ARTICLE

Neurocognitive Variance and Neurological Underpinnings of the X and Y Chromosomal Variations

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X and Y chromosomal variations including tetrasomy and pentasomy conditions are rare and occur in 1:18,000–1:100,000 male births. The most common sex chromosome aneuploidy is 47, XXY for which there is a rich literature delineating the physical and neurobehavioral phenotype. Although the more complex chromosome aneuploidies 48, XXYY, 48, XXXY, and 49, XXXXY are often compared with 47, XXY (Klinefelter syndrome) because of shared features including tall stature and hypergonadotropic hypogonadism, there is a wider spectrum of physical and cognitive abilities that have recently been delineated. The phenotypic presentation of the boys with more severe aneuploidy shares some characteristics with 47, XXY, but there are also other unique and distinctive features. Previously unappreciated intact nonverbal skills have been demonstrated in association with severe developmental dyspraxia. MRI findings of white matter hyperintensities may underlie cognitive deficits and deserve further study. This report discusses what is known about clinical variability in the XY syndromes collectively evaluated through careful multidisciplinary clinical evaluation including the clinical and neurobehavioral aspects of these conditions. Variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or epigenetic factors that warrant further investigation.

KEY WORDS: aneuploidies; sex chromosome; 47, XXY; 48, XXXY; 49, XXXXY; dyspraxia

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INTRODUCTION

48, XXYY, 48, XXXY, and 49, XXXXY syndromes are rare sex chromosome aneuploidies characterized by the presence of two or more extra X and/or Y chromosomes in males. The presence of one or more additional X chromosome(s) results in testicular dysgenesis with resultant hypergonadotropic hypogonadism. The impact of early lack of testosterone has been discussed in the setting not only of gonadal functions, but of later neurocognitive development, and early repletion of testosterone may improve cognitive outcomes [Samango-Sprouse et al., 2011, in press]. Prior to cohort studies, 48, XXYY, 48, XXXY, and 49, XXXXY have often been considered "severe variants" of 47, XXY (Klinefelter syndrome) because of these shared features.

With each additional X chromosome, there are increased risks for congenital malformations outside of endocrine function, as well as more complex and varied neurocognitive variance, thus making a distinction from 47, XXY clinically relevant for these patients.

Conflict of interest: None.

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However, with longitudinal cohort studies, the remarkable clinical variability within and among the syndromes has been realized. With each additional X chromosome, there are increased risks for congenital malformations outside of endocrine function, as well as more complex and varied neurocognitive variance, thus making a distinction from 47, XXY clinically relevant for these patients [Peet et al., 1998; Tartaglia et al., 2008].

47, XXY is the most common of the X chromosome aneuploidies in males with an incidence rate of approximately one in 650 males, making it one of the most common chromosome anueploidies [Evans et al., 1982; Coffee et al., 2009] and there is a robust literature regarding neurodevelopmental profile and brain neuroimaging [Lenroot et al., 2009]. With regard to the more rare X chromosome aneuploidies, 48, XXYY syndrome is the most common of these three syndromes and is estimated to occur in 1:18,000–1:40,000 male births [Sørensen et al., 1978], whereas the incidence of 48, XXXY is estimated to be 1:50,000, and the most rare, 49, XXXXY occurs in 1:85,000–1:100,000 male births [Kleczkowska et al., 1988].

GENETIC ETIOLOGY

The majority of cases of 48, XXYY syndrome result from a nondysjunction event in which there is fertilization of a normal female oocyte (Xm), with an aneuploid sperm (XpYpYp) that is produced through nondisjunction events occurring in both meiosis I and meiosis II of spermatogenesis. Postzygotic nondisjunction may occur during mitosis, (and accounts for 8% of cases with 47, XXY and 14% of cases with 47, XXX), resulting in XmXmYpYp [Hassold et al., 2007]. Where parental studies have been performed, the additional X (and Y) chromosome has been shown to be paternal in origin [Rinaldi et al., 1979; Leal et al., 1994].

Similarly, 49, XXXXY results from nondisjunction of the X chromosome during meiosis I and meiosis II, leading to an aneuploid oocyte (Xm Xm Xm Xm) which is then fertilized with a normal male sperm (Yp). Parent of origin effects have been described and may influence the phenotype through imprinting [Rinaldi et al., 1979]. There are limited studies that address additional epigenetic factors that may influence the clinical presentation of these boys, and this research is needed to explain phenotypic variability.

DEVELOPMENTAL AND NEUROCOGNITIVE SPECTRUM IN THE X AND Y CHROMOSOMAL VARIATIONS

Androgens influence neurodevelopment, brain function, and behavioral outcomes from as early as 16 weeks gestation, continuing throughout adulthood [Knickmeyer and Baron-Cohen, 2006]. Fetal testosterone affects development of the cortex and limbic systems [Hines et al., 2006; Genazzani et al., 2007]. Hormones have an important place in modulating mood, neurocognitive capacities, and even the aging process [Collacott et al., 1990; Chura et al., 2010; Verri et al., 2010]. Variation in brain morphology and linear growth which varies between girls and boys has been attributable to hormonal interplay. The effect of androgen deficiency on behavior, neurodevelopment, and cognition have not been well explored in boys or men with 47, XXY; however, to date, small studies suggest the positive effects of testosterone treatment in adult males with 47, XXY [Patwardhan et al., 2000; Lanfranco et al., 2004; Steinman et al., 2009]. Androgen deficiency may be contributing to the complex neurodevelopmental issues of boys with 49, XXXXY as well as boys with 47, XXY [Samango-Sprouse et al., 2011, in press].

The earlier literature presented a rather dismal picture of the neurocognitive expectations of boys with 48, XXYY, 48, XXXY, and 49, XXXXY syndromes. Across the board, developmental delays are common in infancy and early childhood, with speech delays being more evident and often leading to clinical evaluation. However, neuromotor delays and associated hypotonia are present in about 75–100% of boys, impacting their average age of independent ambulation and quality of gross and fine motor skills development.

It has been suggested that cognitive abilities decrease by 10–15 IQ points for each additional X chromosome [Visootsak et al., 2007]. However, a cognitive profile that emerges in these boys includes strengths in visual perceptual and nonverbal cognitive skills. The weaknesses encompass verbal skills and language formulation which has been previously well described [Samango-Sprouse and Rogol, 2002; Visootsak et al., 2007; Gropman et al., 2010].

47, XXY

47, XXY syndrome is the most common human sex chromosome disorder [MacLean et al., 1961]. The cognitive phenotype in 47, XXY includes language-based learning disabilities, decreased fine motor skills, and discrepancies between nonverbal and verbal cognitive abilities. Delayed speech development requiring speech therapy [Ratcliffe, 1982; Leggett et al., 2010] has also been observed in both boys with 47, XXY and boys with 47, XYY.

Previous studies in boys with 47, XXY or Klinefelter syndrome (KS) have shown language-based learning deficits with frontal lobe dysfunction [Samango-Sprouse, 2001; Simpson et al., 2003; Giedd et al., 2007] that lead to academic difficulties in school.

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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. This leads to delay in acquisition of single words and phrases. Expressive language is generally more affected than receptive skills [Pallister, 1982]. In the less severe X & Y chromosomal variation, 47, XXY, brain morphometry has shown gray matter reductions in the insula, temporal gyri, amygdala, hippocampus, and cingulate gyrus [Giedd et al., 2007]. These areas are anatomically consistent with the language based learning difficulties in the boys with 47, XXY [Patwardhan et al., 2002].

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 young children with alternate communication such as gestural language and an augmentative communication system have demonstrated reduced behavioral issues.

Boys with XXY are known to have increased risk for psychosocial problems and may present with impaired motor development, decreased verbal abilities, and they are more likely than other boys to require extra educational support and speech therapy services [Cohen and Durham, 1985; Nielsen and Pelsen, 1987; Nielsen and Wohlert, 1990; Sørensen, 1992; Rovet et al., 1995; Rovet et al., 1996; Ross et al., 2008; Girardin et al., 2009]. The cognitive phenotype of XXY is generally characterized by impaired performance on measures of language development, attention, and academic abilities. In younger boys delays in speech milestones may be observed, whereas significant deficits in higher aspects of expressive language are more common in older patients. In a recent study, Samango-Sprouse et al. [in press] have demonstrated reduction in symptomology from a short course of testosterone.

A higher prevalence of psychiatric disorders such as autism spectrum disorders (ASD), attention deficit/hyperactivity disorders (ADHD), and schizophrenia in patients with XXY compared with the general population has been reported. Bruining et al. [2009] found a high incidence of ADHD in 63% and ASD in 27% of 51 boys with XXY aged 6–19 years. These studies have been flawed to some degree by inadequate sample size and incomplete evaluations of familial learning disorders and history of mental illness. The complexity and the variability of some boys with XXY is an intriguing question regarding the relationship between brain function, family learning patterns, and chromosomal anomalies such as XXY.

48, XXYY

Neurological phenotyping of the first 53 described cases of 48, XXYY included seizures in some, intention tremor, hypotonia, and tics in small series of patients [Sørensen et al., 1978; Vanyan, 1984; Donati et al., 1992; Izumi and Tsubahara, 2000; Zelante et al., 2003]. Brain MRI showed abnormal, but nonspecific findings in some boys including agenesis of the corpus callosum [Nyberg et al., 1994] or frontoparietal cortical atrophy [Demirhan, 2003]. Not all boys have undergone neuroimaging. Volumetric averaging has not been performed to date in this cohort.

Similar to the cognitive profile in 47, XXY, speech and motor delays with poor coordination and motor planning are evidenced in the first few years of life [Garvey and Kellett, 1975; Fryns et al., 1995]. IQ profiles generally show a discrepancy with a higher overall performance than verbal IQ [Zack, 1990]; with the majority having an IQ in the 70–80 range [Netley, 1986]. Co morbid attention deficit and autism spectrum behaviors have also been described; however, this data is based on extremely small sample sizes of case studies [Schlegel et al., 1965; Sørensen et al., 1978; Fryns et al., 1995]. The variability of the boy with 48, XXXY is quite significant and some boys have IQ in the low normal range with early treatment and services [Samango-Sprouse, unpublished data, 2011].

In a large cohort study of 95 males with 48, XXYY syndrome, ranging from 1 to 55 years of age, cognitive profiles revealed strengths in visuoperceptual skills relative to language-based tasks.

In a large cohort study of 95 males with 48, XXYY syndrome, ranging from 1 to 55 years of age, cognitive profiles revealed strengths in visuoperceptual skills relative to language-based tasks.

Interesting, it was found that VIQ significantly decreased with age; however, this may was attributed to variable educational opportunities across such a broad age range ascertained, especially in the older males who may have been diagnosed later and had more limited educational interventions. Cognitive abilities did not predict adaptive functioning, as has been seen in other chromosome based disorders [Martin et al., 2006]. Neurobehavioral co-morbidities included ADHD and ASD, for which many of the subjects were receiving medication.

In typically developing populations, adaptive functioning correlates with cognitive ability (IQ). Additionally, measures of adaptive functioning are part of the criteria necessary for the diagnostic criteria for intellectual disability [Tassé et al., 2012]. Furthermore, as adaptive functioning scores are also often used for eligibility for disability support services, it is necessary to study sub domains of adaptive functioning as it allows for the identification of individual—strengths and weaknesses for each individual and can be used to determine services.

Visootsak et al. compared the results of adaptive functioning using the Vineland Adaptive Behavior Scales in a cohort of 13 males with 48, XXYY and 11 males with 48, XXXY and 49, XXXXY. The mean standardized scores for adaptive functioning were in the disability range in both groups. The boys with 48, XXYY showed significantly higher

scores in the domains of daily living skills and communication compared with the boys comprising the 48, XXXY/49, XXXXY group. Curiously, they found no significant differences in social skills [Visootsak et al., 2007]. Adaptive functioning skills were further explored in a cohort of 47 males with 48, XXYY syndrome and were found to be significantly lower than IQ in most cases, with a mean adaptive functioning score of 68.9. These findings suggest that overall daily functioning is often more impaired than would be expected for these males based on cognitive (IQ) scores alone. The reason for these deficits in adaptive skills warrants further exploration and it is plausible that motor planning deficits and hypotonia are contributing factors.

49, XXXXY

The 49, XXXXY syndrome first reported in 1960, is often considered the most severe variant of the spectrum. Clinical features include characteristic facial appearance, intellectual disability, 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]. Formal cytogenetic analysis is necessary to make a definitive diagnosis because of milder presentations and later diagnosis.

Boys with 49, XXXXY have been assumed to be universally cognitively impaired. Previous reports gave IQ ranges from 20 to 60. The personality of the boys is rather shy and friendly, with irritability and temper tantrums, low frustration tolerance, and difficulty transitioning and changing routines [Samango-Sprouse, 2001]. Whereas previous reports have suggested severe intellectual disability, more recent reports are more optimistic, including larger cohort studies have identified milder cognitive delays and learning styles similar to 47, XXY individuals [Sheridan et al., 1990; Samango-Sprouse, 2001; Samango-Sprouse and Rogol, 2002; Visootsak and Graham, 2006; Visootsak et al., 2007]. 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.

Neurological features in these boys include generalized hypotonia in all, delayed neuromotor skills and verbal and oral motor dyspraxia. Very few patients exhibit seizures. Those that have seizures, tend to exhibit febrile events or abnormal EEGs without a clinical correlate. MRI scans, obtained in a handful of boys, demonstrate delays in myelination and T2 hyperintensities in the white matter (Fig. 1). White matter abnormalities are recently being recognized as a component to this disorder [Hoffman et al., 2008] and may be related to the underlying cognitive findings.

The most common speech and language based anomaly found was developmental dyspraxia affecting verbal and oral motor function. In contrast to previous reports in the literature, the majority did not show intellectual disability on nonverbal testing. While many have receptive vocabulary and comprehension falling within the normal range, this further delineates the severity of their expressive language deficits and their dyspraxia in accomplishment of academic and social goals [Samango-Sprouse, 2001; Samango-Sprouse and Rogol, 2002].

NEUROIMAGING AND X AND Y CHROMOSOMAL ABNORMALITIES

Advances in neuroimaging are beginning to help inform the link between cognitive variance and underlying structural damage. Understanding the effects of gene dosage on brain development may help to understand the basis for functional differences in affected individuals.

Previous studies suggest that gender is the single greatest discriminating morphometric factor in brain size in humans [Giedd et al., 1997]. Factors giving rise to sexual dimorphism may be risk factors or protective agents for neurodevelopmental disorders, and understanding the development of sexual dimorphism may provide insights into the pathogenesis of neurodevelopmental disorders. One-way

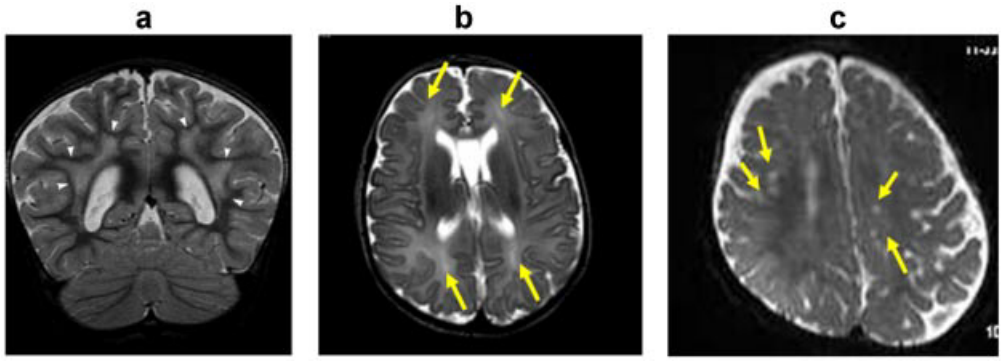

Figure 1. Brain magnetic resonance imaging performed at age 14 months in a patient with 49, XXXXY. There is ventriculomegaly and a slightly thin body of the corpus callosum, which are otherwise nonspecific findings. In coronal T2-weighted images (**a**), there are extensive patchy and confluent areas of abnormal high signal intensity in the periventricular and deep white matter. This affects primarily the parietal and frontal lobes (a and **b**). The subcortical U-fibers are spared. In a second patient (**c**) there are more punctuate lesions (arrows).

TABLE I. Neuroimaging Studies of Sex Chromosome Aneuploidies

Population	Findings	Refs.
47, XXY	Decreased total brain volume, increased ventricular size, increased white matter	Warwick et al. [1999]
47, XXY versus 46, XY	Small amydgala, small temporal lobes	Patwardhan et al. [2000, 2002]
47, XXY versus 46, XY	Small left temporal lobe, increased ventricular volume	Itti [2006]
47, XXY	Decreased total brain volumes, decreases in the frontal and temporal lobes and posterior superior temporal gyrus. DTI: decreased fractional anisotropy (FA) in the XXY males: left posterior internal capsule, left arcuate bundle, and both the right and left anterior cingulate areas	DeLisi et al. [2005]
47, XXY versus 46, XY	Decreased brain volume caudate, all lobar volumes except parietal white matter	Giedd et al. [2007]
47, XXY versus 46, XY	Decreased cortical thickness; fMRI: lateralization index during language related tasks ↓	van Rijn et al. [2008]
49, XXXXY	Volume loss and abnormalities in white matter, sparing U fibers	Hoffman et al. [2008]

study dosage effects of genes on the X and Y chromosomes is clinical imaging and cognitive studies of patients with X and Y chromosome aneuploidies.

Since hormone levels can be manipulated and studied in animal models, theories about the effects of hormones on the brain are put forth. Differences in the neural expression of X and Y genes may be more prominent than previously appreciated [Arnold, 2004; Vawter et al., 2004; Weickert et al., 2009]. The X chromosome, is of great interest in studies of cognition because of the disproportionately high number of X chromosome linked genes that are expressed in the brain, as well as associated X linked syndromes affecting cognitive function [Ropers and Hamel, 2005; Skuse, 2005].

Studies of 47, XXY males make up the majority of references in the current literature of neuroimaging studies in individuals with supernumerary sex chromosomes. A handful of magnetic resonance imaging (MRI) studies have examined the impact of an additional X chromosome in males (see Table I) [Warwick et al., 1999]. MRI findings for the 47, XXY individuals in this cohort included significantly smaller whole brain volume and increased volume of the ventricles. White matter hyperintensities 2 mm or greater in diameter were seen in 5 of the 47, XXY males but in none of the controls. Findings in 47, XXY males typically include decreased gray and white matter volumes, with more marked effects in the frontal and temporal lobes [Lenroot et al., 2009]. These MRI findings correlate with neurodevelopmental performance and androgen receptors are also located in these brain regions. Functional MRI studies have shown evidence of decreased lateralization.

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Gray and white matter segmentation and measurement of lobar, subcortical, and ventricular volumes were performed using automated methods [Steinman et al., 2009], whereas manual tracing was used to delineate the volume of the superior temporal gyrus (STG). Measurements of cognitive function included IQ and verbal fluency. Gray and white matter volumes were found to be similar between XXY males and controls. Smaller temporal lobe volumes and STG volumes were found in the XXY group, although this did not persist after adjustment for total brain volume. However, when comparing individuals who had received or not received testosterone supplementation, there were major differences. XXY individuals who did not receive testosterone supplementation had smaller temporal and STG volumes than did both XXY individuals who had received testosterone or healthy age matched controls.

In a study of 11 self-referred men with 47, XXY, DeLisi et al. [2005] used DTI and structural imaging to compare brain data in a study of 47, XXY versus controls. He found decreased total brain volumes, with specific decreases in the frontal and temporal lobes and posterior STG; but no significant differences in the anterior STG, amygdala/hippocampus complex, or ventricles. Four regions showed decreased fractional anisotropy (FA) in the XXY males: left posterior internal capsule, left arcuate bundle, and both the right and left anterior cingulate areas. However, structural MRI and DTI data did not show significant correlations with behavioral measures.

A quantitative neuroimaging study in children and adolescents with 47, XXY was performed at the National Institute of Mental Health as part of the Sex Chromosome Variations Study [Giedd et al., 2007]. Forty-two nonmosaic 47, XXY males were recruited and compared with an age and sex matched group of 87 healthy controls. All 47, XXY boys over the age of 14 had received testosterone supplementation; none of the group under 12 years had received a supplementation. IQ was found to be significantly lower in the 47, XXY group (95.2 ± 17.1 vs. 120.3 ± 11.3, $P < 0.0001$), although still within the normal range of intelligence, whereas the control group was higher than expected for population norms. Nonverbal IQ was less impaired than verbal IQ as would be expected.

In terms of the argument for decreased brain volume, hypogonadism alone is not sufficient to contribute to the decreased brain volume. Studies in females with 47, XXX also show decreased brain volume in the presence of normal pubertal maturation [Patwardhan et al., 2002]. This would suggest dosage effect of X chromosome genes [Giedd et al., 2007]. Additional X chromosomes, have been shown, such as in 49, XXXXY males, associated with more markedly decreased brain volume and increased incidence of white matter hyperintensities.

Brain MR imaging in 48, XXXY has shown nonspecific T2/Flair white matter hyperintensities in half of the patients which ranged in size and degree and were often overlooked as a nonspecific findings. These same changes have been identified in boys with 49, XXXXY. Whether they represent dysmyelination, demyelination, or glial scars from remote insult (inflammation or trauma), they have been noted in infancy as well as later childhood [Tartaglia et al., 2011].

Functional magnetic resonance imaging (fMRI) was used to study language lateralization in 15 self-referred right-handed 47, XXY adult males [van Rijn et al., 2006, 2008] and they were found to have a lower mean lateralization index.

Two studies have evaluated the effects of an additional X chromosome on brain activity in males using single photon emission computed tomography (SPECT) imaging to measure regional cerebral blood flow (rCBF) in nine self-selected adult right-handed 47, XXY males (average age 27.8 ± 6.6) and nine controls matched on age and handedness [Itti et al., 2003]. The 47, XXY subjects did not show the expected leftward perfusion asymmetries demonstrated in the control subjects, with the exceptions of the a few regions (precentral gyrus, transverse temporal gyrus, and cerebellum). Instead, significant rCBF increase was observed in the 47, XXY subjects in the right hemisphere regions including the prefrontal motor area, parietal associative regions, and temporal language areas. Hippocampi and cerebellum had decreased rCBF.

Three individuals with 49, XXXXY were studied at different ages [Hoffman et al., 2008]. One subject underwent MRI to evaluate significant developmental delay. There were two scans, one at 14 months of age and again at 20 months. Both exams showed decreased brain volume, increased ventricular volume, and decreased width of the corpus callosum. There were many, patchy T2 weighted hyperintensities in the periventricular and deep white matter of the parietal and frontal lobes, that were confluent in appearance. A second subject who was scanned at 7 years of age also showed volume loss, enlarged ventricles, and thinning of the corpus callosum. Periventricular and subcortical white matter showed several puncate foci of increased T2 signal intensity. The third case was an adult age 39 years, who was evaluated by MRI due to onset of generalized tonic–clonic seizures. Consistent with the other subjects, his MRI showed volume loss and atrophy in both cerebrum and cerebellum, associated with increased ventricular volume and thinning of the corpus callosum. Again, multiple foci of increased signal intensity throughout white matter of the periventricular, deep, and subcortical areas were present, much more than would be expected for an individual of his age (i.e., due to vascular etiologies).

DISCUSSION

Early literature suggest that neurocognition in supernumerary X and Y chromosomal variations beyond 47, XXY (i.e., 48, XXXY and 49, XXXXY syndromes), is guarded and more severe as the number of X chromosomes increases. As with the medical features, males with 49, XXXXY are generally more affected boys with 47, XXY and 48, XXXY. Early studies were based on rigid criteria and relied heavily on verbal output as measures of cognition, and area of weakness in these boys. However, more recent reports suggest a much broader spectrum of abilities and disabilities and less significant impairments than originally described, using nonverbal assessments.

Developmental delays are common in infancy and early childhood, with speech delays (especially in expressive language) present in almost all patients. In 48, XXYY, motor delays and associated hypotonia are present in the majority. In our recent large cohort study in 49, XXXXY we found motor delays and hypotonia in 100%, with independent ambulation at a mean of 25.5 months [Gropman et al., 2010].

Cognitive involvement is almost universal and it is estimated that cognitive abilities decrease by 10–15 IQ points for each additional X chromosome. In 48, XXXY, cognitive abilities with full-scale IQ scores reported to range from 20 to 78. In our study, the finding of a low average nonverbal IQ is important however, because it highlights an area of relative strength in the cognitive profile of 49, XXXXY syndrome.

In addition to cognitive and learning problems, other neurodevelopmental and psychological disorders are significant components of the phenotype of 48, XXYY, 48, XXXY, and 49, XXXXY syndromes and are typically more severe and/or complex when compared with 47, XXY.

Social development and behavior can also be affected in these conditions, likely related to an expressive language

and cognitive impairment. Whereas autism spectrum has been reported in some small studies of XXY, autism symptoms have not been studied in 48, XXXY and using the Gilliam Autism Rating Scale screening questionnaire in boys with 49, XXXXY, was not found [Gropman et al., 2010].

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This may reflect better understanding of the language deficit which may misclassify some patients without recognition of the other aspects of the cognitive phenotype. Emotional dysregulation including immaturity, anxiety, obsessive-compulsive behaviors, and impulsivity, are more commonly seen.

Neurological features include generalized hypotonia, delayed neuromotor skills and verbal and oral motor dyspraxia. Very few exhibit seizures or abnormal EEGs. MRI scans, demonstrate delays in myelination.

Neurological features include generalized hypotonia, delayed neuromotor skills and verbal and oral motor dyspraxia. Very few exhibit seizures or abnormal EEGs. MRI scans, demonstrate delays in myelination.

The most common speech and language based anomaly is developmental dyspraxia affecting verbal and oral motor function. However, the majority did not show intellectual disability on nonverbal testing. The preponderance of children with dyspraxia often develops behavioral issues and outbursts presumably due to frustration with their inability to communicate needs and opinions as well as frontal lobe insufficiency. 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 and Rogol, 2002; Gropman et al., 2010].

RECOMMENDATIONS FOR ASSESSMENT

The best approach to cohort studies is establishment of multidisciplinary evaluations. In our own center, we have established a team of physicians and allied health professional to assess the global impacts of X chromosome imbalance on neuromotor and cognitive function in addition to individual variability.

Our patients are evaluated at a single site, where multidisciplinary clinics are conducted. All boys are evaluated by a multidisciplinary team including pediatric endocrinologist, pediatric neurologist, and geneticist, orthopedic surgeon, neurodevelopmental specialist, speech pathologist, and physical therapist.

A routine neurological evaluation tailored to age by single neurologist/geneticist is conducted, which evaluates 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.

Standardized testing is 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. Testing is designed to probe multiple domains of function including neuromotor abilities (tone, strength coordination), fine motor/upper extremity, expressive and recessive speech and language development, neurocognitive and sensory functioning. Because of the high degree of expressive speech impairments, tests chosen include nonverbal measures such as the Leiter International Performance Scale-Revised (LIPS-R), as well as more traditional scales of motor and mental development such as the Bayley Scales of Infant and Toddler Development, 3rd Edition, and focused expressive language tools (Preschool Language Scale-4 (PLS-4), Peabody Motor Scale (GM, VM, total), Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition (VMI), Gilliam Autism Rating Scale (GARS and GARS-2), 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). We recommend MRI of the brain as a way to further understand the underlying anatomic underpinnings of the cognitive disorder.

Together these results coupled with the team's expertise in these rare disorders, targeted treatment, and syndrome specific goals can be configured which reflect the interaction among neurogenetic disorder, neurodevelopmental profile, and brain function. Our team has come to appreciate the great degree of variability in all these disorders and how responsive the boys are to treatment and care that is tailored to their very specific challenges and strengths. This variability in clinical and cognitive functioning may reflect skewed X inactivation, mosaicism, or epigenetic factors, which warrants more investigation in order to better understand the disorders and develop more innovative treatment plans.

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