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Tetrasomy 18p: Report of Cognitive and Behavioral Characteristics

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Our purpose was to describe intellectual and behavioral characteristics of persons with tetrasomy 18p. This is a more detailed investigation into the cognitive and behavioral characteristics of our previously reported tetrasomy 18p cohort of 43 plus six additional participants. We evaluated the intellectual functioning using standard measures of cognitive ability, measures of executive functioning, adaptive and maladaptive behaviors. Intellectual abilities ranged from mild impairment/borderline normal to severe/profound impairment calling into question the assumption that severe cognitive limitation is always a feature of tetrasomy 18p. For persons with tetrasomy 18p with mild cognitive deficits, the main barriers to successful functioning stems from limited social and metacognitive skill development and behavior regulation problems rather than being solely determined by cognitive deficits alone.

Key words: chromosome abnormality; chromosome 18; isochromosome 18p

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INTRODUCTION

Tetrasomy 18p results from an abnormal extra chromosome composed of two copies of the short arm of chromosome 18 creating an isochromosome 18 which is present in each cell. It is a rare condition and, while an exact prevalence rate has not been calculated for this condition, it is estimated to occur in less than 1 in 40,000 [The Chromosome 18 Registry and Research Society, 2009]. Consequently research on this genetic condition has been based on a very limited number of study participants usually presented as single case reports. While these case reports have provided a good first step in understanding tetrasomy 18p with a focus on the delineation of cytogenetic findings and chronicling of dysmorphic features [Takeda et al., 1988; Brambila Tapia et al., 2010; Nucaro et al., 2010] generalizations of findings require caution. The notable exception to studies with limited number of subjects is the [Sebold et al., 2010], article from our research group—that provides molecular and clinical findings on the largest cohort of persons to date with tetrasomy 18p. The medical records of 43 persons with tetrasomy 18p were examined; 30 of whom also underwent a series of comprehensive clinical evaluations. We found that all participants had developmental delay as well as some degree of cognitive impairment. This study is a more detailed investigation into the cognitive and behavioral characteristics of the [Sebold et al., 2010] tetrasomy 18p cohort and includes six additional study participants. In addition to cognitive performance, this study examined aspects of higher order cognitive functioning such as behavior regulation capacities and metacognitive skills (e.g., planning and organization abilities).

A review of the literature revealed a lack of studies regarding the social emotional development and behavioral functioning of persons with tetrasomy 18p. To date the only published study is a clinical report by Swingle et al. [2006] that included the presence of aggressive behavior and self-injury in the discussion of clinical presentation. Thus very little is known about the incidence of maladaptive behavior problems in this population and equally lacking is information regarding the process of gaining social

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emotional competence and adaptive behavior skills. If the assumption is that severe and profound intellectual disability are a core defining feature of the condition, then the logical resultant expectation is that there will also be significant delays in the acquisition of social emotional and behavioral competencies. In contrast when a pattern of cognitive variability exists with some members being profoundly cognitively impaired and others only mildly impaired corresponding variability in behavioral functioning and social emotional development is also expected. We therefore sought to fully describe the spectrum of social emotional and behavioral development in individuals with tetrasomy 18p.

The social emotional development and behavioral competencies were examined for three age group categories (toddler and pre-school children, school-age children and young adults). The incidence of maladaptive behaviors such as externalizing symptoms (hyperactivity, aggression and conduct problems), internalizing symptoms (anxiety, depression, and somatization) and atypical behaviors (autism spectrum disorders) were also investigated.

MATERIALS AND METHODS

Participants

All study participants were enrolled in a longitudinal research study at the Chromosome 18 Clinical Research Center. Eligibility criteria for this study included a diagnosis of tetrasomy 18p confirmed by high resolution microarray Comparative Genomic Hybridization as described previously [Sebold et al., 2010]. Two individuals with mosaicism (one with mild cognitive impairment and the other with moderate cognitive impairment) are included in this paper. Each participant's isochromosome was composed of identical copies of the entire short arm of chromosome 18 with no detectable long arm material. A total of 49 (23 male and 26 female) individuals ranging in age from 13 months to 22 years of age met inclusion criteria. A subset of 30 participants and their families, (14 males and 16 females) participated in a psychological evaluation conducted at the Chromosome 18 Clinical Research Center located at the University of Texas Health Science Center at San Antonio. This evaluation included the administration of a cognitive ability measure and series of questionnaires completed by the parents/guardians. The parents/guardians of the remaining 19 participants who did not travel to the Chromosome 18 Clinical Research Center completed the series of parental questionnaires only, as study funding limitations prevented all participants from participating in the on-site psychological evaluation. All components of this study have been approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All families were and continue to be involved in the informed consent process, which is appropriately documented.

Procedures

Thirty individuals diagnosed with tetrasomy 18p completed a psychological assessment conducted by either a licensed clinical psychologist or a doctoral student. Students were under the supervision of a licensed clinical psychologist. All instruments were administered in a manner consistent with the respective test manuals. The parents/caregivers of 19 study participants who did not travel to the Chromosome 18 Clinical Research Center and thus did not undergo the psychological assessment were mailed a series of questionnaires that asked them to evaluate their child's social emotional and behavioral functioning.

Measures

Measures of Cognitive Ability. Because of wide age range of study participants and the nine-year duration of the longitudinal study, we employed a number cognitive ability measures. Six study participants received either the Bayley Scales of Infant Development, Second Edition (N = 1; BSID-II) [Bayley, 1993] or the Bayley Scales of Infant and Toddler Development, Third Edition (N = 5; Bayley-3) [Bayley, 2006] because their chronological age was between 12 and 42 months. Two participants who were older than 42 months received the Bayley-3 because significant cognitive limitations precluded using an age-based instrument. Fifteen study participants between the ages of 3 and 17 years received either the Differential Abilities Scales (N = 9; DAS) [Elliott, 1990] or the Differential Abilities Scale, Second Edition (N = 4; DAS-II) [Elliott, 2007]. Young adults 18 years to 23 years of age, received the Wechsler Adult Intelligence Scale, Third Edition (N = 7; WAIS-III) [Wechsler, 1997].

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 80's to high 90's with all instruments having demonstrated clinical validity with special populations including those with developmental delay and cognitive impairment.

Parental Questionnaires. For study participants who were at least 5 years of age, executive functioning or meta-cognition was examined using either the Behavior Rating Inventory of Executive Function Parent (BRIEF) [Gioia et al., 2000] or the Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) [Roth et al., 2005]. The Vineland Adaptive Behavior Scales (Sparrow et al., 1984) or the Vineland Adaptive Behavior Scales, Second Edition [Sparrow et al., 2005] was used to assess adaptive behavior. Parents also completed the Behavioral Assessment System for Children (BASC) [Reynolds and Kamphaus, 1992] or 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 [Cabrera et al., 1999; Dowdy et al., 2011].

The probability of characteristics associated with autism was assessed through parental report using either the Gilliam Autism Rating Scale (GARS) [Gilliam, 1995] or the Gilliam Autism Rating Scale, Second Edition (GARS-2) [Gilliam, 2006]. The following domains are evaluated on both versions of the scale: presence of stereotyped behaviors, social interaction problems and communication difficulties while the domain of developmental delay is present only in the GARS. Coefficient alpha estimates range from 0.88 for developmental delay to 0.96 for the overall Autism Quotient. The manual provides construct, content and criterion

validity evidence to support using the scale to rate the probability of autism.

RESULTS

We recruited a total of 49 persons with tetrasomy 18p who were eligible for the study. The sample consisted of 23 males and 26 females.

Cognitive Abilities

The cognitive abilities of 30 participants were assessed using standardized measures of intellectual functioning. Although the overall average summary cognitive score (IQ = 48.43, SD = 14.54) was within the moderate range of cognitive impairment, there was a fair amount of group variability (40% of the sample had overall cognitive scores within the mild range of intellectual disability, 37% of scores were within the moderate range of intellectual disability and 23% of the sample had overall intellectual ability estimates within the severe to profound range (FSIQ level below 35) of cognitive ability (Fig. 1). To evaluate whether the severity of behavioral problems correlated with IQ, we compared FSIQ with parental ratings of behavior on the BASC-II and the BRIEF. There was no significant correlation between parental ratings of the severity of behavioral problems and measured intellectual ability. A comparison of the overall IQ score with the BASC-II internalizing and externalizing composite score revealed a small and non-significant relationship respectively (N = 30; Pearson correlation coefficient = 0.244; and −0.57). Comparison of measured IQ with behavior regulation (BRIEF) parent ratings also found a small and non-significant relationship between these two measures (Pearson correlation coefficient = − 0.073).

We also evaluated whether there were identifiable factors such as differences in parental IQ's or family history of learning difficulties that contributed to the differences in intellectual functioning. Studies have shown a strong relationship between performance on IQ tests and educational attainment [Sattler, 2001] with correlations ranging from 0.50 to 0.70. While it was not possible to obtain parental IQ data, we collected information on paternal and maternal educational attainment. To evaluate whether parental education level was significantly difference between the individuals with severe cognitive impairment and those with mild to moderate cognitive impairment, we generated an average level of parental education for the 30 study participants. The average educational attainment for parents whose children's IQ's fell within the mild to moderate range of cognitive disability was 15 years while the average educational attainment for individuals whose children's IQ's fell within the severe range of cognitive impairment was 14.6 years. In both groups the range of education varied from completion of high school to completion of a graduate degree. Because both groups have fairly comparable educational attainment we cannot meaningfully attribute differences in intellectual disability to genetic background. Only four of the 30 subjects have relatives who received some special education intervention and only one of this group has severe intellectual disabilities and while we did not specifically track effectiveness of kinds of educational interventions received, all study participants had received speech and language as well as physical/occupational therapies.

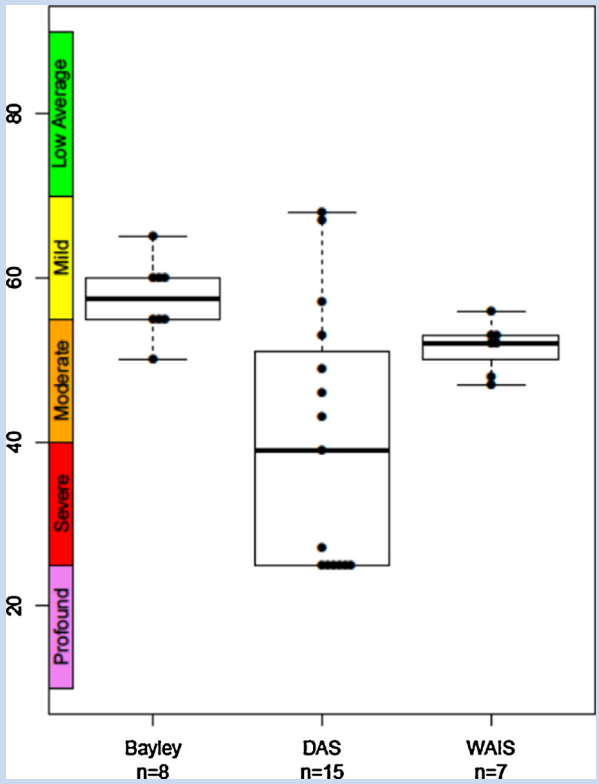

FIG. 1. Cognitive results. Three different cognitive measures were used because of the different age ranges of our participants. Bayley = the Bayley Scales of Infant Development, Second Edition or the Bayley Scales of Infant and Toddler Development, Third Edition. The DAS = Differential Abilities Scales or the Differential Abilities Scale, Second Edition. WAIS = Wechsler Adult Intelligence Scale, Third Edition. The thick black bar denotes the mean score. The box encompasses the standard deviation associated with each IQ measure and the wing lines show the total range of scores. The ages of the subjects who were administered the Bayley ranged from 13 to 27 months. Two persons in their 20's were also administered the Bayley. The ages of the subjects who were administered the DAS ranged from three to 12 years of age. The ages of the subjects who were administered the WAIS ranged from 18 to 23 years of age.

Metacognitive Skills

Executive functioning development was examined using the BRIEF and BRIEF-A which asks the parent to rate the child's or young adult's behavior. We received 33 completed BRIEF and BRIEF-A forms. All questionnaires were scored using same-age and gender-based normative information with the following summary score information generated: the behavioral regulation index, the metacognition index and the global executive composite. Figure 2 presents the T-score means and standard deviations by overall

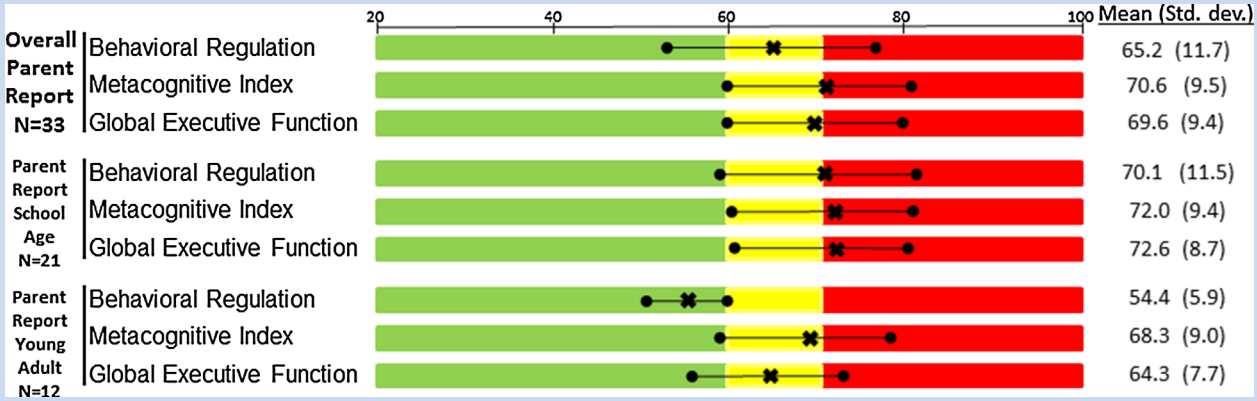

FIG. 2. Behavior Rating Inventory of Executive Function. This figure presents parental ratings of study participants executive functioning using the Behavior Rating Inventory of Executive Function (BRIEF). The medium gray (green) indicates t-scores 59 and below (within normal limits). The light gray (yellow) indicates t-scores 60 to 69 (at-risk for developing problems). The dark gray (red) indicates t-scores 70 and above (area of significant concern). The X is the mean score and the circles denote the standard deviation. The higher numbers, in dark gray (red), signify severe difficulties.

parental report and parental report by age group. Direct comparison of parent ratings by age group (school age compared with young adult) found significant differences between the two age groups on the behavior regulation index $F(1, 32) = 10.13$, $P < .01$ with parents of school age children reporting significantly more difficulties with emotional regulation than parents of young adults. An analysis of the sub-domains within the behavior regulation index indicate significant differences in parental ratings between the two age groups in their ability to inhibit responses and maintaining emotional control $F(1, 32) = 7.13$, $P < .01$ and $F(1, 32) = 9.23$, $P < .01$ respectively (Fig. 3).

Adaptive Behavioral Functioning

The adaptive behavior development of young children (Group 1), school age children (Group 2) and young adults (Group 3) was evaluated by parental rating using either the Vineland or Vineland II. Performance was evaluated across three general areas:

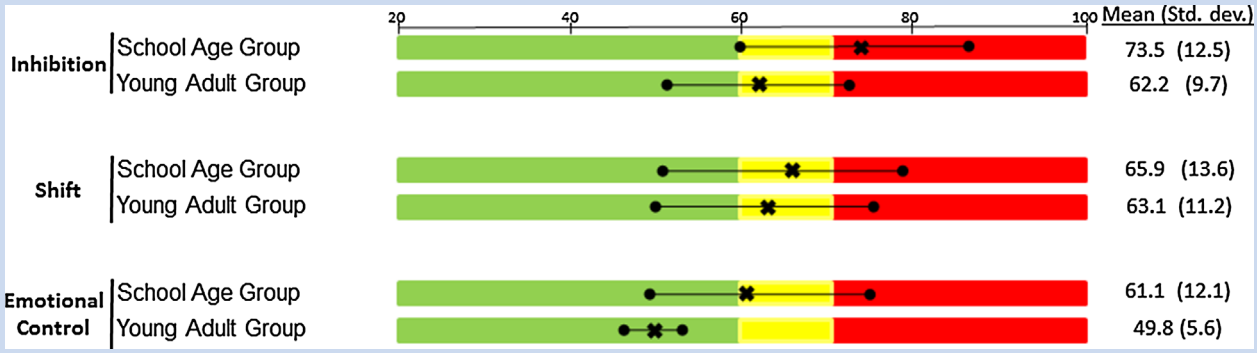

FIG. 3. Comparison of Behavior Rating Inventory of Executive Function (Parent Report) ratings by age group. This figure displays the results of the parental BRIEF behavior regulation sub-domain ratings. These dimensions include ratings of study participant's inhibition, ability to shift set and emotional control. The groups of participants have been divided by age: school age children and young adults. The medium gray (green) indicates t-scores 59 and below (within normal limits). The light gray (yellow) indicates t-scores 60 to 69 (at-risk for developing problems). The dark gray (red) indicates t-scores 70 and above (area of significant concern). The X is the mean score and the circles denote the standard deviation. The higher numbers, in dark gray (red), signify severe difficulties.

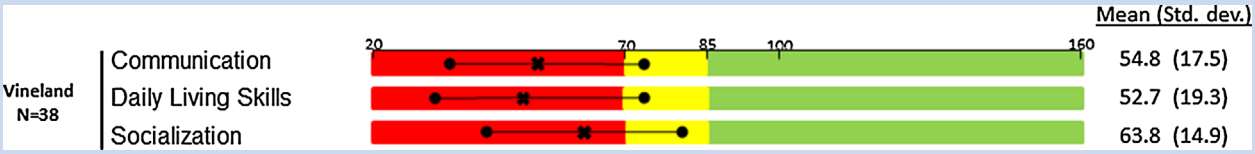

FIG. 4. Adaptive Behavior was measured using the Vineland adaptive behavior scales, first and second editions. The medium gray (green) indicated those participants who scored an 85 or above (average range of functioning). The light gray (yellow) indicates those participants who scored between 71 and 84 (moderately low range of functioning). The dark gray (red) indicates those participants who scored a 70 or below (cognitively impaired functioning). The X is the mean score and the circles show the standard deviation. The higher numbers, in medium gray (green), reflect more skill acquisition while lower numbers, in dark gray (red), indicate significant deficits.

communication (receptive, expressive and written), daily living skills (personal, domestic and community) and socialization (interpersonal relationships, play and leisure time and coping skills) (Fig. 4). As shown in Figure 5, with the exception of parental ratings of socialization development in the youngest age group which is rated moderately low to average, the mean Vineland Adaptive Behavior scores fall within the very low to moderately low levels suggesting that significant adaptive behavior deficits continue to be present across the full spectrum of tetrasomy 18p ages. A second measure of coping behavior was obtained using either the BASC or BASC-2. Comparison of parental ratings across the three groups find continuing social skill, daily self-care and functional communication difficulties as children progress in age (Fig. 6).

Maladaptive Behaviors

To evaluate whether problems with maladaptive behavior were present, parents completed the BASC or BASC-2. Behavior is rated along the following dimensions: Externalizing Behaviors (e.g., problems with hyperactivity, aggression, and conduct), Internalizing Behaviors (e.g., problems with anxiety, depression, and somatization) and Behavioral Symptoms (atypicality, withdrawal and attention problems). As shown in Figure 7, the overall average parental ratings were within the typical to at risk score range on the externalizing behaviors and behavioral symptoms indices and were within the typical range on internalizing behaviors. At the time of cognitive and behavioral assessment, 20 out of 30 study participants

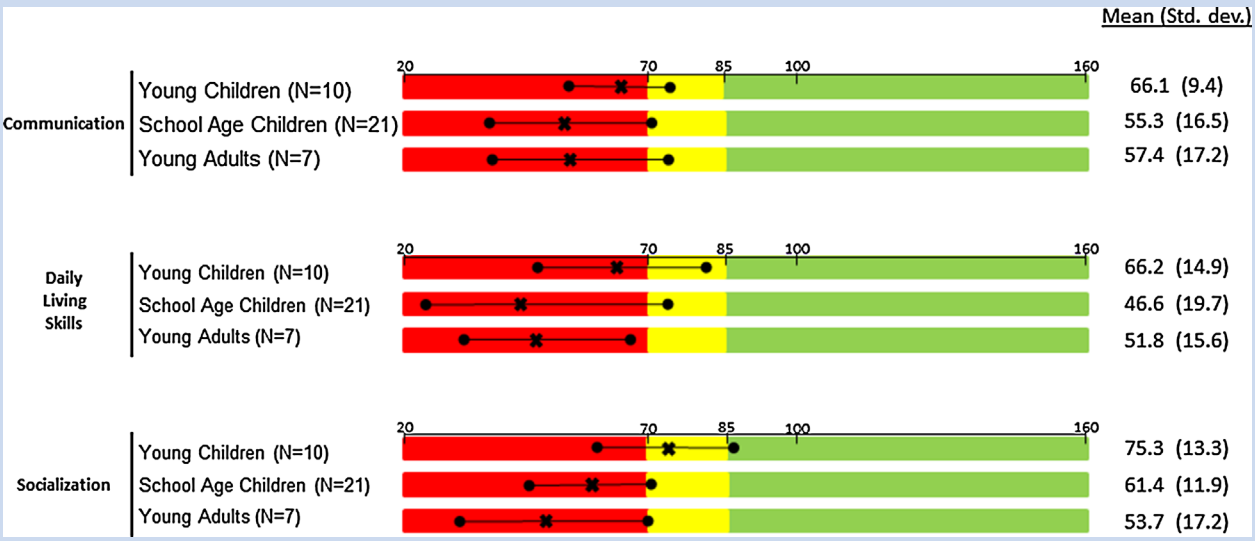

FIG. 5. Comparison of Vineland Adaptive Behavior by age group. This figure presents the three areas of adaptive behavior measured by the Vineland Adaptive Behavior scales by two age groups (school age children and young adults). The medium gray (green) indicated those participants who scored an 85 or above (average range of functioning). The light gray (yellow) indicates those participants who scored between 71 and 84 (moderately low range of functioning). The dark gray (red) indicates those participants who scored a 70 or below (cognitively impaired functioning). The X is the mean score and the circles show the standard deviation. The higher numbers, in medium gray (green), reflect more skill acquisition while lower numbers, in dark gray (red), indicate significant deficits.

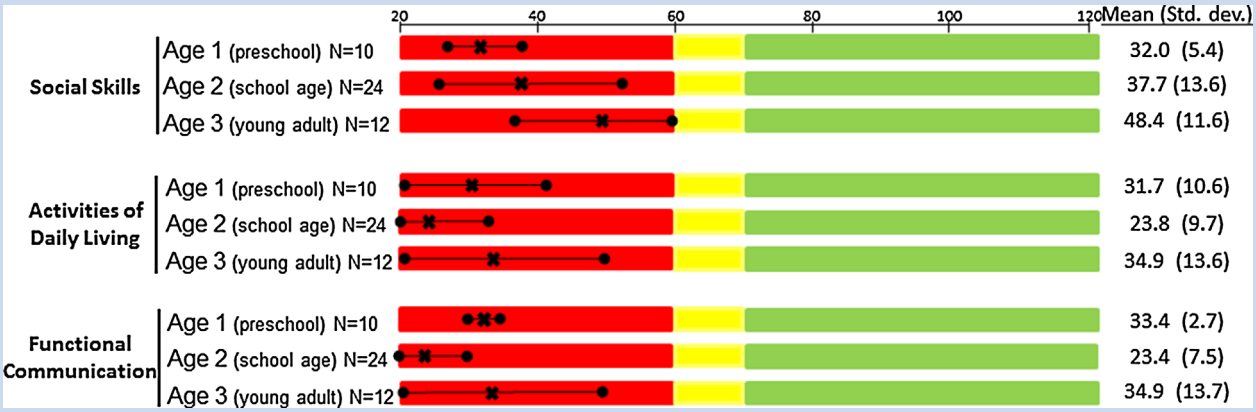

FIG. 6. Behavioral Assessment System for Children, 2nd Edition – Coping Skills. This figure displays parental ratings of participant's coping skills using the either the Behavioral Assessment System for Children (BASC) or the Behavioral Assessment System for Children Second Edition (BASC-2). The participants are divided into three groups (preschool age, school age and young adult). The medium gray (green) indicates t-scores 41 and above (within normal limits). The light gray (yellow) indicates t-scores 31 to 40 (at-risk for developing problems). The dark gray (red) indicates t-scores 30 and below (area of significant concern). The X is the mean score and the circles denote the standard deviation. The higher numbers, in medium gray (green), reflect more skill acquisition while lower numbers, in dark gray (red), indicate significant deficits.

were not taking any medication for behavior management. Ten of the study participants were taking stimulant medication (Ritalin alone = 3, Ritalin and Clonidine = 2, Strattera alone = 2, Strattera and Risperidol = 1). Risperidol was used along with Depakote as a mood stabilizer for one study participant and Clomipramine was used for obsessive compulsive behavior for another study participant. All medication used was reported by parents as being effective.

Autistic Behaviors

The parents of 43 study participants completed either the GARS or the GARS-2 in order to determine whether their child exhibited behaviors similar to individuals diagnosed with autism. Although the overall average autism probability ratings for all three age groups were within the possibility to very likely ranges, there

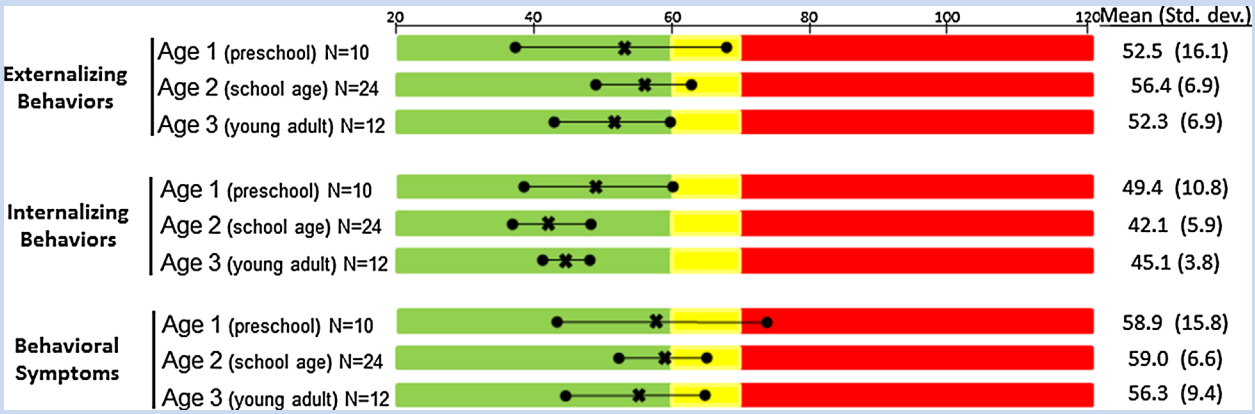

FIG. 7. Behavioral Assessment System for Children, 2nd Edition – Maladaptive Behaviors. This figure displays parental ratings of participant's maladaptive behaviors using the either the Behavioral Assessment System for Children (BASC) or the Behavioral Assessment System for Children Second Edition (BASC-2). The participants are divided into three groups (preschool age, school age and young adult). The medium gray (green) indicates t-scores 59 and below (within normal limits). The light gray (yellow) indicates t-scores 60 to 69 (at-risk for developing problems). The dark gray (red) indicates t-scores 70 and above (area of significant concern). The X is the mean score and the circles denote the standard deviation. The higher numbers, in dark gray (red), signify severe difficulties.

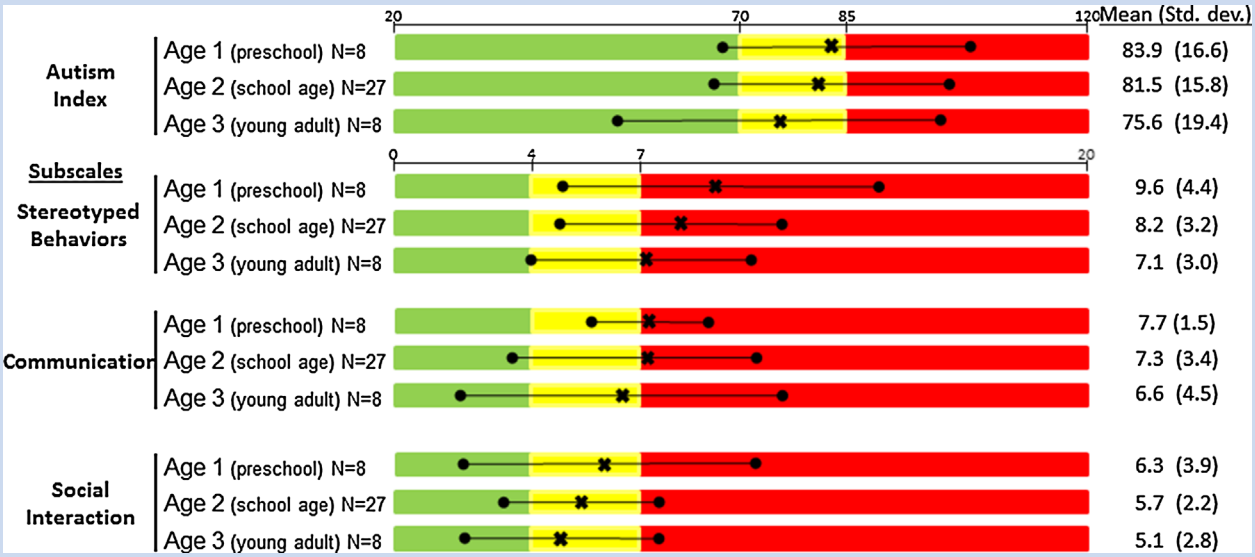

FIG. 8. Gilliam Autism Rating Scale. The probability of characteristics associated with autism was assessed through parental report using either the Gilliam Autism Rating Scale (GARS) [Gilliam, 1995] or the Gilliam Autism Rating Scale, Second Edition (GARS-2). This figure reports the overall autism index probability and each of the three subscales that make up the autism index. The participants have been divided into three groups (preschool age, school age and young adult). For the autism index, the medium gray (green) indicates scores 69 and below (low probability of autism). The light gray (yellow) indicates scores 70 to 84 (possibility of autism). The dark gray (red) indicates scores 85 and higher (very likely probability of autism). The X is the mean score and the circles denote the standard deviation. For each of the three subscales, the medium gray (green) indicates a score of three or below (low probability of autism). The light gray (yellow) indicates a score between four and six (possibility of autism). The dark gray (red) indicates a score of seven or higher (very likely probability of autism). The X is the mean score and the circles denote the standard deviation. The higher numbers, in dark gray (red), signify severe difficulties.

was variability within each age group indicating that some individuals clearly did not demonstrate behaviors similar to those with autism (Fig. 8).

DISCUSSION

In contrast to previous research which categorized persons with tetrasomy 18p as functioning within the severe and profound ranges of intellectual disability [Swingle et al., 2006; Ramegowda et al., 2006; Balkan et al., 2009], a significant number of the study participants had mild to moderate levels of intellectual disability. This finding calls into question the prevailing assumption of severe cognitive impairment as a core feature in all persons with tetrasomy 18p. The intellectual abilities from our cohort of 30 persons with tetrasomy 18p can best be characterized as falling into two groups: those with mild to moderate cognitive impairment and those with severe and profound cognitive impairment. Implications of this finding include modification of academic, social emotional and behavioral expectations. Persons with mild cognitive impairment will require academic and behavioral modifications. However, expectations of academic achievement (acquisition of basic reading and functional math skills) and self-sufficiency regarding daily care and leisure activities and eventually structured employment opportunities and semi-independent living are realistic goals. Individuals with profound cognitive impairment and autism could profit from a curriculum that employs principles of applied behavior analysis, although full-time care and monitoring will be needed across the lifespan.

Our findings also suggest that despite mild cognitive impairment, many individuals with tetrasomy 18p struggle with behavior regulation and have deficits in higher order planning and organizational skills when compared with typically developing same age peers. Functionally behavior regulation weaknesses translate into difficulty adapting to unexpected changes, into trouble regulating and controlling emotions and involve emotional reactivity. Metacognitive weaknesses include problems with organizing and planning activities (e.g., getting materials needed for a project, completing steps in a sequential fashion). It also involves an appreciation of other's behavior and an awareness of the impact one's behavior has on others (e.g., peers).

Having less well developed metacognitive skills can translate into social interaction problems. While the overall the social emotional skill development and adaptive behavior functioning of study participants is below expectation, the severity of impairment is somewhat unexpected given the variability of cognitive abilities within the group, especially for those persons with mild cognitive impairment. Also noteworthy is the finding that delays in coping with frustration, understanding social interactions and proficiency with daily living activities are present in very young children (12–25 months of age) and that deficits in these general areas continue to be present during the school age and young adult years. Behavior

regulation and organizing skills will need to be explicitly taught using behavior management techniques tailored to the person's intellectual level. It will be important to continue to provide explicit teaching as the developmental expectations of the child changes. For example, the social skill requirements of a pre-school child differ from those of an elementary school child and a teenager/young adult. Each one of these developmental transitions will need to be anticipated and the child/adolescents/young adult's adjustment and eventual success be fostered just as one does with typically developing children.

Although parents rated study participants as having difficulties with behavior regulation, they did not endorse significant concern with the behavior management of hyperactivity, aggression or conduct problems. They also did not report concerns related to anxiety, depression, and somatization (over concern with physical symptoms). Based on parental ratings, individuals with tetrasomy 18p also evidenced behavioral deficits similar to those found in autism (e.g., presence of repetitive behaviors and communication and social interaction deficits).

In summary for persons with tetrasomy 18p who have mild cognitive deficits, the main barriers to successful functioning appears to stem from limited social and metacognitive skill development and behavior regulation problems rather than being solely determined by cognitive deficits alone. Problematic behaviors such as noncompliance, disorganization, and emotional "meltdowns" commonly seen in persons with executive function problems and autism spectrum difficulties stem from skill deficits and require comprehensive behavioral and academic intervention that focuses on both compensatory strategies and direct skill training [Ozonoff and Schetter, 2007]. Miller and Chan [2008] found that for persons with intellectual disabilities having a social support system and being successful interpersonally were significantly associated with positive life satisfaction. A study evaluating midlife psychological functioning of persons with mild cognitive impairments stressed the importance of role models of achievement, planning for the future and encouraging the achievement of aspirations discussed in high school [Seltzer et al., 2009]. Consequently the development of social skills and behavior regulation capabilities for persons with tetrasomy 18p needs to be one of the targeted goals of early intervention efforts and integrated into academic training and occupational planning.

Limitations and Considerations

A primary consideration is related to the diagnosis of autism. The Gilliam Autism Rating Scales (GARS; GARS-2) are parent rating scales where the study participant's behavior is compared against a group of individuals diagnosed as meeting criteria for autism spectrum disorder. This is a behavior rating scale and was utilized as a screening instrument and a way to obtain a rough measurement of the probability of autism within this cohort. Definitive diagnosis of autism spectrum disorder requires the one-on-one administration by psychologists or neuropsychologists using multiple instruments.

The data presented in this paper are based on a cross-sectional design so it is not possible to delineate progressive neurological, cognitive and behavioral changes. Our previous paper [Sebold et al., 2010], also cross sectional in design, presented neurologic and brain MRI data. Future studies with this cohort of individuals will build upon this body of research and with subsequent evaluations be better able to address neurological, cognitive, and behavioral changes that occur across the lifespan.

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