Published in final edited form as:
Dev Disabil Res Rev. 2009 ; 15(4): 309–317. doi:10.1002/ddrr.85.

An extra X or Y chromosome: contrasting the cognitive and motor phenotypes in childhood in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome

Judith L. Ross[1,*], **Martha P.D. Zeger**[1], **Harvey Kushner**[2], **Andrew R. Zinn**[3], and **David P. Roeltgen**[4]

[1]Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, USA, A. I. duPont Hospital for Children, Wilmington, DE

[2]Biomedical Computer Research Institute, Philadelphia, PA

[3]Department of Internal Medicine and McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[4]Department of Neurology, Georgetown

Abstract

Objective—The goal of this study was to contrast the cognitive phenotypes in boys with 47,XYY (XYY) karyotype and boys with 47,XXY karyotype (Klinefelter syndrome, KS), who share an extra copy of the X-Y pseudoautosomal region but differ in their dosage of strictly sex-linked genes.

Methods—Neuropsychological evaluation of general cognitive ability, language, memory, attention, visual-spatial abilities, visual-motor skills, and motor function.

Results—Study cohort: 21 boys with 47,XYY and 93 boys with 47,XXY (KS), ages 4-17 years, and 36 age-matched control boys. Both the XYY and KS groups performed less well, on average, than the controls on tests of general cognitive ability, achievement, language, verbal memory, some aspects of attention and executive function, and motor function. The boys with XYY on average had more severe and pervasive language impairment, at both simple and complex levels, and the boys with KS on average had greater motor impairment in gross motor function and coordination, especially in running speed and agility.

Conclusions—The results from these large XYY and KS cohorts have important neurocognitive and educational implications. From the neurocognitive standpoint, the presenting findings afford an opportunity to gain insights into brain development in boys with XYY and those with KS. From the educational standpoint, it is critical that boys with XYY or KS receive appropriate educational interventions that target their specific learning challenges. These findings also provide important information for counseling clinicians and families about these disorders.

Keywords

XYY; XXY; Klinefelter syndrome; sex chromosome

*To whom correspondence should be addressed: Judith L. Ross, M.D., Department of Pediatrics, Division of Endocrinology, Thomas Jefferson University, 1025 Walnut Street, Suite 726, Philadelphia, PA 19107, Judith.Ross@mail.tju.edu Tel: 215-955-1648 Fax: 215-955-1648.

Introduction

Two sex chromosome aneuploidy disorders, 47,XYY and 47,XXY (Klinfelter syndrome, KS), affect only males. Both disorders are relatively common and are underdiagnosed. In addition, there may be confusion about what distinguishes one from the other. The XYY syndrome affects 1 in 1,000 males and is characterized by physical findings such as tall stature as well as neurological, cognitive, and behavioral phenotypes (Aksglaede et al. 2008; Kent et al. 2008; Ratcliffe et al. 1992; Ratcliffe et al. 1982; Robinson et al. 1990; Welch 1985). Testicular function, testosterone levels, and fertility are usually normal (Aksglaede et al. 2008; Baghdassarian et al. 1975; Benezech 1985; Geerts et al. 2003; Price and van der Molen 1970; Ratcliffe et al. 1994; Rudd et al. 1968; Welch 1985). KS, the most common sex chromosome disorder (MacLean 1961; Robinson et al. 1990; Rovet et al. 1995), occurs in 1 in 426 to 1 in 1000 males (Bojesen et al. 2003). Like XYY, the KS phenotype includes tall stature and characteristic cognitive attributes, but, in contrast to XYY, also includes childhood onset testicular failure.

The cognitive phenotype in boys with XYY typically includes normal to mildly diminished general intelligence as measured by full-scale IQ (Bender et al. 1984; Evans et al. 1986; Netley 1986; Robinson 1985), with Verbal IQ impaired more than Performance IQ (Christensen and Nielsen 1973; Ratcliffe et al. 1982; Welch 1985). These boys tend to have delayed speech development and to require speech therapy (Bender et al. 1984; Daly 1969; Geerts et al. 2003; Ratcliffe 1982; Robinson 1985; Valentine 1979). Often they have difficulty mastering school curricula and need educational support services in reading and writing (Bender et al. 1984; Netley 1986). Increased risk for hyperactivity and attention problems has also been reported (Ruud et al. 2005). Boys with XYY are at increased risk for have delayed motor milestones and impaired fine and gross motor function, coordination, and tone (Bender et al. 1984; Geerts et al. 2003; Ratcliffe 1999; Ratcliffe et al. 1982; Robinson 1985).

The overall cognitive phenotype in boys with KS is similar to XYY, with depressed Verbal IQ relative to Performance IQ in both in children and adults (Graham et al. 1988; Rovet et al. 1995; Walzer et al. 1990). This cognitive profile may be accompanied by moderate to severe problems with reading, spelling, writing, and arithmetic (Nielsen et al. 1981; Stewart et al. 1986). Language and speech impairments are evident in some form at all ages. Attentional problems characterized by errors of omission rather than commission have also been described in children with (Ross et al. 2008).

Thus, there appears to be some overlap in the cognitive phenotypes in these two disorders, especially in the area of language dysfunction. However, in the absence of a systematic comparison of these two groups, the similarities as well as the differences are not well defined. The goal of this study was to compare and contrast the cognitive phenotypes in boys with XYY, boys with XXY, and age-matched control boys.

Methods

I. Subjects

Subjects were referred to the pediatric endocrine clinic at Thomas Jefferson University by their health care providers or were self-referred after learning about the clinical and research services at our institution. All were diagnosed with XYY or XXY (KS) by karyotype. The control boys were recruited from families participating in other studies and through advertising in the endocrine clinic. The study was approved by the Human Studies Committee at Thomas Jefferson University and UT Southwestern Medical School. All subjects and their parents gave informed consent and assent. The clinical evaluation was performed at Thomas Jefferson

University and the karyotyping was performed by the clinical cytogenetics laboratory at UT Southwestern Medical School.

II. Test procedures

Anthropometric Measurements—The clinical assessment included conversion of measurements to SD scores (SDS) using age- and gender-specific norms of height (by stadiometer), weight (Hamill et al. 1979), and head circumference (Hall 1995). Pubertal development was assessed according to standard methods (Marshall WA 1993). Testicular size was measured using standard Prader orchidometer beads (Hall 1995).

Cognitive and motor evaluation—Subjects were individually administered a battery of neuropsychological tests specifically designed to assess memory, attention, executive function, visual-spatial abilities, visual-motor skills, and language. The evaluation was administered by trained and experienced psychometricians under the supervision of a licensed neuropsychologist. Raw scores were converted to standard scores (mean of 100, standard deviation of 15), based on the test-specific norms or our own population of 50 age-matched control boys. The evaluation was completed over two days. The XYY population were less likely than the KS or controls to complete the full evaluation because of a tendency for less cooperation for the evaluation. The DAS (see below) was administered first and the remainder of the test battery was administered in a randomized sequence.

We chose the Differential Ability Scales (DAS) (Elliott 1983), to assess general cognitive ability in children between ages 4 years to 17 years, 11 months. The DAS cognitive battery includes three composite scores: the Verbal Cluster (VC) score measures semantic knowledge, verbal expression, and verbal comprehension, the Spatial Cluster (SC) score measures nonverbal spatial cognitive ability, and the Nonverbal Reasoning Cluster (NV) score measures nonverbal aspects of fluid reasoning. Performance on subtests was combined to yield a General Conceptual Ability (GCA) score, which is a general index of an individual's ability to perform complex mental processing involving conceptualization and manipulation of information.

Academic achievement was assessed with the Reading, Spelling, and Arithmetic subtests from the Wide Range Achievement Test-3 (WRAT3) (Wilkerson 1993). The tasks used to assess attention/executive function included Conners' Continuous Performance Test (CPT-II) (Connors 1995), Conners' Kiddie CPT (ages 4-5 years) (Connors 1995), and the Delis-Kaplin Executive Function System (D-KEFS) Color-Word Interference Test (Delis 2001). These tasks measure processing speed, sustained attention, response inhibition, and inhibitory control. We examined aspects of verbal memory using the Children's Memory Scale (CMS) (Cohen 1997) for Story Recall and Digit Span (Cohen 1997), and California Verbal Learning Test-Children's Version (CVLT-C) (Delis 1994). We assessed visual-motor and visual memory with the Rey-Osterrieth Complex Figure–Copy and Organization scores (Waber and Holmes 1985) and the Beery Test of Visual Motor Integration (Beery 1997).

Language ability was evaluated at the level of single words with the Expressive One-Word Vocabulary Test (EOWPVT) (Williams 1997) and the Receptive One-Word Vocabulary Test (ROWPVT) (Brownell 2000). Phonological processing was assessed with the Comprehensive Test of Phonological Processing (CTOPP) (Rashotte 1999), and fluency with the Delis-Kaplin Executive Function system (D-KEFS) subtest, which tapped both phonemic and semantic fluency (Korkman M 1998). We evaluated more complex levels of language processing with the Test Of Language Competence–Expanded Edition (TLC-E) (Wiig 1989).

The tasks used to assess fine and gross motor skills included the Lafayette Pegboard (Klove 1963), the Bruininks-Oseretsky Test of Motor Proficiency (BOT)(Bruininks 1978) and PANESS (Physical and Neurological Evaluation for Soft Signs) (Close 1976).

Socioeconomic Status (SES)—SES estimate was calculated for children using the Hollingshead 2-Factor Index of Social Status based on education and occupation of parents (Hollingshead and Redlich 1958).

Handedness and lateralization—The Crovitz Laterality battery was administered to document hand preferences (Crovitz and Ziner 1962). Children were asked to demonstrate which hand they use for 8 activities (right hand = RH and left hand = LH). A laterality quotient was calculated using the following formula: ((RH-LH)/(RH+LH)*100). Right-handedness was defined as a score of 100% (performance of 8 of 8 tasks with the right hand). Non right-hand dominance was characterized as a score < 100% (Isaacs et al. 2006; Spreen 1991).

III. Testosterone measurement

Total testosterone was measured in the morning, using a commercial assay performed by Esoterix Endocrinology (Calabasas Hills, CA).

IV. Genetic Testing

Karyotype—A postnatal G-banded peripheral blood karyotype was obtained for all subjects, but not from the male controls.

V. Statistics

Results are presented as the mean ± SD of standard scores. Statistical comparisons included ANOVA comparing the three groups (XYY, XXY and male controls) for demographic and auxologic measurements. The P-value threshold for significance was $p < 0.01$, to adjust for multiple comparisons. In addition, an analysis of covariance (ANCOVA) compared the same three groups, adjusting for pubic hair Tanner stage, head circumference SDS, testicular volume SDS, lateralization index, and general conceptual ability from the DAS. The six pairwise comparisons among the three groups (XYY, XXY and male controls) were performed using Scheffe's test. P-values less than 0.05 were considered to be statistically significant. Nominal P-values are reported and were not adjusted for multiple comparisons.

Results

Genetic results

Karyotype results were: 21 boys with XYY and 93 boys with 47,XXY; no mosaicism was detected.

Demographics

Our study included 21 boys with XYY, ages 4.3-14.4, 93 boys with KS, ages 4.1-17.8 years, and 36 control boys, ages 4.5-13.8 (Table 1). The groups were well matched for age, SES, race, handedness, and for pubic hair Tanner stage development. Most participants were Caucasian. The boys with XYY and XXY were, on average, taller than the control boys but had similar weight SDS. Testicular volume SDS was the lowest in the boys with KS ($P<0.0001$), consistent with testicular failure in that group and was increased in the XYY boys, compared to controls. Testicular size was increased for age (> 1 SD) in 11/22 boys with XYY (ages 4.3 to 13.6 years), reflecting early pubertal development in some cases.

Diagnosis of XYY was made in infancy in 8 boys (6 for prenatal screening [advanced maternal age], 1 for hypotonia, and 1 for other reasons), in childhood (ages 2-12 years) in 12 (2 for language issues, 3 for behavior issues, and 7 for other developmental reasons), and after age 12 years in 1 boy (behavioral reasons). Of the 21 boys, 20 had received speech and/or reading therapy and 18 received occupational and/or physical therapy by the time of the evaluation.

No boys with XYY were diagnosed with testicular failure or had received testosterone treatment by the time of the evaluation.

Diagnosis of KS was made in infancy in 61 boys (51 for prenatal screening [advanced maternal age], 1 for hypotonia, 1 for small genitalia, and 8 for other reasons), in childhood (2-12 years) in 24 boys (7 for language issues, 5 for behavior issues, 1 for tall stature, and 11 for other reasons), and after age 12 in 8 (2 for language issues and 6 for puberty issues). Of the 93 boys, 83 had received special education services in school by the time of the evaluation: 75 received speech and/or reading therapy and 61 received occupational and/or physical therapy. Twenty-one boys with KS had received testosterone treatment by the time of the evaluation (duration of 0.1-2.2 years).

Lateralization and handedness

Based on the Crovitz Handedness Questionnaire, 63% (12/19) of the XYY group, 73% (68/93) of the KS group, and 72% (26/36) controls were completely right-handed (laterality index of 100%). The occurrence of non right-handedness did not differ among the groups.

Cognitive results

Results from the Differential Ability Scales (DAS) as well as measures of language and academic achievement are presented in Table 2. General Conceptual Ability (GCA), the DAS indices, and subtests revealed, on average, higher scores (by > 1 SD) in the control group, compared to the XYY and KS groups ($P < 0.0001$). Performance was similar in the XYY and KS groups for the Verbal cluster (Word Definitions and Similarities subtests) and the Nonverbal cluster (Matrices and Sequential and Quantitative reasoning subtests) and was lower than controls ($P < 0.0001$). For the Spatial cluster (Recall of design and Pattern construction subtests), the KS but not the XYY group scored lower than the control group, although both groups had lower scores than the controls. After adjusting for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability in the ANCOVA, only the XYY group performed significantly less well than the controls for the Verbal cluster.

Academic Achievement

Results from the Wide Range Achievement Test – 3rd Edition (WRAT-3) for reading, spelling, and arithmetic subtests are shown in Table 2. Mean scores were lower in the XYY and KS groups versus controls ($P < 0.0001$) for all three achievement tests. After ANCOVA adjustments for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability, the XYY group but not the KS group performed significantly less well than the controls for the WRAT-3 Reading test.

Language

Results from tests of language are shown in Table 3. One-word receptive vocabulary expression and retrieval, as assessed by ROWPTCT and EOWPVT performance, was significantly lower in the XYY and KS groups, compared to the control group ($P < 0.0001$) by ANOVA. The XYY group had lower scores than the KS group on the ROWPVT. Rapid naming from CTOPP Rapid Naming composite yielded lower levels of performance in the XYY and KS groups, compared to controls. In contrast, performance for the Rapid Alternating Naming composite was similar for the three groups. Phonetic but not semantic fluency was lower in the XYY and KS groups, compared to the controls. After ANCOVA adjustment for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability, the XYY group performed significantly less well than both the KS and the control groups for the ROWPVT, but not the EOWPVT. There were no differences in the CTOPP for the three groups.

On tests of higher-level language, the XYY and KS groups performed more poorly than controls, specifically in the areas of semantics, syntax, pragmatics and also with expressing and interpreting intent ($P < 0.0001$, Table 3) by ANOVA. The lowest performance in both the XYY and KS groups was in the ability to formulate propositions in grammatically complete sentences using key words from the context of a given situation (Oral Expression subtest) and the ability to recognize and interpret alternative meanings of lexical and structural ambiguities (Ambiguous Sentences subtest). After ANCOVA adjustment for differences in Tanner stage, Testicular volume SDS, head circumference SDS, and DAS general conceptual ability, the XYY scores were significantly less than control scores for Ambiguous Sentences, Expressing Intent, Interpreting Intent and the Composite and the KS scores were less than controls only for Expressing Intent.

Verbal Memory

The results from the tests of verbal memory are shown in Table 4. Performance for immediate and delayed memory for short story content (CMS Stories subtest) and for Digit Span, forward and reverse sequence (CMS Numbers, and word list learning), was lower in the XYY and KS groups, compared to the control group by ANOVA. After ANCOVA adjustment for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability, CMS performance was similar in the three groups, and Performance on the CVLT-II list recall was lowest in the XYY group for Trial 5 recall and for the learning slope, compared to both the KS and the control groups.

Attention and Executive Function

On the Conners' Continuous Performance Test (CPT-II), performance was similar in the three groups for the tendency to produce an incorrect response as measured by Commission and Perseverative errors (ANOVA, Table 4). The KS but not the XYY group had significantly more Omission errors, compared to controls. Reaction time and Variability were increased for both the XYY and KS groups, compared to the controls ($P < 0.001$). On tests of executive function (Color-Word Interference Test), scores for inhibition and switching were lowest in the XYY group compared to the KS and the control groups. The three groups did not differ significantly for Color interpretation but did for reading the Words, with both groups performing less well than the controls ($P = 0.0003$). After ANCOVA adjustment for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability, performance for Switching was lower in the XYY group only, compared to the control group.

Visual-Motor Function and Visual Memory

Performance on these tests of visual memory and spatial ability showed the lowest performance on Rey Copy and Immediate and Delayed recall and the VMI in the KS group (ANOVA, Table 4). In contrast, organization of the Rey figure copy was significantly decreased in both the XYY and KS groups and was lowest in the XYY group, compared to the control group. After ANCOVA adjustment for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability, performance was similar in the three groups.

Motor Skills

On the BOT, performance on the Fine Motor, Gross Motor, and the Battery Composites, Fine Motor Integration, Bilateral Coordination, Upper Limb Speed, Visual Motor Control, and Response Speed was decreased in the KS and the XYY groups (Table 5), compared to the controls (ANOVA, $P < 0.006$), indicating motor skills deficits. Performance tended to be lowest in the KS group for all subtests except Upper Limb Coordination and Visual-Motor Control.

Overall, the worst performance was observed in the KS group on the Running Speed and Agility subtest, which measures running shuttle speed. Performance on Upper Limb Speed and Dexterity and the Strength subtests was slightly lower in the XYY compared to the KS group. After ANCOVA adjustment for differences in Tanner stage, testicular volume SDS, head circumference SDS, and DAS general conceptual ability, the KS but not the XYY group differed from the control group for Running Speed, Bilateral Coordination, and Strength subtests.

For selected tests from the Physical and Neurological Examination of Soft Signs (Paness) and the Lafayette Pegboard Test (measure of motor dexterity and coordination), performance was similar in the XYY and the KS groups and was generally slower than the control group (ANOVA). The KS group, on average, was slightly slower than the XYY group for the Paness but not the Lafayette Pegboard. After ANCOVA adjustment, there were no major differences in the three groups for these tasks.

Discussion

The goal of this study was to compare and contrast the neuropsychological profile and motor function in boys with the sex chromosome disorders, 47,XYY and 47,XXY (KS) versus controls. All three populations were similar in age (mean age around 9 years), socioeconomic status, handedness, and pubic hair stage. The primary physical phenotypic differences were that boys with KS had below average testicular size, while those with XYY had above average testicular size. Both aneuploid groups were taller than controls. Cognitive function evaluation revealed considerable overlap with deficits that likely relate to the presence of additional sex (pseudoautosomal) chromosome genes. Both groups performed less well than controls on tests of general cognitive ability, achievement, language, verbal memory, some aspects of attention and executive function, and motor function. The XYY boys, on average, had more severe and pervasive language impairment, at both simple and complex levels. The KS boys, on average, had greater motor impairment in gross motor function and coordination (ANCOVA analysis), especially in running speed and agility, which may be related to testicular failure.

General cognition

Previous studies of boys with XYY and KS concluded that general intelligence is relatively preserved, but verbal ability is decreased in both groups (Ratcliffe 1999; Warwick et al. 1999; Welch 1985) [XYY] and (Graham et al. 1988; Porter et al. 1988; Ratcliffe et al. 1986; Robinson et al. 1986; Ross et al. 2008; Rovet et al. 1996; Walzer et al. 1990) [KS]. In this study, scores on the DAS GCA suggest that general cognitive ability is mildly diminished in both groups, compared to controls. This general cognitive profile reflects not just decreased verbal, but also decreased nonverbal abilities in both groups and diminished spatial ability in the KS group. Importantly, after adjusting for GCA differences between the groups, the DAS Verbal Cluster in the XYY group still differed significantly from the control group.

Language and Achievement

Most previous studies have described some features of language that are impaired in both groups. Delayed speech, impaired word retrieval, speed of linguistic processing, expressive and receptive capabilities and processing of narration have been described in both the XYY and KS groups (Christensen and Nielsen 1973; Leonard and Sparrow 1986; Ratcliffe et al. 1982; Walzer 1985; Welch 1985). Although the pattern of impairment is similar in our results, the severity appears to differ. The XYY group appears to have a more severe and pervasive language impairment than the KS group that is present at varying levels of complexity of oral and written language. We noted greater impairment in the XYY versus the KS group particularly for higher-level metalinguistic abilities, as demonstrated by significant difficulty in understanding figurative language, interpreting ambiguities in language, as well as in oral expression and verbal memory.

This language impairment appears to have important academic implications. The boys with XYY, more than KS, produced lower achievement in Reading and Spelling, compared to the control group. Our findings are similar to previous studies in XYY that reported school difficulties out of proportion to what would be expected on the basis of IQ. Boys with XYY and boys with KS commonly have difficulty mastering school curricula and require special education help in reading and writing (Ross et al. 2008) (Bender et al. 1984; Netley 1986).

Attention and Executive function

This study shows that both the XYY and KS groups had a similar degree of impairment relative to controls on attention and executive function tasks, although cognitive flexibility, as exemplified by inhibition and switching, was more impaired in the XYY than the KS group. Both groups have been reported to have increased distractibility (Walzer et al. 1990), and an increased risk for hyperactivity and attention problems (Geerts et al. 2003) (Money et al. 1974; Theilgaard 1984; Welch 1985) (Ross et al. 2008). Executive dysfunction has been reported in adults with KS (Geschwind 2000).

Visual Spatial function

Performance results for visual-spatial and visual-motor function was significantly lower in the KS but not the XYY group, compared to the controls. This dissociation may reflect testosterone deficiency in the KS group only. Higher testosterone levels in males may be related to increased male performance in visual-spatial tasks involving mental rotation, spatial perception, spatial visualization (Arceneaux JM 1996).

Motor function

Similar to previous observations, both the XYY and the KS groups had impairment of motor function (Bender et al. 1993; Ross et al. 2008; Salbenblatt et al. 1987). However, the KS group appeared to have more pervasive motor impairment than the XYY group. Motor function was examined using fine motor and gross motor tasks as well as measures of strength, speed and agility, and coordination. On portions of the PANESS, including repetitive thumb finger tapping and foot tapping, the XYY and KS groups performed at or close to levels expected for age, similar to previous results (Bender et al. 1993; Salbenblatt et al. 1987). However, as the tasks became more complex (tapping four sequential fingers to thumb), both groups did not perform as well as controls. The more complex tasks require greater utilization of coordination and attention, which are impaired in both groups. Both groups also performed less well than expected for their age on the Strength and the Upper limb speed and dexterity subtests. These motor difficulties are not just of academic interest but have importance for these boys because of psychosocial implications and the likely impaired athletic ability that accompanies these particular deficits. Performance by the KS group was lower than the XYY group on the test of Running Speed and Agility from the BOT, which indexes an array of motor and cognitive skills. This may be due to androgen deficiency having a negative impact in only the KS group and not the XYY group.

Summary and conclusions

In general, the cognitive phenotype in boys with XYY and KS overlap with some important differences. Both have mild generalized cognitive impairment, with impaired language verbal memory, attention, visual-motor and motor function. The similarity of cognitive findings in these two genetic disorders of males may be related to overlapping gene dosage abnormalities. The X and Y chromosomes share identical sequences in the pseudoautosomal region (PAR1), a 2.6 Mb interval at the tips of Xp and Yp, and genes are equally expressed from the X or Y PAR1 (Rappold 1993; Vaknin et al. 2008). Specifically, tall stature in both of these populations is thought to be due to increased expression from three instead of two copies of the height determining SHOX gene (Aksglaede et al. 2008; Rao et al. 1997).

The differences between cognitive phenotypes in the KS and XYY groups may be related to either chromosomal or hormonal causes. The results show that XYY boys have a more profound language impairment and the KS boys have a more profound motor impairment. We hypothesize that the more severe language-based cognitive phenotype in XYY versus KS is likely to be genetically determined on the basis of abnormal dosage of specific Y chromosome genes, but not abnormal levels of testosterone because XYY is not associated with testicular failure. The parental origin of the extra chromosome may differentially impact KS and XYY because in KS, the supernumerary X chromosome may be maternal or paternal, whereas in males with XYY, the extra Y chromosome always originates from the father. Hormonal differences (normal testosterone in XYY versus testosterone deficiency in KS) may account for differences in the cognitive phenotype in boys with XYY versus XXY. The testosterone deficiency in KS and the known relationship between muscle function and testosterone may also account for some of the motor impairment in this group.

Another potential factor related to the observed difference in the XYY and KS groups relates to their ascertainment. In our cohort, most of the boys with XYY were diagnosed postnatally on the basis of behavior/developmental issues, consistent with the observation that diagnosis of XYY is often delayed (Abramsky and Chapple 1997; Fryns et al. 1995; Geerts et al. 2003). In contrast, most of the KS boys in our cohort were diagnosed prenatally on the basis of advanced maternal age. Thus, there may be a bias in our cohort towards greater severity among the XYY boys. However, boys with XYY ascertained from screening studies of male newborns for sex chromosome abnormalities also have associated speech, language-based, motor, and behavior findings (Bender et al. 1993; Bender et al. 1984; Salbenblatt et al. 1987), suggesting that the findings are associated with the karyotype, independent of ascertainment.

The results from these large XYY and KS cohorts have important neurocognitive and educational implications. From the neurocognitive standpoint, the difficulties present represent an opportunity to gain insights into brain development and the interactions of cognitive systems in boys with XYY or KS. From the educational standpoint, the difficulty in complex language processing and impaired attention as well as motor function identified in the XYY and KS populations may be missed. This can be a challenge to educators. It is critical that boys with XYY and boys with KS are provided with appropriate educational interventions that target their learning challenges in school. These findings would also be an important component of counseling clinicians and families about this disorder.

Acknowledgments

We thank the families who participated in these studies.

Supporting Grants: **NIH RO1NS050597**

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Table 1

Demographics and auxologic measurements (Mean ± SD)

	n	XXY	n	XYY	n	Controls	P-Value*
Age	93	9.4±3.4	21	9.4±2.8	36	9.5±2.6	0.99
SES	93	51±10	21	52±10	36	54±8	0.32
Height SDS	93	0.9±1.2	21	0.9±1.1	36	0.1±1.0	**0.001**
Weight SDS	93	0.6±1.2	21	0.6±1.2	36	0.4±1.2	0.65
Head Circ SDS	93	0.4±1.6	21	1.2±2.3	36	0.9±1.4	0.08
Tanner stage-pubic hair	93	1.6±1.1	20	1.3±0.9	34	1.3±0.8	0.18
Testicular volume SDS (mean of 2)	92	-1.3±1.5	20	2.7±4.1	34	1.0±2.6	**0.0001**
Testosterone	87	55±111	21	47±92	-	Not done	0.66
Race (% Caucasian)	93	85%	21	95%	36	78%	0.16

* ANOVA, comparison of three groups

Table 2

General cognitive ability and achievement results (Mean standard standard score ± SD)

	n	XXY	n	XYY	n	Controls	P-Value*
DAS Index							
Verbal cluster (VC) SS	92	89±14^	17	88±18**	35	113±14	**< 0.0001**
Nonverbal cluster (NVC) SS	92	92±15^	18	93±21**	36	111±16	**< 0.0001**
Spatial cluster (SC) SS	75	91±15^	16	96±16	30	107±16	**< 0.0001**
General conceptual ability (GCA) SS	90	90±14^	17	93±18**	35	112±15	**< 0.0001**
DAS Subtests							
Word definitions SS	76	89±14^	17	86±15**	30	111±14	**< 0.0001**
Similarities SS	77	90±15^	17	91±20**	29	116±15	**< 0.0001**
Matrices SS	76	93±15^	18	92±24**	30	110±13	**< 0.0001**
Sequential and quantitative reasoning SS	77	92±15^	17	94±20**	30	114±18	**< 0.0001**
Recall of design SS	75	90±16^	16	95±20	30	103±17	**< 0.002**
Pattern construction SS	92	96±15^	19	95±15**	36	110±13	**< 0.0001**
WRAT-3 Subtest							
Reading SS	87	95±16^	16	86±18**	34	112±13	**< 0.0001**
Spelling SS	87	90±14^	14	91±13**	33	107±16	**< 0.0001**
Arithmetic SS	87	90±17^	17	84±17**	34	111±16	**< 0.0001**

* ANOVA, comparison of three groups

** $P < 0.05$ XYY versus controls, post hoc

~ $P < 0.05$, XYY versus XXY, post hoc

^ $P < 0.05$, XXY versus controls, post hoc

Table 3

Language results (Mean standard standard score ± SD)

	n	XXY	n	XYY	n	Controls	P-Value*
EOWPVT SS	92	100±14^~	17	96±16**	36	113±13	**< 0.0001**
ROWPVT SS	92	101±13^	18	90±15**	36	116±13	**< 0.0001**
CTOPP Composite SS							
Rapid naming composite SS	84	86±16^	13	82±17**	33	99±16	**< 0.0002**
Rapid alternate naming composite SS	72	77±18	12	84±24	29	86±19	0.08
CTOPP Subtest							
Rapid digit naming SS	70	89±14^	11	85±15**	28	100±16	**0.002**
Rapid letter naming SS	70	88±14^	11	87±14	28	98±13	**0.004**
Rapid color naming SS	86	85±15	14	88±17	34	90±15	0.18
Rapid object naming SS	86	79±16^	14	84±22	34	91±16	**0.004**
D-KEFS							
Phonetic fluency SS	59	94±17^	9	93±13**	25	110±18	**0.0008**
Semantic fluency SS	51	101±18	9	96±25	25	110±17	0.09
TLC Composite							
Expressing intent SS	78	79±12^	14	80±14**	29	101±17	**< 0.0001**
Interpreting intent SS	78	84±13^	13	84±19**	28	103±15	**< 0.0001**
Total Composite Score SS	77	79±12^	14	80±17**	28	102±16	**< 0.0001**
TLC Subtest							
Ambiguous sentences SS	81	83±12^	14	83±15**	29	102±16	**< 0.0001**
Listening comprehension SS	80	90±13^	13	90±20**	27	104±12	**< 0.0001**
Oral expression SS	78	82±12^	14	83±12**	29	99±17	**< 0.0001**
Figurative language SS	78	84±13^	14	86±15**	29	103±15	**< 0.0001**

* ANOVA, comparison of three groups

** P < 0.05 XYY versus controls, post hoc

~ $P < 0.05$, XYY versus XXY, post hoc

^ $P < 0.05$, XXY versus controls, post hoc

Table 4

Verbal memory, attention, visuomotor, and visual memory results (Mean standard score ± SD)

	n	XXY	n	XYY	n	Controls	P-Value*
Verbal Memory							
CMS Stories							
Immediate recall SS	83	90±14^	14	87±17**	33	103±18	**0.0002**
Delayed recall SS	82	90±15^	14	87±21**	33	102±18	**0.002**
Delayed recognition SS	80	93±18^	14	89±15**	33	104±13	**0.0007**
Digit Span							
Digit span forward SS	89	91±15^	15	86±17**	34	103±15	**0.0002**
Digit span backward SS	89	93±15^	15	92±14	34	102±20	**0.02**
CVLT-II							
Trial 1-5 list A recall SS	85	89±18^	14	82±20**	33	103±15	**< 0.0001**
Trial 5 list A recall SS	85	90±17^	14	84±21**	33	103±13	**< 0.0001**
Learning Slope SS	86	93±16	14	90±18	33	100±15	**0.04**
Attention/Executive funcion							
Conners CPT							
Omissions (more errors = lower SS)	83	81±26^	16	83±27	30	99±16	**0.004**
Comissions (more errors = lower SS)	83	97±15	16	99±16	30	92±16	0.18
Reaction time (increased = lower SS)	83	87±19^	15	85±22**	30	105±16	**< 0.0001**
Variability (increased = lower SS)	83	86±14^	15	85±14**	29	98±16	**0.001**
Perseverative errors SS	83	83±26	15	85±29	29	86±29	0.89
DKEFS- Color Word Inference Test							
Color SS	65	91±20	10	87±21	26	100±18	0.08
Word SS	65	89±18	10	86±19	26	105±14	**0.0003**
Inhibition SS	65	92±20	10	85±17**	26	101±12	**0.02**
Switch SS	62	92±20	10	78±14**	26	102±14	**0.001**
Visuomotor and Visual Memory							

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	n	XXY	n	XYY	n	Controls	P-Value*
Rey-Osterreith Figure							
Copy organization SS	83	89±14^	13	85±18**	34	100±17	**0.007**
Copy accuracy SS	87	75±25^	13	85±26	32	95±17	**0.0002**
Immediate recall SS	82	93±14	13	101±17	34	99±13	0.06
Delay recall SS	82	92±14	13	100±19	34	97±13	0.08
Beery Test of VMI SS	84	88±13^	16	87±19	36	97±14	**0.004**

*ANOVA, comparison of three groups

**P < 0.05 XYY versus controls, post hoc

~P < 0.05, XYY versus XXY, post hoc

^P < 0.05, XXY versus controls, post hoc

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Table 5

Motor function results (Mean standard score ± SD)

	n	XXY	n	XYY	n	Controls	P-Value*
BOT Composite							
Fine motor composite SS	73	81±15^	8	81±22**	21	99±18	**< 0.0001**
Gross motor composite SS	73	80±17^	9	82±16**	20	106±19	**< 0.0001**
Battery composite SS	88	80±15^	14	81±18**	23	103±17	**< 0.0001**
BOT Subtest							
Running speed and agility SS	92	80±18^	18	88±15	36	100±18	**< 0.0001**
Bilateral coordination SS	92	89±13^	19	89±16**	35	107±12	**< 0.0001**
Strength SS	92	88±18^	19	89±16**	35	106±17	**< 0.0001**
Upper limb coordination SS	92	88±16^	19	82±17**	35	99±15	**0.0004**
Visual-motor controlSS	92	87±18^	18	82±16**	36	96±16	**0.006**
Upper limb speed SS	92	82±14^	19	80±15**	36	97±16	**< 0.0001**
Paness							
Hand alternating-dominant SS	71	81±28	14	82±19	30	91±23	0.20
Hand alternating non-dominant SS	71	86±21^	14	85±19	30	99±20	0.009
Hand short dominant SS	72	98±18^	16	96±21**	32	112±12	0.0007
Hand short non-dominant SS	72	95±20^	16	90±26**	32	111±12	0.0002
Foot dominant SS	72	100±17^	16	102±13	32	113±8	0.0009
Foot non-dominant SS	72	95±18^	16	91±23**	32	110±12	0.0002
Lafayette Pegboard							
Lafayette Pegboard dominant SS	80	76±30^~	17	53±37**	33	96±16	**< 0.0001**
Lafayette Pegboard non-dominant SS	80	82±28	17	64±37**	33	96±22	**0.0008**

*ANOVA, comparison of three groups

**P < 0.05 XYY versus controls, post hoc

~ $P < 0.05$, XYY versus XXY, post hoc

^ $P < 0.05$, XXY versus controls, post hoc