

# Recurrent Interstitial Deletions of Proximal 18q: A New Syndrome Involving Expressive Speech Delay

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Most deletions of the long arm of chromosome 18 involve some part of the most distal 30 Mb. We have identified five individuals with cytogenetically diagnosed interstitial deletions that are all proximal to this commonly deleted region. The extent of their deletions was characterized using molecular and molecular cytogenetic techniques. Each participant was assessed under the comprehensive clinical evaluation protocol of the Chromosome 18 Clinical Research Center. Three of the five individuals were found to have apparently identical interstitial deletions between positions of 37.5 and 42.5 Mb (18q12.3 → 18q21.1). One individual's deletion was much larger and extended from a more proximal breakpoint position of 23 Mb (18q11.2) to a more distal breakpoint at 43 Mb (18q21.1). The fifth individual had a proximal breakpoint identical to the other three, but a distal breakpoint at 43.5 Mb (18q21.1). The clinical findings were of interest because the three individuals with the smaller

deletions lacked major anomalies. All five individuals were developmentally delayed; however, the discrepancy between their expressive and receptive language abilities was striking, with expressive language being much more severely affected. This leads us to hypothesize that there are genes in this region of chromosome 18 that are specific to the neural and motor planning domains necessary for speech. Additionally, this may represent a previously underappreciated syndrome since these children do not have the typical clinical abnormalities that would lead to a chromosome analysis. © 2007 Wiley-Liss, Inc.

**Key words:** language delay; interstitial deletion; chromosome abnormality; chromosome 18; expressive language delay

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## INTRODUCTION

In genetic terms, deletions of the long arm of chromosome 18 are relatively common, with an incidence of 1 in 40,000. Most such individuals have terminal deletions; however, the breakpoints in these patients are extremely variable [Cody et al., 1997]. Regardless of whether 18q deletions are terminal or interstitial, most deletions lie within the distal 30 Mb (18q21.1 → qter) of the chromosome. The phenotype of these patients was described previously [Cody et al., 1999].

Proximal interstitial deletions involving the long arm between the centromere and the 46 Mb position are less common, with only 16 patients reported so far [Chudley et al., 1974, 1992; Wilson et al., 1979, 1989; Schinzel et al., 1991; Surh et al., 1991; Krasikov

et al., 1992; Poissonnier et al., 1992; McEntagart et al., 2001; Tinkle et al., 2003]. These individuals have a phenotype that is quite distinct from that of the

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individuals with deletions of the distal 30 Mb region (from 46 Mb → qter).

Phenotypic manifestations of these individuals include minor facial anomalies (frontal bossing, deep-set eyes, midface hypoplasia); several of these individuals also had brachycephaly. Hypotonia was also a common manifestation. Although most individuals did not have major congenital defects, some had genitourinary abnormalities, including hypospadias, cryptorchidism, genital hypoplasia, and a shawl scrotum. Seizures were common in these individuals. Mental retardation was reported to be in the moderate to severe range.

Though many of the deletions reported in the above references appear to have identical breakpoints, it must be noted that the precise breakpoints have not been confirmed molecularly. Indeed, many of these reports were published before such technology was available. Thus, molecular analysis may show that deletions previously thought to be the same actually have different breakpoints. Given advances in molecular genetic techniques, we are now better able to characterize genomic deletions. This is a crucial step in the identification of critical regions for certain phenotypic findings and, ultimately, in the delineation of genotype–phenotype correlations leading to the identification of genes involved in producing the phenotypic traits.

Of the 12 persons with interstitial deletions of 18q we have seen and evaluated, 5 have deletions in the proximal 18q region. Here we will present clinical and molecular data on these five patients. Such data are important for several reasons. From a clinical standpoint, these data will provide more information about the phenotype caused by proximal deletions. From the molecular perspective, recurring deletions may suggest an underlying characteristic of genomic architecture that predisposes to breakpoints in a certain region.

## MATERIALS AND METHODS

All five individuals included in this study were evaluated at the Chromosome 18 Clinical Research Center as a part of an ongoing study of individuals with chromosome 18 abnormalities. All the components of this study were approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio and are performed in conjunction with the Frederic C. Bartter General Clinical Research Center, Audie L. Murphy Veterans Hospital. All families were and continue to be involved in the informed consent process, which is documented appropriately.

### Clinical Evaluation

The gathering of the phenotypic data includes evaluations by multiple specialties, including

neuropsychology, psychiatry, neurotology, audiology, genetics, neurology, radiology, orthopedics, and endocrinology each using a standardized evaluation. None of the evaluations are considered experimental in nature. Four of the five had an MRI at the Chromosome 18 Clinical Research Center. This included T1 and T2 weighted images as well as 3D imaging [Kochunov et al., 2005; Lancaster et al., 2005]. A medical history was obtained and medical records from birth to age of diagnosis were obtained and reviewed on all five patients. Parents also completed the Gilliam Autism Rating Scale (PRO-ED, Austin, TX), the Behavioral Assessment System for Children, Second Edition (BASC-2) (AGS Publishing, Circle Pines, MN), and the Parental Stress Index (Psychological Assessment Resources, Inc., Odessa, FL). Cognitive ability was measured using the age appropriate assessments of either the Mullen (AGS Publishing) or the Differential Abilities Scales (DAS) (Psychological Corporation/Harcourt Assessment, San Antonio, TX).

All but one (Subject 138) were evaluated for growth hormone deficiency and thyroid dysfunction. The evaluation for growth hormone deficiency is made using standard clinical criteria [Hale et al., 2000]. This diagnosis relies on anthropomorphic measures and laboratory data.

Hearing was assessed using age appropriate sound booth audiometry. In addition, Auditory Brainstem Evoked Response (ABR) tests were performed.

### Molecular Analysis

Molecular analysis includes microsatellite PCR, quantitative PCR, and FISH using BAC clones as probes. Microsatellite PCR has been described previously [Cody et al., 1997].

Quantitative PCR was carried out using iQ-SYBR Green PCR Supermix with the iCycler iQ Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA). All samples were run in triplicate and quantification was performed using the  $\Delta\Delta C_t$  method. The fractional  $C_t$  values at which the amount of amplified target DNA reaches a fixed threshold is directly related to the amount of starting target DNA. The PCR primer sets were designed by us and their locations on chromosome 18 are shown in Table I (see the online Table I at <http://www.interscience.wiley.com/jpages/1552-4825/suppmat/index.html>).

FISH analysis was performed on metaphase spreads of participant lymphocytes. Chromosome 18 was identified using  $\alpha$ -satellite probes (Vysis, DesPlaines, IL). BAC clones used as FISH probes from the region of interest were identified by their location on chromosome

18 using the UCSC Genome Browser (<http://genome.ucsc.edu>) and NCBI Human Genome Resources (<http://www.ncbi.nlm.nih.gov>).

## RESULTS

### Molecular Results

The data are presented in Figure 1. The deletions of all children had a region of overlap and the three smaller deletions appear to be identical. This is the first instance of recurring breakpoints that we have seen involving 18q in our analysis of over 100 individuals with 18q deletions. Subject 129 has a 19.5 Mb deletion extending from a position at 23.5 to 43 Mb, Subject 140 has a 7.5 Mb deletion extending from a position at 37.5 to 45 Mb. The three participants who have identical 5 Mb deletions have breakpoints at positions 37.5 and 42.5 Mb.

We determined the parental origin of the chromosome with the deletion for each participant. The chromosome with the deletion was of maternal origin in Subject 129. In all the other participants the chromosome with the deletion was of paternal origin. This proportion is consistent with our parental origin data on individuals with terminal deletions of 18q.

### Clinical Results

As shown in Table II, the clinical presentation of these five patients varies significantly. The two individuals with the larger deletions had more medical complications than the others. Some generalizations may be suggested based on these data. Perhaps most notable is the lack of dysmorphic facial features. The anthropomorphic measures are shown in Table III. Major congenital defects were also not common in our population, although some genitourinary anomalies were reported and required surgery. Interestingly, in four of the five individuals, receptive language skills were better preserved than expressive language.

The average age of diagnosis was approximately 18 months. In all cases, the presenting concern that prompted chromosome analysis was developmental delay. In all five cases, the deletion appears to be a *de novo* event. Interestingly, two of our five mothers had amniocentesis on the affected pregnancy due to advanced maternal age; however, in both cases, the interstitial deletion was not identified suggesting that diagnosing this deletion in amniocytes can be difficult.

The behavioral findings are shown in Table IV. Three of the five children showed clinically significant difficulties in attention on the Behavioral Assessment System for Children (BASC) completed by their parents. These difficulties indicate problems with following directions, attending to a task for

more than a minute, and completing tasks. Two children showed clinically significant problems with overactivity. In addition, two of the three children showed significant signs of sadness scoring above the clinical cutoff for depression on the BASC. Two of the five children scored in the above average range on a measure indicating autistic symptoms (Gilliam Autism Rating Scale, GARS). Reviewing the pattern of scores on the GARS indicated significant problems with communication (three of five) and in developmental delays (three of five). These scores significantly inflated the probability of autism for these children and it is likely that the measure is indicating problems with verbal communication and delays in development rather than true autism. None of the five children showed scores in the significant range on a measure of social interaction, further supporting this suggestion that their social skills are not within the autistic spectrum. Cognitive ability for this group of five children averaged 68.2 using age appropriate scales. The detailed neuropsychological results are shown in Table V.

Several manifestations of the terminal 18q deletion phenotype were missing from this group of patients; as would be expected. None of these individuals had stenotic ear canals, cleft lip or palate, or growth hormone deficiency. Only one of the study patients had documented delayed myelination (Subject 140).

## CLINICAL REPORTS

### Participant: 18q-129

This male patient was born to a 33-year-old G<sub>2</sub>P<sub>1</sub> mother. Paternal age was 39 at delivery. The pregnancy was generally unremarkable, with the exception of a maternal sinus infection requiring antibiotics. Labor was induced at 40 weeks. The delivery was complicated by maternal hemorrhage, meconium staining, and fetal decelerations caused by a short umbilical cord. Forceps were required for the delivery. He weighed 2,806 g at birth, was 47 cm in length, and had a head circumference of 33.5 cm. He required supplemental oxygen for 10–15 min after birth. Apgars were 3 and 7 at 1 and 5 min, and 10 at 10 min. He had bilateral cryptorchidism and a minimal umbilical hernia. From birth, he had a history of feeding problems secondary to low muscle tone, suck-swallow coordination problems, tongue protrusion, and reflux. As a result of these feeding problems, he was diagnosed with failure to thrive. At 2 months, a skeletal survey was completed that showed no major skeletal anomalies. An echocardiogram completed at 4 months of age was normal. At 11 months, his feeding problems necessitated the placement of a G-tube and fundoplication. At 11 months, he was diagnosed with a seizure disorder that is currently treated by phenobarbital and Lamictal<sup>®</sup>. At approximately 1 year of age, he

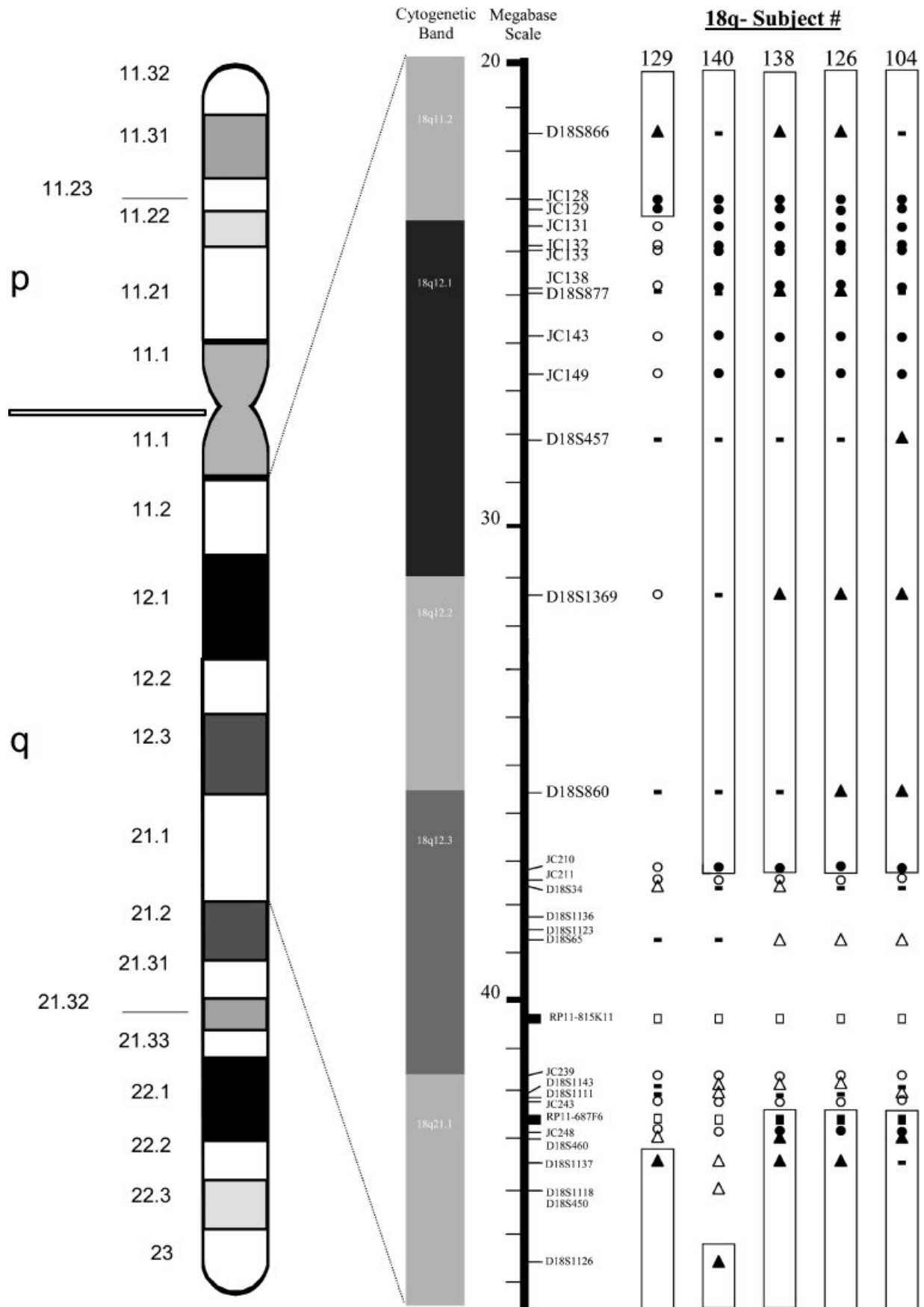


FIG. 1.

developed worsening obstructive sleep apnea, requiring a tonsillectomy and adenoidectomy with alveopalatal pharyngoplasty. He had PE tubes placed at 18 months due to recurrent otitis media. He had esotropia that was surgically corrected at 20 months. Other medical problems included several bouts with pneumonia; profound plagiocephaly requiring a helmet for correction, torticollis, eczema, and orthopedic anomalies requiring AFOs.

He had significant developmental delays. He rolled over at 7 months, sat independently at 9 months, crawled at 18½ months, and walked at 4 years. He started receiving Early Intervention Services at approximately 6 months of age, including speech, occupational, and physical therapy.

At 6 years 7 months, the patient was evaluated at UTHSCSA. An MRI showed a small corpus callosum and enlargement of both lateral ventricles and the third ventricle, possibly related to callosal hypoplasia. There was also fourth ventricle enlargement with some abnormal signal. Endocrinology evaluation was negative for growth hormone deficiency. Thyroid testing was also completed. TSH level was normal, but T4 was below normal. Neurological examination identified spastic cerebral palsy. Otologic examination did not show any structural defects, although he did have a large tongue. ABR showed a mild hearing loss bilaterally. It was suspected that this was primarily conductive hearing loss due to the presence of PE tubes.

#### Participant: 18q-140

The patient was born to a 39-year-old G<sub>2</sub>P<sub>1</sub> woman. There was maternal use of Zoloft<sup>®</sup>, Ambien<sup>®</sup>, and Zyrtec<sup>®</sup> as well as some social drinking in the first 2 or 3 weeks following conception. The pregnancy was further complicated by Rh incompatibility. An amniocentesis was performed secondary to advanced maternal age; the results were reported as 46,XY. A prenatal ultrasound showed hydronephrosis. Patient was born at 39 weeks gestation following a vacuum-assisted delivery. He weighed 3,175 g at birth and had Apgar scores of 8 at 1 min and 9 at 5 min. He required supplemental oxygen for several minutes after birth as well as phototherapy for jaundice. Shortly after birth, a voiding cystourethrogram identified bilateral Hutch diverticuli. For the first 7 months of life, he had feeding difficulties. These difficulties were attributed to oral motor delays, generalized hypotonia, and recurrent kidney infections, resulting in failure to thrive. However, following double ureter reimplantation at 7 months, his growth improved significantly. At 10 months of

age, plagiocephaly was noted, but did not require intervention. He had an MRI at 16 months that demonstrated hypoplastic corpus callosum and delayed myelination. A vision screen at 20 months was normal. He had a history of recurrent otitis media and had PE tubes placed at 22 months.

The patient sat without support at 8 months and walked alone at 20 months. He started receiving weekly physical therapy at 8 months and occupational and speech therapy between 12 and 18 months of age. At 12 months, an evaluation by a developmental pediatrician confirmed global developmental delays, with the most significant area of delay in prelinguistic language production. A feeding team evaluation at 15 months of age identified a continuing oral motor delay. Contributing factors included hypotonia and global developmental delays as well as an abnormal suckle transport pattern, resulting in food getting stuck to the roof of the mouth.

The patient was evaluated at UTHSCSA at 23 months of age. An MRI confirmed delayed myelination and a small corpus callosum and identified right-sided maxillary sinus disease, and bilateral mastoiditis. A mild hearing loss was detected on ABR, consistent with the presence of PE tubes. Otologic evaluation was otherwise normal. A neurology exam identified coordination and gait difficulties as well as ptosis and decreased reflexes. The endocrinology evaluation was negative for growth hormone deficiency. Total T3 and T4 as well as TSH levels were normal.

#### Participant: 18q-138

This female patient was born to a 37-year-old G<sub>2</sub>P<sub>1</sub> mother. Paternal age was 35. The pregnancy was complicated by maternal hypothyroidism treated with Synthroid<sup>®</sup>. The mother underwent an amniocentesis due to advanced maternal age; the results were reported as 46,XX. The patient was born at 41 weeks following labor induction. The delivery was complicated by meconium staining. The patient's birth weight was 3,770 g, and she required supplemental oxygen immediately following birth. However, Apgar scores were 9 at 1 min and 10 at 5 min. For several weeks after birth, she had problems with breast feeding due to a decrease in lingual, labial, and buccal strength and coordination secondary to low tone. Feeding was also complicated by a partial tongue tie, a high palate, and a slightly short frenulum. She developed febrile seizures at approximately 16 months of age. These later developed into complex seizures that are currently managed by Keppra<sup>®</sup>. She had a history of blunt head trauma at 26 months, and a follow-up CT scan was normal.

FIG. 1. The deleted region is depicted for each participant showing a subset of the data acquired. The subject numbers are above each box that indicates the intact part of the chromosome. Circles represent the Q-PCR data with open circles indicating one allele and closed circles indicating two alleles. Triangles represent microsatellite PCR data with open triangles representing one allele and closed triangles representing two alleles. The squares represent the FISH data with open squares representing one allele and closed squares representing two alleles.

TABLE II. Phenotypic Features

Patient number	129	140	138	126	104	UTHSCSA patient summary	Literature review	Total
Deleted	46,XY,del(18)(q11.2q21.1)	46,XY,del(18)(q12.2q21.1)	46,XX,del(18)(q12.2q21.1)	46,XX,del(18)(q12.3q21.1)	46,XY,del(18)(q12.2q21.1)			
M/F	M	M	F	F	M			
Age at UTHSCSA eval	6 years 7 months	23 months	4 years 5 months	6 years 1 month	3 years 10 months			
Age at diagnosis	4.5 months	18 months	2 years 7 months	17 months	19 months			
C-section vs. SVD	SVD	SVD	SVD	SVD	SVD			
GA at delivery	40 weeks	39 weeks	41 weeks	39 weeks	38 weeks			
Birth weight	2,806 g (10th–25th)	3,175 g (10th–25th)	3,770 g (75th–90th)	3,430 g (50th–75th)	2,722 g (3rd–10th)	Full term		
Apgar (1.5)	UK <sup>b,c</sup>	8,9 <sup>b</sup>	9,10 <sup>c,d</sup>	8,9 <sup>c,d,e</sup>	8,9 <sup>f</sup>	Avg. 3,181 g	Avg. 3,017 g	Avg. 3,072 g
Birth complications								
Postpartum O <sub>2</sub> required	+	+	+	+	–	4/5		
Birth defects	Cryptorchidism	Hutch diverticuli	–	–	–	2/5	4/17	6/22
Failure to thrive	+	+	–	–	–	2/5	1/17	3/22
Hypotonia	+	+	+	+	+	5/5	8/17	12/22
Seizures	+	–	+	–	–	2/5	10/17	12/22
Vision	+	–	–	+	–	2/5	11/17	13/22
Hearing loss	+	+	–	–	–	2/5	0/17	2/22
Recurrent otitis	+	+	–	–	–	2/5	3/17	5/22
Recurrent URI	+	–	–	–	–	1/5	2/17	3/22
GH deficiency	–	–	a	–	–	0/5	0/17	0/22
Obesity	–	–	–	–	–	0/5	3/17	3/22
GU abnormalities	+	+	–	–	–	2/5	2/17	4/22
Delayed myelination	–	+	–	–	–	1/5	1/17	2/22
Other MRI findings	+	+	–	–	–	2/5	1/17	3/22
Developmental delays	+	+	+	–	–	2/5	1/17	3/22
# hospitalizations by age	13 by 6.5 years	1 by 23 months	0 by 3 years	0 by 6 years	0 by 3 years 9 months	5/5	17/17	22/22
Other	g	h			i			

UK-unknown.  
<sup>a</sup>Has not had laboratory evaluations to screen for growth hormone deficiency.  
<sup>b</sup>Vacuum or forceps assistance required.  
<sup>c</sup>Meconium staining.  
<sup>d</sup>Difficulty with breast feeding.  
<sup>e</sup>Difficulty in regulation of body temperature.  
<sup>f</sup>Maternal fever.  
<sup>g</sup>G-tube placed at 11 months; profound plagiocephaly (required helmet); foot anomaly requiring AFOs; sleep apnea.  
<sup>h</sup>Plagiocephaly; mild ptosis.  
<sup>i</sup>Brachycephaly.  
 Chudley et al., 1974; Wilson et al., 1979; Wilson and Al Saadi, 1989; Schinzel et al., 1991; Surh et al., 1991; Chudley et al., 1992; Krasikov et al., 1992; Poissonnier et al., 1992; McEntagart et al., 2001; Tinkle et al., 2003; Kotzot, 2005.

TABLE III. Anthropomorphic Measurements for Four Individuals With Interstitial Deletions of 18q

	129	140	126	104
Age	6 years 7 months	23 months	6 years 1 month	3 years 9 months
Height (cm)	108 <sup>a</sup> (<3rd)	89.2 (75th)	111.5 (10–25th)	97 (~50th)
Weight (kg)	26.9 (90th)	14 (75th–90th)	22.4 (50th–75th)	17.2 (50–75th)
OFC (cm)	51.5	NA	51.8	52
Inner canthal distance	2.6 (–1 to –2 SD)	2.3 (–1 to –2 SD)	2.5 (–1 to –2 SD)	3.1 (+1 to +2 SD)
Outer canthal distance	7.6 (<–2 SD)	NA	7.5 (<–2 SD)	7.9 (–1 to –2 SD)
Right palpebral fissure (cm)	2.5 (–1 to –2 SD)	NA	2.5 (–1 to –2 SD)	2.4 (–1 SD)
Left palpebral fissure (cm)	2.5 (–1 to –2 SD)	NA	2.5 (–1 to –2 SD)	2.4 (–1 SD)
Right ear (cm)	5.6 (50th to 1 SD)	5.2 (+1 SD)	5.8 (+1 to +2 SD)	5.1 (–1 SD to 50th)
Left ear (cm)	5.7 (50th to 1 SD)	5.2 (+1 SD)	6.0 (+1 to +2 SD)	5.3 (50th to +1 SD)
Philtrum length (cm)	1.5 (50th)	NA	1.2 (3rd–25th)	1.4 (50th)
Other features	Right posterior whorl; coarse hair; left occipital flattening; ptosis	Right-sided posterior whorl; mild ptosis; smooth philtrum	None noted	None noted

NA—not available.

Source: Hall et al. [1989]. Handbook of Normal Physical Measurements.

<sup>a</sup>With knees slightly bent.

An MRI completed at 31 months was normal. At 34 months, an ABR and tympanometry were performed and were both normal. Lastly, there is a history of skin problems, including scabies, contact dermatitis, and seborrhea. Per parental report, the patient had no history of vision abnormalities. She has never been evaluated for growth hormone deficiency.

Developmentally, the patient sat alone at 6 months and rolled over at 7 months. She crawled at 12 months, cruised at 14 months, and stood without support and walked at 19 months. She spoke her first word at 12 months. She received speech, occupational, and physical therapy on a weekly basis starting at approximately 24 months. A speech-language evaluation at 27 months identified a moderate-to-severe expressive communication/language disorder, based on the MacArthur Communicative Development Inventory: Words and Gestures. At 30 months, a second evaluation by a developmental pediatrician indicated that while receptive skills were actually advanced, expressive communication skills were delayed by approximately 1 year. During this evaluation, the patient was diagnosed with oral apraxia.

### Participant: 18q-126

This female was born to a 26-year-old G<sub>2</sub>P<sub>1</sub> mother; the father was 25 years old at time of the delivery. The patient was born at 39 weeks, 5 days and weighed 3,442 g. The delivery was complicated by the passage of meconium during labor. The patient required supplemental oxygen for several minutes following birth. She also had a low core body temperature that was responsive to a warmer. She had Apgar scores of 8 at 1 min and 9 at 5 min. The neonatal period was characterized by colic and feeding problems; she had poor tongue movement and a tendency to pool food in the mouth. Hypotonia was also noted during childhood and was thought to contribute to the patient's developmental delays. Starting at 19 months, she required AFOs secondary to the hypotonia. Based on repeated visually reinforcement audiometry evaluations, she had normal hearing. At 21 months of age, an ataxic gait was noted. Per the parents' report, a vision test showed a mild myopia.

Developmentally, the patient had global delays. She rolled over at 9 months of age; sat between

TABLE IV. Behavioral Rating Scale and Cognitive Ability Performance Scores

Psychological instrument/ scale	Average performance score range	129	140	138	126	104
BASC/attention scale	T-score (40–60)	NA	NA	80	68	71
BASC/over activity scale	T-score (40–60)	NA	NA	57	73	67
BASC/depression scale	T-score (40–60)	NA	NA	62	48	69
GARS	Standard score range (90–110)	88	65	65	85	67
Mullen	Standard score (85–115)	55	83	70	NA	61
DAS/nonverbal ability score	Standard score (85–115)	NA	NA	NA	72	NA
DAS/spatial ability score	Standard score (85–115)	NA	NA	NA	56	NA

BASC, Behavior Assessment System for Children; GARS, Gilliam Autism Rating Scale; Mullen, Mullen Scales of Early Learning; DAS, Differential Ability Scales, NA, not available or not applicable.

GARS, The standard score range depicted in the table reflects the score values within the Average Probability of Autism.

TABLE V. Neuropsychological Results

	129	140	138	126	104
Age at evaluation	79 months	23 months	53 months	73 months	45 months
Mullen Scales of Early Learning					
Gross motor (age equivalent)	16 months	17 months	28 months	a	22 months
Visual reception (age equivalent)	14 months	20 months	45 months	a	21 months
Fine motor (age equivalent)	16 months	18 months	30 months	a	22 months
Receptive language (age equivalent)	23 months	22 months	42 months	a	31 months
Expressive language (age equivalent)	16 months	6 months	51 months	a	12 months
Vineland Adaptive Behavior Scale					
Communication (percentile)	<0.1	7th	82nd	<0.1	<0.1
Daily living skills (percentile)	<0.1	3rd	1st	0.1	<0.1
Socialization (percentile)	<0.1	18th	70th	6th	<0.1
Motor skills (percentile)	b	19th	10th	b	<0.1
Adaptive behavior (percentile)	<0.1	5th	25th	0.1	<0.1
Bayley					
Mental scale (age equivalent)	a	18 months	a	a	a
Motor scale (age equivalent)	a	16 months	a	a	a

a—Scale not utilized during the neuropsychologic evaluation.

b—Subscale not completed.

18 and 24 months, and stood and walked independently at approximately 24 months. An evaluation by a developmental pediatrician at 21 months indicated global delays. However, based on the Preschool Language Skill-3 Scale, her expressive language was her largest deficit, suggesting developmental apraxia of speech. She had also been diagnosed with ADHD. She started receiving speech, occupational, and physical therapy at approximately 14 months of age.

The patient was evaluated at UTHSCSA at the age of 6 years, 1 month. MRI was normal. Otologic examination and ABR were also normal. An endocrinology evaluation did not identify growth hormone deficiency. In addition, she had normal T4, TSH, and prolactin levels.

#### Participant: 18q-104

This male was born to a 34-year-old G<sub>1</sub>P<sub>0</sub> mother following a pregnancy complicated by maternal hypertension and flu. A prenatal ultrasound revealed concern for hydronephrosis. Paternal age at delivery was 37 years. The patient was born at 38 weeks gestation weighing 2,722 g, and birth length was 44.5 cm. The delivery was complicated by a maternal fever. He had Apgar scores of 8 at 1 min and 9 at 5 min. In the first week of life, he had some transient feeding difficulties that resolved without intervention. A renal ultrasound performed at 1 month revealed no abnormalities. During infancy, he was noted to have mild to moderate hypotonia in the trunk and all four extremities, possibly contributing to developmental delays. At 4 months, brachycephaly was noted and required a dynamic orthotic cranioplasty band. At 20 months, a bone age study showed a bone age of between 6 and 12 months. Other medical complications included recurrent ear infections, which required the placement of PE tubes at 3 years and 1 month. At 1 year

4 months, he had an MRI with no structural abnormalities.

The patient sat without support at 8 months of age and rolled at 10 months. He started crawling at approximately 17 months. At 17 months, the patient started receiving early intervention services, including speech, physical, and occupational therapy on a weekly basis. These services have continued to the present day. At 24 months, a developmental evaluation indicated persistent global deficits. A slight discrepancy was noted between receptive and expressive language skills, with receptive skills being better preserved.

The patient visited UTHSCSA on two separate occasions, the most recent being at the age of 3 years and 9 months. At this age, an MRI revealed normal myelination as well as mild, right-sided mastoiditis. Behavioral audiometry indicated normal hearing. Otologic examination identified no structural abnormalities. An endocrinology evaluation did not identify a growth hormone failure, and he had normal T4 and TSH levels.

#### DISCUSSION

We have described five children with deletions of 18q whose deletions are proximal to the more commonly deleted terminal 30 Mb region of 18q. Of the 106 individuals in our study with deletions of 18q that involve no other chromosome, 94 (89%) have terminal deletions. Of the 12 with interstitial deletions, 5 have deletions that are within the proximal long arm; above the 46 Mb position. Three of the five children have the apparently identical breakpoints as identified by molecular and molecular cytogenetic techniques. This is the first time we have seen more than one individual with the same breakpoints within 18q.

This leads us to hypothesize that there may be other individuals in whom this deletion was not found. That is because children with no major anomalies, severe speech delay, and hyperactivity are not typically tested for chromosome abnormalities. If this deletion of 18q accounts for even a small percent of the cause of speech delay, then this may not be a rare condition. It should also be noted that two of these children were described as having a normal karyotype by amniocentesis. So a normal amniocentesis result would not negate the need to do a chromosome analysis on a child with significant speech delay.

Several regions of the genome have been identified that are prone to interstitial deletions and the reciprocal duplication; 7q11.23 [Somerville et al., 2005], 17p11.2 [Lupski and Stankiewicz, 2005], and 22q11.22 [McDermid and Morrow, 2002]. This leads us to ask if there may be an unidentified syndrome caused by the duplication of this region of 18q.

The elucidation of genetic determinants of language acquisition and expression has been elusive. Disruptions of the *FOXP2* gene were identified in individuals with verbal dyspraxia [Lai et al., 2001]. More recently an individual with severe speech impairment was identified with a chromosome deletion including the *FOXP2* gene [Zeesman et al., 2006]. This demonstrates that the process of verbalization is sensitive to gene dosage and that haploinsufficiency can be a mechanism. Considering that speech and language impairment are relatively common, the identification of genes involved in this process is important.

There are 15 known genes in this region of 18q, several of which are predominantly expressed in the brain. Little is known about the function of most of these genes, which includes *RIT2*, *SETBP1*, *ATP5A1*, *ST8SIA5*, and *SYT4*. The most is known about Synaptotagmin IV (*SYT4*) which codes for a synaptic vesicle protein involved in presynaptic modulation of neurotransmission [Ting et al., 2006].

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