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# Whole Arm Deletions of 18p: Medical and Developmental Effects

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Deletions of the short arm of chromosome 18 have been well-described in case reports. However, the utility of these descriptions in clinical practice is limited by varied and imprecise breakpoints. As we work to establish genotype–phenotype correlations for 18p-, it is critical to have accurate and complete clinical descriptions of individuals with differing breakpoints. In addition, the developmental profile of 18p- has not been well-delineated. We undertook a thorough review of the medical histories of 31 individuals with 18p- and a breakpoint in the centromeric region. We collected developmental data using mailed surveys and questionnaires. The most common findings included neonatal complications; cardiac anomalies; hypotonia; MRI abnormalities; endocrine dysfunction; strabismus; ptosis; and refractive errors. Less common features included holoprosencephaly and its microforms; hearing loss; and orthopedic anomalies. The developmental effects of the deletion appear to be less severe than reported in the literature, as average IQ scores were in the range of borderline intellectual functioning. Based on responses to standardized questionnaires, it appears this population has marked difficulty with activities of daily living, though several young adults were able to live independent of their parents. This manuscript represents the most comprehensive description of a cohort of 18p- individuals with identical breakpoints. Despite identical breakpoints, a great deal of phenotype variability remained among this population, suggesting that many of the genes on 18p- cause low-penetrance phenotypes when present in a hemizygous state. Future efforts will focus on the clinical description of individuals with more distal breakpoints and the identification of critical regions and candidate genes. 

**Key words:** 18p-; deletion 18p; chromosome 18

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## INTRODUCTION

Deletions involving the short arm of chromosome 18 have been well-described in the literature. Turleau has most recently reviewed this condition, the primary features of which include cognitive impairment of varying severity, speech delay; short stature, holoprosencephaly; ptosis; pectus excavatum; and kyphoscoliosis [Turleau, 2008]. Pituitary hormone deficiencies have also been reported [Leisti et al., 1973; Artman et al., 1992; Portnoi et al., 2007]. Characteristic dysmorphic features include a depressed nasal bridge; wide mouth with short upper lip; small mandible; large, protruding ears; and a short, webbed neck. The underlying molecular basis of 18p- has been described by Schaub et al. [2002]. The majority of individuals have a breakpoint within the pericentromeric region of the chromosome.

However, it is important to note that much of the clinical and molecular characterization of this condition occurred before the widespread use of microarray analysis. Many of the early case reports that form the basis of the phenotypic description did not report breakpoints [Leisti et al., 1973; Jacobsen and Mikkelsen, 1968; Jones and Carey, 1982]. In addition, when breakpoints were reported, they varied significantly and are less precise than breakpoints defined by microarray [Fryns et al., 1986; Kanjilal et al., 1988]. This has limited the ability to identify genotype–phenotype correlations, a necessary step in providing genotype-specific information to families with a diagnosis of 18p-.

We have undertaken a thorough review of the medical and developmental findings of individuals with 18p- who have a

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breakpoint at the centromere. The ultimate goal of this project is to describe the phenotype associated with a centromeric breakpoint more thoroughly, providing a clinical picture of a large, molecularly similar cohort. This information will provide a baseline for comparison to individuals with non-centromeric breaks, a critical step in establishing genotype–phenotype correlations for 18p-.

## MATERIALS AND METHODS

### Study Participants

All study participants are enrolled in a large longitudinal research program at the Chromosome 18 Clinical Research Center. Eligibility criteria for the study reported here included a diagnosis of 18p- confirmed by a routine karyotype. In some cases, this was the result of an unbalanced translocation with an acrocentric chromosome. In these instances, microarray CGH confirmed that there were no additional gains or losses. 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. Individuals with a breakpoint between 14,953,043 and the centromere are reported here. In addition, parental origin of the abnormal chromosome was also determined as previously described using PCR-based polymorphic microsatellites [Cody et al., 1997].

### Collection of Medical History

***Chart review and family interview.*** Medical records were obtained from all participants. All available records were reviewed in detail. Following the record review, the families were contacted by an investigator to confirm the medical history and to provide any new information. 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.

***UTHSCSA evaluations.*** In addition to the chart review, four individuals came to San Antonio for additional clinical evaluations. The gathering of phenotypic data included evaluations by multiple specialties, including audiology, genetics, 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 post-pubertal individuals. Participants also had brain MRI's. Hearing was assessed using sound booth audiometry and/or an Auditory Brainstem Evoked Response (ABR). These records were used in the medical record review process.

### Collection of Developmental Data

Cognitive ability data were collected by obtaining psychological reports from the parents/guardians of the study participants. These assessments were performed in the participant's hometown by a licensed psychologist. Multiple test instruments were used. The instrument choice was dependent upon the age and ability of the person being tested. Instruments used included: Bayley Scales for Infant Development, 2nd Edition; Differential Ability Scales; Mullen Scales of Early Learning; Wechsler Intelligence Scale for Children, 4th edition; Wechsler Intelligence Scale for Children, Gurjati adaptation; Wechsler Intelligence Scale for Children, 3rd edition, Australian adaptation; Wechsler Adult Intelligence Scales, 3rd edition; Wechsler Abbreviated Scale of Intelligence; Wechsler Preschool and Primary Scale of Intelligence, 3rd edition; Wechsler Preschool and Primary Scale of Intelligence, 3rd edition, UK adaptation; and Stanford-Binet Intelligence Scale, 4th edition [Elliott, 1990; Bayley, 1993; Mullen, 1995; Wechsler, 2003a; Bhatt, 1971; Wechsler, 1993; Wechsler, 1997; Wechsler, 1999; Wechsler, 2003b; Thorndike, 1986]. All measures of cognitive ability are rigorously standardized instruments with excellent psychometric properties. Internal and test-retest reliabilities for the summary cognitive indices used in this study typically range from high 80s to high 90s with all instruments having demonstrated clinical validity with special populations including those with developmental delay and cognitive impairment.

In addition to collecting reports on cognitive abilities, we sought an estimate of executive functioning. Parents were asked to complete and return the Behavior Rating Inventory of Executive Function, Parent Form – BRIEF or the Behavior Rating Inventory of Executive Function – Adult Version, Informant Report – BRIEF-A [Gioia et al., 2000; Roth et al., 2005].

To obtain a measure of adaptive behavior functioning and social emotional development, we collected standardized behavioral questionnaire(s) from parents of study participants. The choice of behavioral questionnaire was based on the chronological age of the child and included the following instruments: Vineland Adaptive Behavior Scales, Second Edition and the Adaptive Behavior Assessment System, Second Edition (ABAS-II) [Harrison and Oakland, 2003; Sparrow et al., 2005]. Additionally, to investigate the prevalence of maladaptive behavior, we requested that parents complete the Behavioral Assessment System for Children, Second Edition (BASC-2) [Reynolds and Kamphaus, 2004]. All of the behavioral questionnaires chosen are well-normed instruments with demonstrated reliability and validity information provided by the test publishers and by post-publication validation studies.

The probability of autism spectrum disorder was assessed by parental report using the Gilliam Autism Rating Scale (GARS) or

the Gilliam Autism Rating Scale-Second Edition (GARS-2) and the Gilliam Asperger's Disorder Scale (GADS) [Gilliam 1995; Gilliam 2006; Gilliam 2001]. On the GARS/GARS-2 the following domains are evaluated: presence of stereotyped behaviors, social interaction problems, developmental delay (present only in the GARS), and communication difficulties. On the GARS, coefficient alpha estimates range from 0.88 for developmental delay to 0.96 for the overall Autism Quotient. On the GADS, the following domains are evaluated: social interaction problems, restricted patterns of behavior, problems with cognitive patterns and difficulty with pragmatic skills.

# RESULTS

## Molecular Results

Of the 91 individuals enrolled in the 18p- study, 34 had breakpoints in the centromeric region of chromosome 18. One participant did not have records available in English and was eliminated from this report. Eleven of the remaining individuals had 18p- as the result of an unbalanced translocation involving an acrocentric chromosome. On microarray analysis, none of these had copy number changes on other chromosomes. The unbalanced translocation was confirmed to be de novo in seven of the 11 translocation carriers. The mother of 57C1 and 57C2 was found to be a carrier of a balanced 18:21 translocation. Parental chromosome results were not available for the remaining two individuals, both of whom have been lost to contact.

While none of the translocation carriers had copy number changes on other chromosomes, two did have duplications on 18q in addition to an 18p deletion. Individual 13C had a duplication extending from 75,045,066 to 75,055,432. Individual 57C1 had a duplication extending from 23,946,309–23,948,752 to 23,957,974–23,960,037. To ensure homogeneity within the population, these two individuals were removed from the analysis.

Parental origin analysis indicated that sixteen of the abnormal chromosomes were of maternal origin, ten were of paternal origin, and the remaining five could not be determined, either due to missing parental samples or uninformative results (Table I).

## Medical History

There were 31 individuals who met the molecular criteria for the study and who also had medical records available in English. We attempted to contact the families to review medical history and obtain additional information. However, not all surveys and interviews were able to be completed by every family. In instances where the family was unavailable for interviews, information was obtained from the medical records provided at the time of enrollment. Four of the study participants were also evaluated in person at the Chromosome 18 Clinical Research Center in San Antonio as a part of the research study.

The final cohort included 17 females and 14 males. The average birth weight was 2872.78 grams, and the average birth length was 48.0 cm. At the time of the study participants' birth, the average maternal age was 32.4 years and the average paternal age was 33.4 years. Table I lists the features identified in this cohort by study participant number. A list of the most common findings and their prevalence within our study population is shown in Table II.

***Neonatal complications.*** Twenty-two patients had complications in the neonatal period, with the most common being jaundice, respiratory difficulties, and feeding problems. Several additional findings were reported in a small number of people or single individuals, including meconium staining, bradycardia, tachypnea, hypoglycemia, urosepsis, nuchal cord, and abdominal swelling of unknown etiology.

***Cardiac abnormalities.*** Sixteen individuals had undergone an echocardiogram. Seven had completely normal evaluations. Abnormalities detected in the other patients include tetralogy of Fallot (2), VSD (2), an ASD, pulmonary stenosis, mild aortic valve abnormality (2), trivial tricuspid regurgitation, and a PFO. One individual had an unspecified type of septal defect that reportedly closed on its own. This individual was 56 years old at the time of the study, and records clarifying the type of defect were no longer available.

***Neurologic abnormalities.*** *Seizures.* Four had seizures. One had infantile spasms; two had grand mal seizures; and one had partial-complex seizures. An additional patient had febrile seizures as an infant.

*Tone abnormalities.* Hypotonia was very common in our population. Twenty-three of 31 had hypotonia. An additional four had mixed muscle tone abnormalities (truncal hypotonia with hypertonia of the extremities).

*MRI abnormalities.* Of the 15 individuals that had undergone cranial MRI's, five had normal studies. Two were identified with delayed myelination, one of whom was also diagnosed with a hypoplastic pituitary stalk. Septo-optic dysplasia was identified in one individual. One patient had lobar holoprosencephaly. Two patients had large ventricles. Four had white matter abnormalities, and another had a CSF cystic area in the occipital horn as well as a "large pituitary". Lastly, two had areas of increased signal.

*Holoprosencephaly.* As mentioned above, only one individual in our study population had been identified with incomplete separation of the hemispheres of the brain. However, three had a single central incisor while another had a coloboma, both known, microforms of holoprosencephaly.

***Orthopedic abnormalities.*** Isolated scoliosis was identified in four individuals and kyphosis in one. Pectus excavatum was diagnosed in seven individuals. There was one individual with a congenital kyphosis and pectus excavatum, most likely related to the presence of a T12 hemivertebrae. One individual had congenital hip dysplasia. Two participants had sacral agenesis. One person had a valgus deformity of the elbow. Genu recurvatum and genu valgus were each diagnosed in one person. Pes planus was identified in six, while pes cavus was identified in one. Two had mild 2–3 syndactyly of the toes.

***Gastrointestinal abnormalities.*** The most common GI abnormality was chronic constipation, which was identified in ten people. Four had reflux. Hernias were also fairly common. Two had hiatal hernias; three had inguinal hernias; and four had umbilical hernias. Three had been diagnosed with diastasis recti, and an additional two had a proximally placed anus.

***Genitourinary abnormalities.*** Cryptorchidism was identified in two of the fourteen males, while an additional two had

## TABLE I. Clinical Features of Study Cohort

| | Neonatal Complications | | | | Cardiac | Neurologic | | | | Orthopedic | | | | Gastrointestinal | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Jaundice | Respiratory difficulties | Feeding difficulties/FTT | Other | Echocardiogram findings | Holoprosencephaly Findings | Other MRI findings | Seizures | Hypotonia | Mixed | Scoliosis/kyphosis | Pectus excavatum | Pes planus | Other | Reflux | Constipation | Other |
| 1C | | | | hypoglycemia | * | | abnmyelination; hypoplastic pituitary stalk | - | + | | - | | | congenital hip dysplasia | | | anterior anus |
| 2C | | | | anemia | * | | † | - | + | | S | + | | | + | | HH |
| 3C | + | | | | * | | † | - | + | | S | | | | | | IH |
| 4C | | | | meconium staining | WNL | | WNL | - | | + | - | | + | | | | food allergies |
| 7C | + | | + | transient hypoglycemia; TTN | * | SCI | WNL | - | + | | - | | | | | | |
| 8C | | | | | * | | white matter lesion | - | - | | - | | | | | | |
| 10C | + | | | | * | | small CSF cystic area | - | + | | - | | + | | | | UH |
| 11C | | | | | aortic valve defect | | † | - | + | | - | | | | | | |
| 12C | | | + | | * | | † | - | + | | - | | | | | + | |
| 14C | | | + | | WNL | | † | - | - | + | S | + | + | valgus elbow deformity | | | IH |
| 16C | | | | | TOF | | † | - | - | | - | + | | | | | |
| 21C | + | | + | | * | | † | - | + | | - | | | | | + | UH |
| 23C | | + | | urosepsis | membranous VSD | | white matter hyperintensities; large 4th ventricle; abnormal corpus callosum; small pituitary | + | - | + | - | | | genu recurvatum | | + | |
| 26C | | + | + | | PFO; trivial tricuspid regurgitation | HPE | no additional abnormalities | + | + | | - | + | | sacral agenesis | | + | UH; diastasis recti |
| 32C | | + | + | | * | | WNL | - | + | | - | | + | genuvalgus; metatarsus | | | |
| 33C | | | | hypoglycemia | * | SCI | SOD | - | + | | - | + | | | | | |
| 34C | | | | | Conoventricular heart defect | | † | - | + | | S | + | | | | | diastasis recti |
| 36C | + | | | | WNL | | WNL | - | + | | - | | | sacral agenesis | | + | anterior anus |
| 37C | + | | + | | * | | † | - | + | | - | + | | pes cavus | | | |
| 39C | | | | | WNL | | † | - | + | | - | | | | | | |
| 40C | | | | | Septal defect | | † | - | - | | K | + | | | | | HH |
| 41C | | | | nuchal cord | * | | † | - | - | | - | | | | | + | |
| 45C | + | + | + | | * | | large ventricles, white matter abnormalities | + | + | | - | | | | + | + | |
| 50C | + | | | | WNL | | delayed myelination; increased signal in white matter | - | + | | - | | | | | + | |
| 57C2 | | | | | * | | † | - | + | | - | | | | | | |
| 58C | + | + | | | TOF | SCI | † | Febrile | + | | - | | + | | | | |
| 59C | | + | + | abdominal swelling | WNL | | T2 hyperintensities | + | + | | - | | + | genu recurvatum | + | + | UH; diastasis recti |
| 67C | | | | | * | | † | - | + | | - | | | | + | + | |
| 69C | | | + | | ASD; pulmonary artery stenosis | | WNL | - | + | | - | | | | | | |
| 76C | | | | | WNL | | † | - | - | | | | | | | | |
| 77C | | + | | slow heart rate | abnormal aortic root with dilated aortic valve | | White matter lesions | - | - | + | K | + | | T12 hemivertebrae | | | IH |

TTN=transient tachypnea of the newborn

TOF=Tetralogy of Fallot
ASD=Atrial septal defect
VSD= Ventricular septal defect
PFO=Patent foramen ovale
*No echocardiogram completed*

HPE=holoprosencephaly
SCI=single central incisor
SOD=septo-optic dysplasia
*†=no MRI completed*

S=scoliosis
K=kyphosis

IH=inguinal hernia
HH=hiatal hernia
UH=umbilical hernia

TABLE I. (*Continued*)

| | ENT/Vision | | | | | Endocrinology | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Hearing Loss | Strabismus | Refractive errors | Ptosis | Other | GH deficiency | Thryroid anomalies | Other | Additional Findings | Parental Origin |
| 1C | - | + | A | + | | + | | | IgA deficiency during childhood | P |
| 2C | + | + | M,A | | | | | | | M |
| 3C | - | + | + | + | | | | | | M |
| 4C | + | + | H,A | + | | + | | | | M |
| 7C | + | + | H,A | + | | + | hypothyroidism | ACTH deficiency | lupus; death at 22 years due to complications from pneumonia | M |
| 8C | - | | | | | | | | | P |
| 10C | + | + | M | | | | | | psoriasis | P |
| 11C | - | | H | + | congenital cataracts | | | | | M |
| 12C | - | + | A | + | | | | Precocious puberty | | M |
| 14C | + | + | H | + | | | | | cryptorchidism | P |
| 16C | - | | | | congenital cataracts | | | | | P |
| 21C | - | + | | + | | + | hypothyroidism | | IgG deficiency requiring treatment | P |
| 23C | + | + | + | M,A | + cortical visual impairment | + | | | obstructive sleep apnea | M |
| 26C | - | | | | | + | | ADH deficiency | | M |
| 32C | - | + | + | | nystagmus | | | | mild IgA deficiency | M |
| 33C | - | | + | H | + ONH | + | hypothyroidism | ACTH deficiency; absent ovaries | | P |
| 34C | - | + | + | | + | | Graves' disease | | | M |
| 36C | - | | | N | + | + | | | recurrent UTI's; syrinx | M |
| 37C | - | + | | | + iris coloboma | | multinodular goiter | | | M |
| 39C | + | + | | | + | + | | | | ? |
| 40C | - | | + | | | | | | | ? |
| 41C | - | + | + | H,A | + | | | | | ? |
| 45C | - | + | + | H | | + | | | cryptorchidism | M |
| 50C | - | | + | H,A | N | | | | | P |
| 57C2 | - | | | | | | | | | M |
| 58C | - | | | | N | | | | choanal stenosis | ? |
| 59C | - | + | + | H,A | N ONH | + | hypothyroidism | | | M |
| 67C | - | | + | M,A | N | | | | | P |
| 69C | - | | + | | + nystagmus | | | | | M |
| 76C | - | + | | | + | | | | | P |
| 77C | - | + | + | H,A | + | | | | hydrocele; mild IgA and IgM deficiencies | ? |

M=myopia
H=hyperopia

UTI=urinary tract infection

M=maternal
P=paternal

hydroceles. Seven patients had undergone renal ultrasounds, and none had a kidney abnormality.

***Hearing loss.*** Seven people had been diagnosed with hearing loss. Seventeen had chronic otitis media, twelve of whom required placement of PE tubes.

***Ophthalmologic abnormalities.*** Strabismus was quite common and had been identified in thirteen individuals. Sixteen had refractive errors. Eleven had astigmatism; four had myopia; and ten had hyperopia. One person had anisometropia. Ptosis was present in thirteen individuals, many of whom required surgical correction. Other ophthalmologic abnormalities noted included: congenital cataracts (2); nystagmus (2); iris coloboma (1); optic nerve hypoplasia (2); and transient cortical blindness.

***Endocrinology.*** Pituitary abnormalities were common. Eleven people had documented growth hormone deficiency; five of which had at least one other anterior pituitary hormone deficiency (Table I), thus qualifying them for a diagnosis of either hypopituitarism or panhypopituitarism. One of these individuals (a female) underwent an abdominal ultrasound at puberty, revealing that the ovaries were absent. Four additional individuals were on growth hormone, despite not being diagnosed with an underlying growth hormone deficiency. Two other patients were diagnosed with Graves' disease and multinodular goiter. One female participant had precocious puberty.

***Dysmorphology.*** In 25 individuals, reports from a clinical geneticist were available. These records were reviewed for dysmorphic features. Thirteen had epicanthal folds, while only four had either upslanting or downslanting palpebral fissures. Eight had a wide depressed nasal bridge, while six had a small nose. However, there were no additional common dysmorphic features. Figure 1 shows images of several participants at differing ages.

***Growth parameters.*** Using the most recent measurements available, records were reviewed for growth parameters. Short

TABLE II. Findings Present in the Study Population

| | Number affected (n = 31) | Percentage affected |
|---|---|---|
| *Neonatal complications* | 22 | 71% |
| *Congenital anomalies* | | |
| Holoprosencephaly or HPE microform | 4 | 13% |
| Sacral agenesis | 2 | 6% |
| Myelomeningocele | 1 | 3% |
| Heart defects | 9 of 16* | 56% |
| *Neurologic abnormalities* | | |
| Hypotonia/mixed tone abnormalities | 26 | 84% |
| Non-HPE MRI abnormalities | 10 of 15** | 66% |
| Seizures | 4 | 13% |
| *Endocrine abnormalities* | | |
| Panhypopituitarism or hypopituitarism | 4 | 13% |
| Isolated growth hormone deficiency | 7 | 23% |
| *ENT/Vision abnormalities* | | |
| Recurrent otitis media | 19 | 61% |
| Hearing loss | 7 | 23% |
| Strabismus | 13 | 42% |
| Ptosis | 17 | 55% |
| Refractive errors | 16 | 52% |
| Optic nerve hypoplasia | 2 | 6% |
| Congenital cataracts | 2 | 6% |
| Nystagmus | 2 | 6% |
| Iris coloboma | 1 | 3% |
| *Orthopedic abnormalities* | | |
| Pes planus | 6 | 19% |
| Pectus excavatum | 9 | 29% |
| Scoliosis/kyphosis | 6 | 19% |
| *Other* | | |
| Autoimmune disorder | 3 | 10% |
| IgA, IgG, or IgM deficiency | 4 | 13% |

*16 individuals had undergone echocardiograms
**15 individuals had undergone MRI's

stature, defined by a height at or below the 3rd centile, was identified in 15 of the 27 individuals for whom measurements were available. Of the 25 individuals with documented head circumference, eight had a head circumference at or below the 3rd centile.

***Other.*** Of interest, several individuals had been diagnosed with an autoimmune disorder. These diagnoses included Graves disease (as mentioned previously), psoriasis, and lupus. Four individuals had some type of immunodeficiency (IgA, IgG, or IgM). Only one required treatment with immunoglobulins. One individual had choanal stenosis.

***Early death.*** One study participant has died after enrollment in the research study. This individual (7C) died at 22 years of age following a bout of pneumonia complicated by an underlying diagnosis of lupus.

## Neuropsychological Results

The ages at which participants achieved developmental milestones are shown in Figure 2. Although we received data from the parents of 28 individuals, there are some missing data, despite review of medical records and subsequent data follow-up requests. When parents were unsure of exact milestone acquisition, we chose to count this information as missing data rather than add potentially inaccurate information to our dataset. The age range at which these milestones were achieved was significantly greater than that of a typical population. The mean age at which these developmental milestones were achieved deviated further from the normal range as the skills progressed with age and complexity. One individual stood out from the rest of the group as having more severe cognitive deficits. At 16.7 years of age, this person is nonambulatory, cannot speak in full sentences and has not achieved night-time toilet training.

Information on cognitive ability was available on 18 individuals and is shown in Figure 3. One report provided only a full-scale IQ score while three other reports provided a verbal and full-scale IQ score only. The scores in the figure are in age order and range from 2.1 years to 24.0 years. The average Verbal IQ ranged from 55 to 104 with an average of 74. The nonverbal IQ scores ranged from 56 to 101 with an average of 74. The average full scale IQ score was 69 with a range from 51 to 99.

The results of the parental ratings of their children's behaviors are shown in Figure 4. The data from three measures of adaptive functioning (Vineland-2, ABAS-II, BASC-2) revealed that the majority of the participants have problems with activities of every-day life compared with same age peers. These include activities related to communication, home living, self-care and managing social and leisure activities. It is interesting to note that, of the fourteen adults in this cohort, three live in an apartment with a roommate while a fourth lives in an independent living facility.

Parental ratings of executive function skills (BRIEF) such as impulse control, adapting to unexpected changes, and planning and organizational skills were rated as typically developing or only somewhat below expectancy. Additionally, most individuals were not described by their parents as having significant difficulties with behavior regulation (BASC-2 externalizing problems) or problems with depression, anxiety, or somatization (translation of anxiety into physical symptoms).

While the average overall adaptive behavior fell slightly within the clinically significant range, these behaviors did not, on average, include autism spectrum behaviors. Twenty-one of the 31 individuals reported here had completed the GARS survey. Although the average autism spectrum behaviors fell within the normal limits range, there were several individuals whose scores on measures of autistic behaviors put them clearly on the autistic spectrum. Four were rated as possibly having autism, and another four were rated as very likely to have autism. There was no correlation between cognitive ability and autistic behavior.

## DISCUSSION

The advent of microarray analysis has enabled the identification of critical regions and eventually candidate genes in several chromosomal conditions, including 18q- [Cody et al., 2009; Feenstra et al.,


**FIG. 1. Images of seven study participants at varying ages. (A) 3.5 years (B) 4 years (C) 10 years (D) 11 years (E) 18 years (F) 18 years (G) 26 years. All images provided courtesy of Rick Guidotti of *Positive Exposure* (www.positiveexposure.org).**

2011; Hasi et al., 2011]. Our goal is to make similar strides in the characterization of deletions of 18p. As such, this manuscript serves as an important step in this process by providing a phenotypic description of a specific 18p- genotype: deletions of the entire p arm.

Of the 91 patients that have enrolled in our study and undergone aCGH analysis, 34 had a breakpoint at the centromere. This is consistent with our previous report of a breakpoint cluster in the pericentromeric region of 18p11.1 [Schaub et al., 2002]. Two of the 34 were eliminated from this report as additional genomic imbalances were identified on microarray, while another was excluded because no medical records were available in English. In general, findings from the medical record review were consistent with the phenotype previously described in the literature.

Of note, this manuscript represents the most comprehensive data collected on the developmental and behavioral effects of a deletion of 18p. It appears that developmental delays are indeed common within the 18p- population, and that, as skills advance, the gap between individuals with 18p- and their typically-developing peers seems to increase. There was a wide range of IQ scores, with the lower end being in the mild range of impairment and the upper end being within the normal range of functioning. Average IQ scores fell in the range of borderline intellectual functioning. This is in contrast to the developmental profile suggested by Turleau, which suggested that an IQ of 50 is typical in this patient population [2008]. However, when evaluating our cohort for other neuropsychological deficits, we did find that most participants exhibited some difficulty with aspects of daily living. It is interesting to note that this population did not have many difficulties in terms of executive functioning. In addition, although a few had test scores that suggested autism, these individuals appeared to be the exception rather than the rule.

As discussed above, one of the ultimate goals of the Chromosome 18 Clinical Research Center is to establish genotype–phenotype correlations in an effort to provide genotype-specific prognostic information as well as to develop therapies appropriate for affected individuals. Some work has already been done in establishing genotype phenotype correlations of 18p-. *TGIF* has long been known to be associated with the holoprosencephaly phenotype [Gripp et al., 2000]. Within our population, only one participant had a "classic" form of holoprosencephaly. However, several had microforms of HPE, including several with a single central incisor and one with an iris coloboma. Of interest, we had several individuals with midline defects that are not traditionally considered a part of the holoprosencephaly spectrum, including one with isolated septo-optic dysplasia. To our knowledge, there have been no reports of septo-optic dysplasia in someone with 18p-. We also had one patient with a hypoplastic pituitary stalk. Recently, Tatsi et al reported a point mutation in *TGIF* in an individual with an

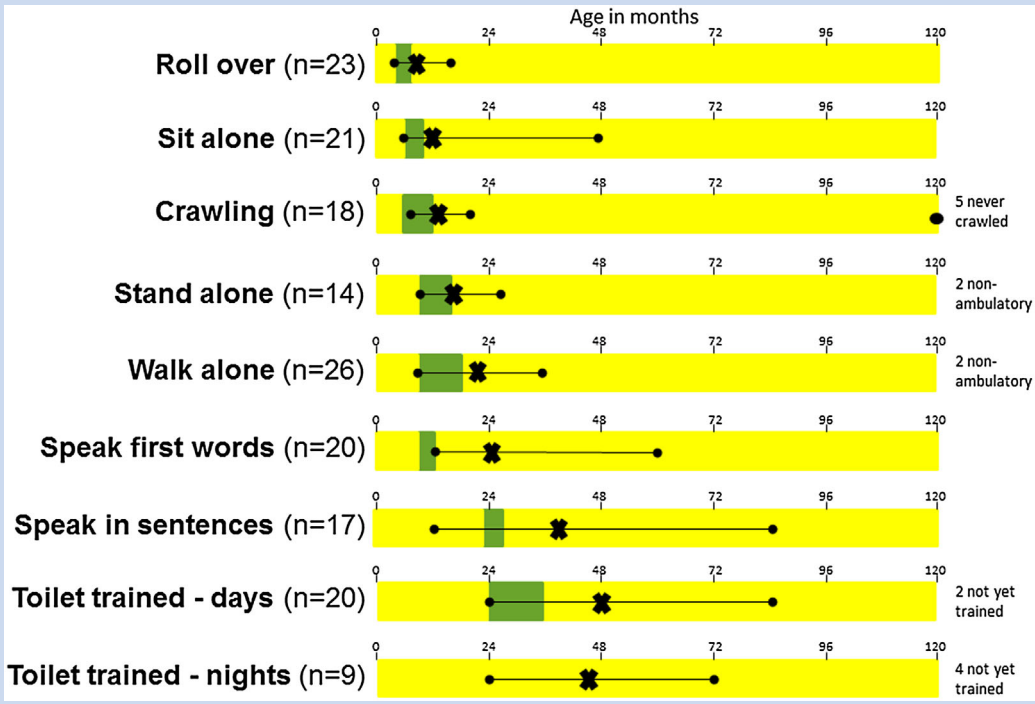


FIG. 2. Age of milestone acquisition in study participants. "X" indicates the average age of milestone acquisition, while the horizontal ball point line indicates range at which this milestone was achieved. The darker (green) segment indicates the average age of milestone acquisition in a typical population.

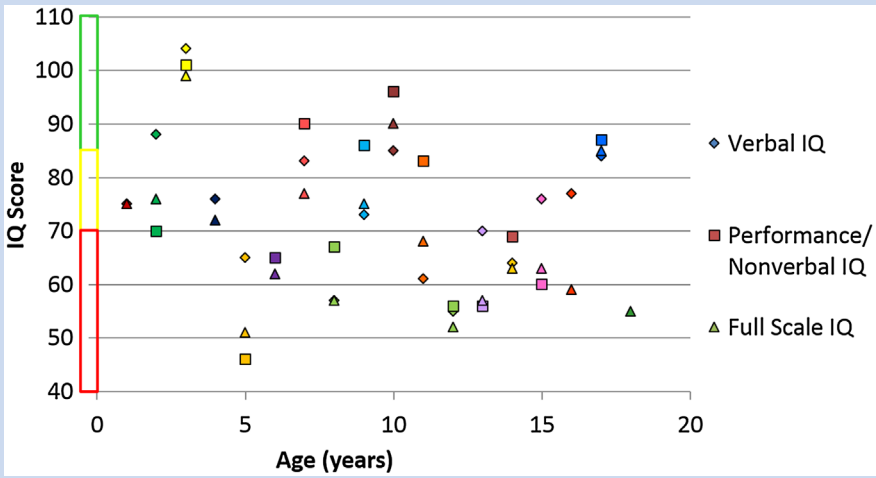


FIG. 3. Cognitive ability in study participants. The normal range is indicated on the vertical scale by the medium grey (green) bar, the borderline range is indicated by a light grey (yellow) bar and the cognitive disability range is indicated by a dark grey (red) bar. Each participant's Verbal IQ, Performance/Nonverbal IQ and Full Scale IQ are indicated where available. Each participant's data is shown at the age at which it was measured allowing the scores from the same individual to be identified.

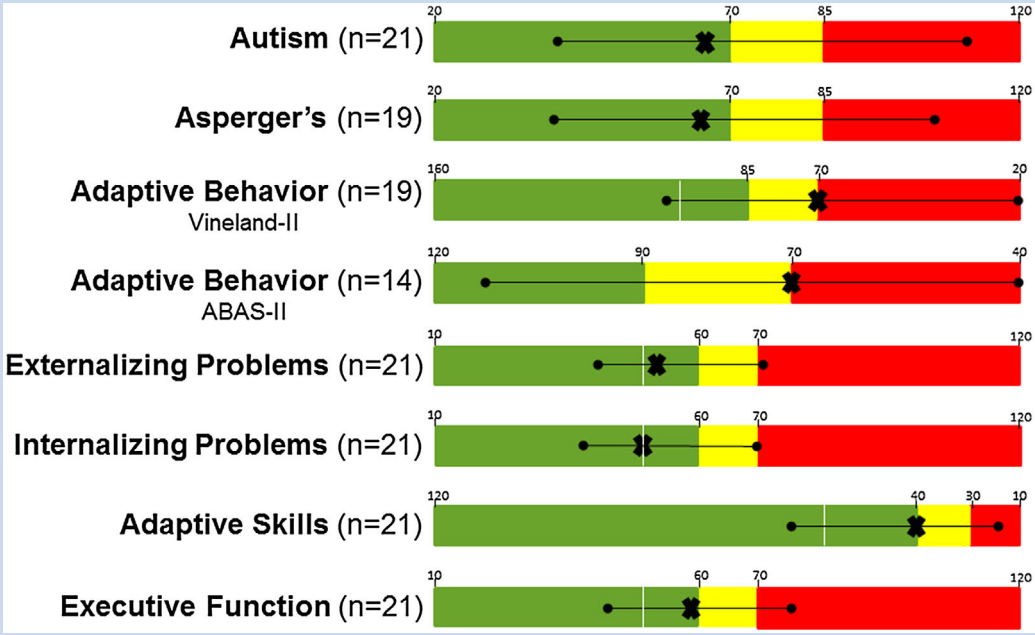


**FIG. 4. Parental ratings of study participants' behavior using a variety of behavior scales. The normal range is indicated by the medium grey (green) bar, the borderline range is indicated by a light grey (yellow) bar and problematic range is indicated by a dark grey (red) bar. The mean score is indicated by the "X" and the range of scores is indicated by the ballpoint lines. The vertical line within the medium grey (green) bar indicates the average score for a typically developing population.**

abnormal pituitary stalk, suggesting that the gene plays a role in non-holoprosencephaly-related midline defects [Tatsi et al., 2013]. Pituitary issues, such as isolated growth hormone deficiency or panhypopituitarism, are common in individuals with 18p- and known midline defects [Portnoi et al., 2007]. Unsurprisingly, the individuals within our cohort with holoprosencephaly, septo-optic dysplasia, and a structural pituitary abnormality all had endocrine disorders. However, it is interesting to note that several participants had pituitary hormone deficiencies and a normal MRI.

Recently, loss of function mutations in several genes on 18p have been linked with various adult-onset conditions, including dystonia, fascioscapulohumeral muscurophy-type 2, and spinocerebellar ataxia type 28 [Fuchs et al., 2013; Di Bella et al., 2010; Lemmers et al., 2012]. Given that a whole arm deletion includes all of these genes, it is reasonable to hypothesize that some of our older participants would be affected by these neurological issues. Indeed, dystonia has been reported in association with 18p- [Klein et al., 1999; Postma et al., 2009; Kowarik et al., 2011]. Nearly half of our study cohort was over eighteen years of age. None of these individuals had been diagnosed with any of these conditions at the time of submission. However, we are currently interviewing our entire cohort with 18p- and collecting data from neurologic evaluations to determine the incidence of these conditions within our population.

Previous authors have noted that the dysmorphic profile of 18p- is fairly nonspecific [Turleau, 2008]. Indeed, other than the common finding of ptosis, the only dysmorphic findings that were seen somewhat frequently in our population included epicanthal folds; a wide, depressed nasal bridge; and a small, upturned nose. However, even these features were seen in less than 50% of individuals.

There are some limitations to the study. As we were unable to bring most patients to the Research Center for a full evaluation, we relied on medical records. It is possible that some records were incomplete, though we attempted to ensure that we had all available medical records by interviewing families regarding their history. Also, as we were unable to evaluate cognitive abilities in person, we relied on the reports of participants' local specialists, who used different scales and protocols to ascertain IQ. Notwithstanding, this is the most cognitive data reported on this population to date.

Since the first report of 18p- was published in 1963, there have been over a hundred cases described in the literature. The reported range of physical, intellectual, and behavioral effects has been very broad, from major physical and cognitive disability to mild medical complications and borderline adult functioning ability. Historically, these differences have been attributed to the genetic heterogeneity of the hemizygous region and our inability to sufficiently distinguish the molecular difference. Here, we report on a cohort of individuals with 18p- deletions who have genetically identical 18p hemizygosity, yet the variability in phenotype remains. This leads us to hypothesize that many of the genes on 18p-, when hemizygous, cause phenotypes with very low penetrance.

There have already been some attempts to identify the critical regions for various features of 18p-, including intellectual disability, round facies, postnatal growth retardation, seizures, ptosis, and short neck [Wester et al., 2006; Brenk et al., 2007]. However, these

findings have not yet been reproduced, and much work remains to be done to narrow the critical regions and identify new ones for other features of 18p-. This paper represents the largest cohort of individuals with 18p- with the same underlying genotype, serving as a critical first step in identifying these regions. Future studies will focus on determining the phenotype of individuals with more distal breakpoints and narrowing the critical regions for the various phenotypes associated with 18p-.

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