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Clinical Variability and Novel Neurodevelopmental Findings in 49, XXXXY Syndrome

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49, XXXXY is a rare chromosomal syndrome due to double nondisjunction of the replicating X chromosome. Considered a severe variant of XXY or Klinefelter syndrome, boys with this chromosome constitution are assumed to have severe mental retardation (MR) in addition to craniofacial, genital, endocrine, and heart abnormalities. Here, we present a multidisciplinary analysis including the clinical and neurobehavioral aspects of this condition in 20 boys with 49, XXXXY who share a common phenotype and neurobehavioral profile. The phenotypic presentation of the boys with 49, XXXXY shares some characteristics with 47, XXY, but there are also other unique and distinctive features. Previously unappreciated intact nonverbal skills are evident in conjunction with moderate to severe developmental dyspraxia. Variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or other factors that warrant further investigation.

Key words: chromosome; dyspraxia; 49; XXXXY; klinefelter

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INTRODUCTION

The[Q2] 49, XXXXY syndrome, first reported in 1960, is often considered a severe variant of Klinefelter syndrome (47, XXY) [Hayek et al., 1971]. The approximate prevalence is 1 in 85,000 male births. The syndrome arises from nondisjunction of the X chromosome during both meiosis I and meiosis II [Peet et al., 1998]. Clinical features that have been reported include characteristic facial appearance (Figs. 1 and 2), mental retardation (MR), hypogonadism, severe speech delay, multiple skeletal anomalies, and cardiac defects [Hayek et al., 1971; Morić-Petrović et al., 1973; Pallister, 1982; Linden et al., 1995; Peet et al., 1998]. Commonly described physical features include short stature, microcephaly, ocular hypertelorism, flat nasal bridge, and upslanting palpebral fissures (Figs. 1 and 2). More variable features that have been reported include bifid uvula, cleft palate, heart defects (most commonly patent ductus arteriosus), radioulnar synostosis, genu valgum, pes cavus, fifth-finger clinodactyly, hypotonia, joint laxity, and small genitalia with hypergonadotropic hypogonadism. Formal cytogenetic analysis is necessary to make a definitive diagnosis because of milder presentations and later diagnosis.

Boys with 49, XXXXY have been shown to be cognitively impaired. Previous reports indicate the IQ of boys with 49, XXXXY ranges from 20 to 60. The boys have been described as shy and friendly, with irritability and temper tantrums, low frustration tolerance, and difficulty transitioning and changing routines [Geschwind et al., 2000; Samango-Sprouse, 2001]. Although previous reports have suggested severe to moderate MR, more recent reports have noted cognitive delays not as significant as previously reported, as well as personalities and learning styles similar to 47,

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FIG. 1 and 2. Boys[03] with 49, XXXXY.

XXY individuals [Sheridan et al., 1990; Samango-Sprouse, 2001; Samango-Sprouse et al., 2002; Visootsak and Graham, 2006; Visootsak et al., 2007].

Here we describe 20 boys age primarily between 1 year and 8 years with 49, XXXXY syndrome, with an emphasis on the neurodevelopmental and behavioral phenotype and recommendations for targeted treatment and syndrome specific goals.

METHODS

Subjects

The subjects were evaluated at a single site, where a multidisciplinary clinic was conducted during consecutive summers (July 2004, 2005, 2006, and 2007) at the Neurodevelopmental Diagnostic Center for Young Children (NDCYC) in Davidsonville, Maryland, in which boys with 49, XXXXY were invited to attend. The program was advertised to parent advocacy groups and open to the public. Parents signed informed consent for their sons to be evaluated. Inclusion criteria included karyotype consistent with 49, XXXXY and those who were able to travel to the Baltimore–Washington area for 2.5 days of evaluation. Twenty children were participated and were evaluated, ranging in age from 11 months to 85 months (mean: 35.8 months and the median is 26.5 months). All medical records were obtained and reviewed prior to the visit. All subjects were seen by a multidisciplinary team and were evaluated by either of two pediatric endocrinologists (AR and IF), pediatric neurologist and geneticist (AG), neurodevelopmental specialist (CASS), speech and language pathologist (PLA), and physical therapist (FM, JC).

Medical evaluations.

Endocrinologic. One of two endocrinologists with experience in sex chromosome anomalies examined all 20 subjects (AR and IF) in Maryland. Anthropomorphic measurements including height, weight, and head circumference were assessed. Growth velocity was assessed on six children based on records from their primary care physicians. Medical examination included genital development and pubertal status using Tanner staging on eight of the 20 children.

Neurological examination. The 20 subjects in Maryland had a routine neurological evaluation tailored to age by single neurologist/geneticist (AG). In general, cognitive function, cranial nerves, motor (tone, strength, coordination, and tendon stretch reflexes), sensory systems function, and gait were assessed. In addition, all subjects were screened for the presence or absence of oral motor or verbal apraxia.

Neurobehavioral and Neurodevelopmental Testing

Standardized testing was administered and selected based on the subject's chronological age and recognized neurodevelopmental disturbances in this disorder including the complex language delay and behavioral disturbance. Therefore, testing probed multiple domains including neuromotor abilities (tone, strength coordination), fine motor/upper extremity, expressive and recessive speech and language development, neurocognitive and sensory functioning. Tests included the Leiter International Performance Scale-Revised (LIPS-R), Bayley Scales of Infant and Toddler Development, 3rd/Edition, Preschool Language Scale-3 or 4 (PLS-3/4), Peabody Motor Scale (GM, VM, total), Beery–Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition (VMI), Gilliam Autism Rating Scale (GARS-2) [Gilliam, 2006], Receptive One Word Picture Vocabulary Test-, Revised (ROWPVT-R), Expressive One Word Picture Vocabulary Test, Revised (EOWPVT-R), Dunn's Sensory Profile for Infants and Toddlers Caregiver Questionnaire and The Sensory Profile Caregiver Questionnaire for Children (3–10 years).

RESULTS

Patient demographics are shown in Table I. Of the 20 males with 49, XXXXY who participated in the Maryland conference, 18 were Caucasian and two Hispanic. All but three of the subjects resided in the United States (one each from Canada, Spain, and Honduras).

TABLE I. Patient[Q4] Characteristics and Demographics[Q5] of Study Population (N = 20)

Patient background	
Mean age at diagnosis	4 months, N = 16, range = 0.1–16
Mean age at evaluation	35.8 months, N = 20, range = 11–85
Mean birth weight	2.57 kg, range = 2.0–3.7
Parental background	
Mother's age N = 18	Mean = 31 years, range = 22–37
Father's age N = 17	Mean = 33 years, range = 21–43
Prenatal complications	
None	4
Preterm labor	2
Bleeding	1
Urinary tract infection	1
Polyhydramnios	2

Race	N	%
Caucasian	18	90
Hispanic	2	10

FIG. 3. Corrected club foot.

The average maternal age at the time of conception was 31 years and the average paternal age was 33 years. The mean birth weight of this cohort was 2.7 kg with a range of 2.0 km to 3.7 kg. Prenatal complications included preterm labor in two, vaginal bleeding in one, urinary tract infection in one, and polyhydramnios in two. The remaining pregnancies were uncomplicated. The mean age at which the patients underwent initial neurodevelopmental testing was 35.8 months at this program.

All the children were identified because of dysmorphic features (Table II). The average age of diagnosis was 4 months (range: neonatal to 16 months). Common findings included a characteristic facial appearance (upslanting palpebral fissures, hypertelorism, synophyrs, arched eyebrows) as well as radioulnar synostosis. Less common clinical features included cleft lip and palate in two, ear malformation in five (ear tag, abnormal helix), kidney malformation in two, hip dysplasia in five, pterygium in one, hyperextensible skin in one, fifth finger clinodactyly in six, and syndactyly in one. Torticollis was present in six individuals. All patients had generalized hypotonia with decreased tonus in trunk, extremities, and oral facial musculature[Q6] (Fig. 3).

TABLE II. Patient Characteristics Dysmorphic and Clinical Features of the Cohort of Boys Evaluated With 49, XXXXY

Characteristic	N	Percent
Hypotonia	15	100
Small birth weight	9	60
Severe speech delays	15	100
Facial appearance	15	100
Radioulnar synostosis	15	100
Torticollis	6	30
Seizures	4	26.6
Microphallus	3	20
Synophrys (arched eyebrows)	14	93.3
Cleft palate	1	6.6
Ear malformation	2	13.3
Kidney dysplasia	2	13.3
Upslanting palpebral fissure	14	93.3
Ptygerium	1	6.6
Hip dysplasia	5	33.3
VSD	1	6.6
Clinodactyly	2	13.3

Eight of nine patients ranging in age from 11 months to 15 years demonstrated normal growth centiles from the 12th to the 98th centile of height and 10th to 95th centile of weight (Fig. 4) resulting in a body mass index (BMI) centile = 70.67 ± 27.21 for those over 2 years of age, and weight for height centile = 61.20 ± 35.95 (Table III). Growth velocity was variable by age group with a z-score = 0.50 ± 0.77 for those 3–5 years of age, 0.85 ± 69 for those 5–9 years of age and −0.09 ± 9.17 for those over 9 years of age.

Penile length ranged from <2.5 in a 5-year-old child to a maximum of 5.5 cm in a 13-year-old undergoing testosterone therapy, all below the 10% for typically developing prepubertal or early pubertal male. Testicular size was universally small with a range of 1–3 cm, though within normal range for the 10 of 11 patients who were prepubertal (Table IV). One was in early pubertal development. Five patients had received or were receiving testosterone therapy for treatment of microphallus, and two patients had required surgical repair of penile–scrotal reversal.

MRI of the brain had been performed for clinical reasons in 10 individuals and six studies were abnormal. The findings included paucity of white matter, delayed myelination, cortical dysgenesis, and cavum septum pallucidum. Three subjects had febrile seizures and two subjects had a single afebrile seizure. Electroencephalograms had been performed on five individuals and were normal.

Motor milestones were delayed in all patients with the average age for independent ambulation being 25.5 months (range 16–27 months). Motor testing revealed significant asymmetry with shortened musculature in pelvic region and upper trunk. Gait was characterized by shortened stride with over utilization of extension and decreased truncal rotation and flexion. Dexterity and fine motor skills were more intact than locomotion and balance.

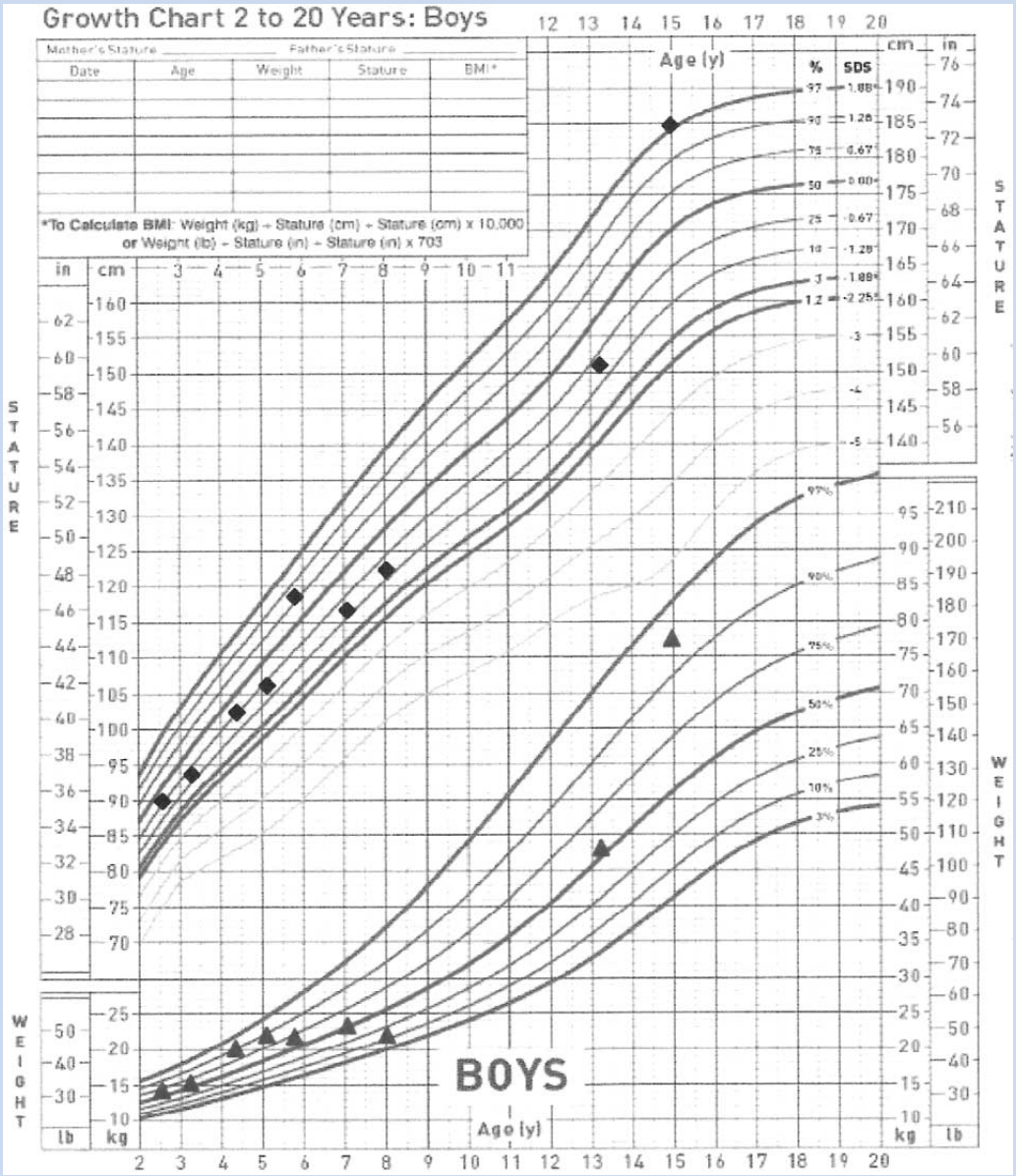

FIG. 4. The height and weight centiles of nine boys with 49, XXXXY karyotype.

Sensory processing skills were atypical in all boys in the auditory and vestibular domains as measured by the sensory profiles developed by Winnie Dunn. Endurance and modulation were atypical. All boys had sensory dysfunction in the majority of the domains.

Speech was universally delayed with mean age for consonant and vowel sounds being 15.2 months with a range of 4–36 months. Speech and language testing showed significant deficits in expressive language relative to receptive language with better nonverbal capabilities (Tables Va and Vb), a pattern typical in children with developmental dyspraxia. Decreased muscle tonus in the oral facial musculature with paucity of movement in the facial muscles was noted and also characteristic of oral and verbal dyspraxia. Neurodevelopmental testing revealed depressed verbal capabilities with more intact nonverbal capabilities in most children. On the Bayley Scales, the MDI and PDI average scores were 79.5 and 70.6 respectively. Using the Leiter-R in 13 older children, the mean age was 51.7 months for the 19 scores, a mean nonverbal IQ of 89.3 was obtained, which is within the normal range limits (Table Vb).

Completing all, the neurodevelopmental testing was challenging for many of the children and four out of the 13 older children were unable to complete the Leiter-R because of either compliance or fatigue. The language testing was completed by 15 of the 17 children over 24 months. Although the test of Visual Motor Integration-5th Edition begins at 3 years of age, children with 49, XXXXY were unable to complete the testing prior to 55 months of age because of suspected graphomotor dysfunction and limb dyspraxia.

TABLE III. Growth Parameters of Boys With 49,XXXXY Examined in This Cohort

Parameter	Mean	SEM
HAC (N = 13)	33.38	8.04
WAC (N = 12)	47.94	8.97
BMIC (N = 9)	70.67	9.07
WHC (N = 9)	61.20	11.98
HAZ (N = 13)	−0.4738	0.2849
WAZ (N = 12)	−0.1817	0.3534
BMIz (N = 9)	0.7600	0.34772
WHZ (N = 9)	0.3967	0.4543

HAC, height age centile; WAC, weight age centile; BMIC, body mass index centile; WHC, weight for height centile; HAZ, height age z-score; WAZ, weight age z-score; BMIz, body mass index z-score; WHZ, weight for height z-score.

Seven children above age three were screened for autism spectrum disorder using the Gilliam Autism Rating Scale (GARS), a standardized screening measure. The GARS was developed to identify children with autism spectrum disorder (ASD) from children with behavioral dysfunction but not autism. The scale was based on the diagnostic criteria identified in the DSM-IV and is widely used to identify children in the general population at risk for ASD. Overall, 7/7 patients screened negative for concern for autism spectrum disorders.

DISCUSSION

The 49, XXXXY syndrome is one of the rarest sex chromosome disorders, and has been associated previously with pre- and postnatal growth deficiency, neurocognitive delays with MR, hypogenitalism, and other skeletal, facial and cardio-vascular anomalies [Hayek et al., 1971; Morić-Petrović et al., 1973; Pallister, 1982; Sheridan et al., 1990; Linden et al., 1995; Peet et al., 1998; Samango-Sprouse, 2007]. Here, we present the largest series of boys with this condition to date, and discuss the clinical features and the neurobehavioral and neurodevelopmental profile in 20 boys. There is some ascertainment bias to patient selection since families hear about the conference through parent list serves and word of mouth and there is the cost of travel to the conference. This bias has been minimized to some extent because there are now two foundations providing scholarships to families to broaden the availability of participation in the conference and study.

The common clinical features in these boys were borderline growth deficiency in contrast to previous studies that showed diminished prenatal growth. The growth parameters of boys with 49, XXXXY may be evolving to a more normalized pattern of growth since this is larger and more representative sample of the disorder. Previous studies were quite small and this result in a selection of a skewed population. Previous literature has described the diminished size of the phallus and this is often one of the primary concerns resulting in diagnosis during early infancy. Our study reveals that all boys fall below the 10% for typically developing peers. The fact that all boys fell below the 10% for the size of phallus suggests a pervasive effect and a possible androgen deficiency although four of the boys had received hormonal replacement early in life. Our study results raise more queries in the effect and the role of androgen if any on learning and neurodevelopmental progression. Further investigation is underway for next year's annual conference to explore these complex issues.

TABLE IV. Genital and Pubertal Characteristics in 12 Males With 49, XXXXY

Case	Age (years)	Testicular volume	Penile length	TPH
7	0.99	Retractile		1
12	1.42	1.25	4.5	1
26	2.57	1.00	3.25	1
18	4.35	1.00	4	1
11	4.36	<1.0	2.5	1
1	4.37	<1.0	2.5	1
17	5.07	1.61	<2.5	1
4	5.82	Undescended	5.5	1
3	7.10	1.00	4	1
24	8.06	0.50	4	1
25	13.27	3.00	5.5	2

TPH, tanner stage.

TABLE Va. Results of the Neurodevelopmental Evaluations on Boys With 49, XXXXY Under 36 Months

Patient	CA	PDI	MDI	AC	EC
5	11	59	50	72	69
7	11	70	60	102	82
6	14	100	100	102	100
8	14	67	100	81	77
1	16	60	56	102	106
18	16	50	70	96	71
12	17	67	80	103	103
7[a]	17	64	100	99	83
13	19	x	50	71	67
21	22	70	80	84	81
13[a]	26	50	58	89	77
26	26	x	x	69	x
11	27	x	x	77	51
6[a]	27	x	85	91	68
7[b]	28	76	95	102	71
19	31	50	50	75	67
4	33	64	x	102	57
N	17	12	13	17	15
Mean	22.2	70.6	79.5	94.8	82.0
SD	7.1	13.4	20.0	12.8	15.5
Range	11–85	<50–100	<50–100	50–103	50–106

CA, chronological age; PDI, psychomotor development index; MDI, mental development index; AC, auditory comprehension; EC, expressive communication; N, number; SD, standard deviation. Preschool Language Scale, 3rd and 4th Edition.
x, not given because of fatigue.
[a]2nd visit.
[b]3rd visit.

TABLE Vb. Results of Neurodevelopmental Evaluations on Boys With 49, XXXXY Over 24 Months

Patient	CA	AC	EC	EOW	ROW	VMI	MC	VP	FL	Brief IQ
13[a]	26	89	77	61	77				x	x
26	26	69	x	x	76				75	62
11	27	77	51	64	59				80	87
6[a]	27	91	68	x	82				120	111
7[b]	28	102	71	71	91				x	x
19	31	75	67	x	x				x	x
4	33	102	57	57	102				112	103
18[a]	40	89	59	55	75				122	95
21[b]	40	81	71	89	79				x	x
4[a]	45	86	91	63	96				127	124
5[a]	46	74	60	55	67				79	82
17	48	82	84	77	91				112	115
20	49	76	56	65	75				62	73
18[b]	52	84	50	58	68				x	x
4[b]	56	83	83	71	82	72	82	104	x	x
15	60	66	56	61	64	59	45	53	98	89
23	60	83	54	76	91	80	60	78	104	102
24	60	x	x	55	59	53	45	60	79	76
9	62	66	50	90	98	45	45	74	80	80
4[c]	68	72	72	80	83	79	x	92	88	93
17[a]	72	97	68	70	84	77	78	62	80	80
24[a]	72	59	50	65	72	x	x	x	79	76
24[b]	84	55	50	56	55	57	63	45	65	67
3	85	50	50	55	58	57	63	45	75	76
24[c]	96	x	x	55	55	x	x	x	60	63
N	25	23	22	22	24	9	8	9	19	19
Mean	51.7	78.6	63.4	65.9	76.6	64.3	60.1	68.1	89.3	87.1
SD	20.2	13.8	12.6	10.9	14.0	12.8	14.6	20.6	21.0	17.6
Range	26–85	50–102	50–84	55–90	55–102	45–88	45–82	45–104	60–127	63–124

CA, chronological age; AC, auditory comprehension; EC, expressive communication; EOW, expressive one word picture vocabulary test-revised; ROW, receptive one word picture vocabulary test-revised; VMI, visual motor integration; MC, motor coordination; VP, visual perception; FL, fluid reasoning; N, number; SD, standard deviation.
Preschool Language Scale, 3rd and 4th Edition.
x, not given because of fatigue.
[a]2nd visit.
[b]3rd visit.
[c]4th visit.

Facial appearance consisted of arched eyebrows, ocular hypertelorism, flat nasal bridge with upslanting palpebral fissures, and radioulnar synostosis. There was more variability with regard to other presenting features including cleft lip and palate, cardiac defects, clubfoot (Fig. 4), and torticollis. Torticollis was present in approximately 30% (N = 6) of the children.

Neurological features include generalized hypotonia, delayed neuromotor skills, and verbal and oral motor dyspraxia. Twenty Percent (five of 20 children) had seizures although EEG's were normal. MRI scans that had been obtained in only 10 of the 20 subjects demonstrate delays in myelination. White matter abnormalities have been recently described as a component to this disorder [Hoffman et al., 2008]. The cognitive findings may be related to the white matter abnormalities and further investigation with brain imaging studies of children with 49, XXXXY is underway.

The most common speech and language based anomaly is developmental dyspraxia affecting verbal and oral motor function. However, many of the boys have both receptive vocabulary and comprehension falling within the normal range, further substantiating the complexity and severity of their expressive language deficits and their dyspraxia [Samango-Sprouse, 2001; Samango-Sprouse et al., 2002]. Additionally, the majority showed more intact skills on nonverbal testing that has not been previously described in the research literature. The mean age of the nonverbal testing was young (51 months), therefore longitudinal data are crucial in order to understand the evolution of the nonverbal capacities in children with 49, XXXXY as the boys mature. Yet, it is intriguing to consider that if these intact nonverbal capacities remain stable they may provide an opportunity to reduce behavioral issues and increase learning as well as further understand the brain variations noted in this rare disorder. The preponderance of children with dyspraxia often develop behavioral issues and outbursts possibly due to frustration with their inability to communicate needs and opinions as well as frontal lobe insufficiency [Samango-Sprouse, 2007]. Both the decreased communicative abilities and their decreased frontal lobe capacity may be contributory to some of the behavioral issues associated with 49, XXXXY. Further studies are needed into the

neurodevelopmental profile and the complex interaction between behavior and brain development.

Our findings indicate that the majority of children with 49, XXXXY have better neurocognitive capacities on a nonverbal domain with intact receptive vocabulary and comprehension skills further substantiating areas of preservation in spite of the deleterious effects of the additional X and the developmental dyspraxia. Alternative communication strategies in children with 49, XXXXY are of the utmost importance in order to minimize their behavioral issues as well as provide a mechanism for them to express their wants and desires (Table VI).

It is plausible that the predominantly young age of the children studied has artificially inflated the nonverbal and receptive domains. Yet, if the young age was causing a positive effect, it should be evenly distributed through all neurodevelopmental domains. In our population, the results indicate a more selective effect that suggests a neurological underpinning than the age alone. The few children who had repeated assessments (Tables Va and Vb) show a consistent neurodevelopmental profile with more normalized receptive and nonverbal capabilities over time. Comprehensive long-term follow-up is underway to further investigate the natural history of these preserved receptive capabilities and more intact nonverbal capacities.

TABLE VI. A Comparison of Nonverbal Scores and Receptive Language Levels

Patient	CA	PLS AC	ROWPV	Leiter-R fluid reason	Leiter-R brief IQ
13[a]	26	89	77	x	x
26	26	69	76	75	62
11	27	77	59	80	87
6[a]	27	91	82	120	111
7[b]	28	102	91	x	x
19	31	75	x	x	x
4	33	102	102	112	103
18[a]	40	89	75	122	95
21[b]	40	81	79	x	x
4[a]	45	86	96	127	124
5[a]	46	74	67	79	82
17	48	82	91	112	115
20	49	76	75	62	73
18[b]	52	84	68	x	x
4[b]	56	83	82	x	x
15	60	66	64	98	89
23	60	83	91	104	102
24	60	x	59	79	76
9	62	66	98	80	80
4[c]	68	72	83	88	93
17[a]	72	97	84	80	80
24[a]	72	59	72	79	76
24[b]	84	55	55	65	67
3	85	50	58	75	76
24[c]	96	x	55	60	63
N	25	23	24	19	19
Mean	51.7	78.6	76.6	89.3	87.1
SD	20.2	13.8	14.0	21.0	17.6
Range	26–96	50–102	55–102	60–127	62–124

CA, chronological age; ROWPV, receptive one word picture vocabulary test-revised; N, number; SD, standard deviation.
PLS-AC Preschool Language Scale, 3rd or 4th Edition, Auditory Comprehension.
x, not given because of fatigue.
[a]2nd visit.
[b]3rd visit.
[c]4th visit.

Previous studies in boys with 47, XXY or Klinefelter syndrome have shown language-based learning deficits with frontal lobe dysfunction [Samango-Sprouse, 2001; Simpson et al., 2003; Giedd et al., 2006, 2007] that lead to academic difficulties in school. Decreased motor control and motor abilities are evident in the boys with 47, XXY and the children with 49, XXXXY as well. Because of the motor planning deficits and dyspraxia in oral motor and verbal abilities, most boys with 47, XXY have a lag in early expressive language skills with delayed acquisition of single words and phrases. Language formulation is more affected than receptive skills [Pallister, 1982]. The pattern of deficits noted in our subjects with 49, XXXXY included problems in both production of nonverbal movements and oral language production, with deficits in morphology, word retrieval abilities, and oral narrative construction.

In the less severe sex chromosome disorder, 47, XXY, brain morphometry has shown gray matter reductions in the insula, temporal gyri, amygdala, hippocampus, and cingulate gyrus [Samango-Sprouse, 2007; Giedd et al., 2007]. These areas are anatomically consistent with the language based learning difficulties in 49,XXXXY as well as the boys with 47, XXY [Patwardhan et al., 2000].

The severity of language-based learning deficits in this group is moderate to severe and affects their ability to develop social interactions and results in behavioral manifestations of frustration and oppositional behavior. Those children with alternate communication such as gestural language and an augmentative communication system have demonstrated reduced behavioral issues and improved neurocognitive capacities. We suspect decreased phonemic awareness in many of these children associated with their severe speech delay and delayed onset of spoken language. This warrants further investigation in order to further understand the phenotypic presentation and the relationship between the severity of the speech delay and the development of reading function.

The deleterious effects on physical and cognitive development increase with the extra number of X chromosomes [Visootsak and Graham, 2006]. This comprehensive study reveals a greater variability to the neurodevelopmental presentation to this disorder than had been previously appreciated. Speech delay and decreased IQ have been reported in this group [Samango-Sprouse, 2001; Visootsak and Graham, 2006; Visootsak et al., 2007]. IQ has been believed to decrease approximately 15 points per additional X chromosome with the mean IQ in 49, XXXXY between 60 and 80. In this group, the mean nonverbal IQ was 89.3, (range 60 to 127; mode of 80). The presence of severe dyspraxia in both oral and verbal domains may explain the significant speech and expressive language delay and to some extent the behavioral manifestations. Early intervention and targeted treatment with syndrome-specific goals focused on the dyspraxia and communication dysfunction may reduce the severity of the language based learning disorders and optimize the child's performance while minimizing the behavioral complications.

Based on these data, recommendations for evaluation and treatment of children with 49, XXXXY include a comprehensive, multidisciplinary evaluation, by a team that is familiar with neurogenetic disorders and complex neurodevelopmental disorders. Consultation with a pediatric endocrinologist to discuss possibility of hypogonadism and possible androgen replacement is important component of this team. A neurodevelopmental evaluation should include neurocognitive, speech-language, and motor skills. Nonverbal cognitive assessment is an important component due to the presence of significant developmental dyspraxia with severe speech delay and expressive language skills. Intensive therapeutic interventions, which should focus on developmental dyspraxia and motor planning deficits including development, speech, occupational, and physical therapies, are highly recommended. These children have complex neurodevelopmental dysfunction and motor planning deficits, which have a profound effect on all aspects of their learning and behavior. When the diagnosis of 49, XXXXY is identified, the variability in clinical presentations and the importance of early and aggressive treatment for the developmental dyspraxia and other neurodevelopmental dysfunction should be discussed with families.

Differences in the clinical presentation may in part be attributed to skewing of X inactivation. Iitsuka et al. [2001] studied the parent of origin and specific X inactivation patterns of patients with 47, XXY and 48, XXYY and found a surprising high percentage (80%) of parental skewing. Because we only had access to the karyotype report, many conducted with 10–20 prometaphases, the possibility of low-level mosaicism may also play a role in the variability of neurodevelopmental presentation. New research has also indicated methylation abnormalities in sex chromosome aneuploidies and hypothetically this could also explain some or even all the variance in phenotypic presentation. We plan to investigate these possibilities in future studies.

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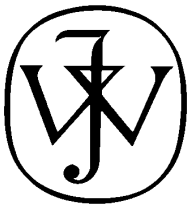

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