrasomy 18p. These individuals had features similar to those reported in individuals with full tetrasomy 18p. Similarly, the UTHSCSA patient with mosaicism also had features of the tetrasomy 18p phenotype, including neonatal feeding problems; cryptorchidism; vision problems; recurrent otitis media; and mild to moderate conductive hearing loss. This individual had also been diagnosed with pneumonia and adenoid hypertrophy.

The high de novo rate of isochromosome 18p in our patients is consistent with the literature. In fact, only a handful of reports of inherited cases exist. Takeda et al. [1989] and Taylor et al. [1975] both reported families in which the mother had a karyotype of 47,XX,del(18p),+i(18p). The mother reported by Takeda was phenotypically normal and had two pregnancies affected by tetrasomy 18p, one of which was stillborn. The mother reported by Taylor et al. [1975] had one daughter with tetrasomy 18p and one daughter with 18p-syndrome. This mother was reportedly phenotypically normal, though small. Abeliovich et al. [1993] reported a family in which the mother was found to have low-level mosaicism (3%) for tetrasomy 18p. This individual was slightly dysmorphic, though her medical and developmental histories were normal. Boyle et al. [2001] reported a family in which two maternal-half sisters had tetrasomy 18p. Karyotype and molecular analysis of the mother was normal, suggesting that she had germline mosaicism for isochromosome 18. Though it appears that tetrasomy 18p is a de novo occurrence in the great majority of cases, these case reports show that, in some families, the abnormality is familial. This has significant implications for genetic counseling for these families and should be taken into account when providing information regarding recurrence risks.

Some authors have suggested that advanced maternal age may play a role in isochromosome 18p formation [Bugge et al., 1996; Kotzot et al., 1996]. This theory is based on the finding that the most frequent mechanism of isochromosome formation involves nondisjunction in maternal meiosis II. In this sample, the average maternal age was 32.8 years with a range of 24–41. Since our clinical findings were consistent with the literature, and given that there is no evidence for any imprinting effects by genes on 18, we did not perform parental origin studies. We felt that such studies were unlikely to provide new information.

There are some limitations to this study. There may have been some degree of ascertainment bias for those studies that were not performed at the Chromosome 18 Clinical Research Center, such as echocardiograms and renal ultrasounds. For example, it is possible that only individuals with a heart murmur were referred for an echocardiogram, or that renal ultrasounds were performed on individual with recurrent urinary tract infections. Thus, there may be some minor heart or kidney defects that have gone undetected. Despite this limitation, this study serves as a critical step in the delineation of the natural history of tetrasomy 18p. This study represents the largest population of individuals with tetrasomy 18p reported to date and can provide some guidance in the management

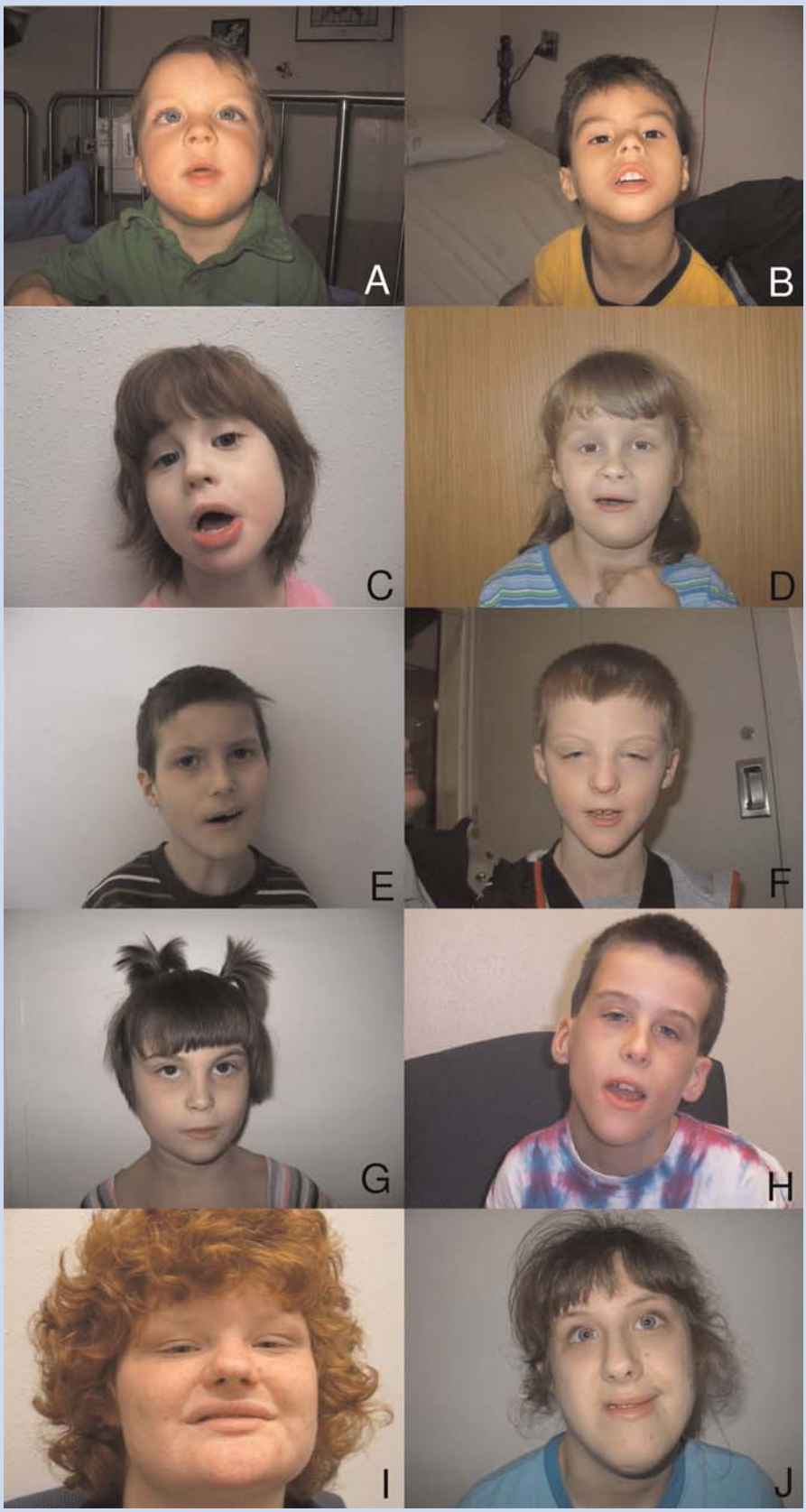

FIG. 1. Photographs of individuals with tetrasomy 18p at varying ages. A: 1 year 8 months, (B) 3 years 10 months, (C) 6 years 2 months, (D) 7 years 2 months, (E) 7 years 3 months, (F) 7 years 7 months, (G) 8 years 9 months, (H) 12 years 11 months, (I) 19 years, (J) 20 years 9 months.

- Genetics evaluation and counseling
- Parental chromosome analysis or FISH
- Periodic ophthalmology evaluation
- Periodic audiology evaluation
- ENT referral for management of chronic otitis media
- Cardiology evaluation
- Renal ultrasound
- Orthopedic evaluation for management of foot abnormalities
- Monitor for scoliosis and kyphosis
- Neurology evaluation for seizures
- Gastrointestinal/nutritional evaluation of failure to thrive, gastroesophageal reflux, constipation
- Endocrinology evaluation for short stature, to include evaluation for growth hormone deficiency
- Referral for developmental services and therapy

FIG. 2. Suggested Evaluations for Individuals with Tetrasomy 18p.

of affected individuals. Future studies include the analysis of the results of comprehensive developmental, behavioral, and neurocognitive evaluations conducted with our subject participants through the Chromosome 18 Research Center.

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