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Attention-Deficit Hyperactivity Disorder Symptoms in Children and Adolescents with Sex Chromosome Aneuploidy: XXY, XXX, XYY, and XXYY

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Abstract

Objective—Attentional problems, hyperactivity, and impulsivity have been described as behavioral features associated with sex chromosome aneuploidy (SCA). In this study, the authors compare attention-deficit hyperactivity disorder (ADHD) symptoms in 167 participants aged 6 to 20 years with 4 types of SCA (XXY n = 56, XYY n = 33, XXX n = 25, and XXYY n = 53). They also evaluate factors associated with ADHD symptomatology (cognitive and adaptive scores, prenatal vs postnatal ascertainment) and describe the clinical response to psychopharmacologic medications in a subset of patients treated for ADHD.

Methods—Evaluation included medical and developmental history, cognitive and adaptive functioning assessment, and parent and teacher ADHD questionnaires containing DSM-IV criteria.

Results—In the total study group, 58% (96/167) met DSM-IV criteria for ADHD on parent-report questionnaires (36% in XXY, 52% in XXX, 76% in XYY, and 72% in XXYY). The Inattentive subtype was most common in XXY and XXX, whereas the XYY and XXYY groups were more likely to also have hyperactive/impulsive symptoms. There were no significant differences in Verbal, Performance, or Full Scale IQ between children with symptom scores in the ADHD range compared with those below the ADHD range. However, adaptive functioning scores were significantly lower in the group whose scores in the ADHD range were compared with those of the group who did not meet ADHD DSMIV criteria. Those with a prenatal diagnosis of XXY were less likely to meet criteria for ADHD compared with the postnatally diagnosed group. Psychopharmacologic treatment with stimulants was effective in 78.6% (66/84).

Conclusions—Children and adolescents with SCA are at increased risk for ADHD symptoms. Recommendations for ADHD evaluation and treatment in consideration of other aspects of the SCA medical and behavioral phenotype are provided.

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Index terms

attention-deficit hyperactivity disorder (ADHD); XXY; Klinefelter syndrome; XYY; XXYY; sex chromosome aneuploidy

Sex chromosome aneuploidies (SCAs) are the most common chromosomal abnormalities in humans and are estimated to occur in 1:400 individuals.[1] The addition of extra X and/or Y chromosomes leads to neurodevelopmental differences, with increased risk for developmental delays, language-based learning disabilities, cognitive impairments, executive dysfunction, and behavioral and psychological disorders. Attentional problems, hyperactivity, and impulsivity are commonly described as behavioral features that can be associated with SCA conditions such as XXY/Klinefelter syndrome (KS) and XYY syndrome, and cases of attention-deficit hyperactivity disorder (ADHD) have been reported in individual case reports and case series.[2,3] Descriptive studies in XYY (n = 26) and XXYY (n = 79) have used survey data to report clinical diagnoses of ADHD in 11% of males with XYY and 72% of males with XXYY.[4,5] A 2009 study by Bruining et al[6] was the first to apply the DSM-IV diagnostic criteria to a cohort of pediatric subjects with XXY/KS, and 63% (32/51) of this self-selected cohort met criteria for a diagnosis of ADHD. In another recent study of 27 children with XXY/KS, 41% (11/27) met criteria for DSM-IV ADHD based on parent interview.[7] For other SCA groups such as trisomy X (XXX) in females, behavioral symptoms of attentional problems have been reported, but prevalence rates or clinical characteristics of ADHD symptoms have not been described.[8–10]

There is significant variability in the presence and severity of associated neurodevelopmental and psychological problems among individuals with SCA; however, patterns of weaknesses in language, verbal cognition, reading, and executive function (EF) are commonly identified. In the trisomy conditions (XXY, XYY, and XXX), the majority of studies report mean full scale cognitive scores within the low average to average range; however, cognitive scores are often lower than expected for family history, and up to 85% require special education supports for learning disabilities. In comparison, due to the additional gene dosage effects in the tetrasomy condition, males with XXYY syndrome usually have more significant cognitive and learning impairments, increased rates of congenital malformations, and 30% to 40% of males with XXYY syndrome have mild intellectual disability. In all SCA conditions, there are additional increased risks for emotional disorders including anxiety, depression, and other mood disorders, as well as medical problems such as seizures, which can make the neuropsychological and behavioral phenotype even more complex. Thus, when considering a diagnosis of ADHD in this population, the contribution of these other factors must also be considered. Although ADHD symptoms may be just 1 component of the neuropsychological phenotype, applying this diagnosis accurately in the clinical setting is important to guide supports and therapies in clinical and educational settings.

In this study, we compare ADHD symptoms in 167 children with 4 types of SCA (XXY, XYY, XXX, and XXYY) and evaluate factors associated with ADHD symptomatology including age, prenatal versus postnatal ascertainment, cognitive and adaptive scores, and parental education. We also describe the clinical response to psychopharmacologic medications for ADHD symptoms in a subset of patients treated for ADHD.

METHODS

Participants

Participants were recruited through support organizations for sex chromosome aneuploidy (SCA) and medical clinics in genetics, developmental pediatrics, and endocrinology to participate in an institution review board (IRB)-approved study of health and development in SCA. Recruitment materials indicated that the purpose of the study was to learn more about medical problems, medications, physical features, and developmental and psychological features of SCA and did not indicate a specific emphasis on attention-deficit hyperactivity disorder (ADHD). Males with XXY, XYY, and XXYY and females with XXX between the ages of 6 and 20 years, of all races and ethnicities, were included. Participants were seen from 2004 to 2010 by a developmental-behavioral pediatrician (N.R.T.) at the University of California—Davis MIND Institute and at the eXtraordinary Kids Clinic in the Child Development Unit at Children's Hospital Colorado. Both the UC-Davis Institutional Review Board and the Colorado Multiple Institutional Review Board approved this study.

Evaluation

The evaluation protocol included a semistructured interview reviewing medical, developmental, and psychological history and a physical examination. The interview yielded information regarding genetic test results (showing SCA status and age at diagnosis), past and current medication use, and history of previous diagnoses of ADHD, mental health disorders (e.g., mood/anxiety disorders), neurological conditions (e.g., seizures), learning disabilities or autism spectrum disorders. The age at SCA diagnosis was recorded to allow for comparison between participants identified by prenatal genetic testing and those ascertained due to developmental-behavioral or medical symptoms. Parental education was used as a proxy for socioeconomic status.

Cognitive scores were available for 138 of the 167 participants in the study. For 134 participants, cognitive abilities were measured using an age-appropriate Wechsler series test, such as the Wechsler Abbreviated Scale of Intelligence (WASI), the Wechsler Intelligence Scale for Children–Third Edition (WISC III), the Wechsler Intelligence Scale for Children–Fourth Edition (WISC IV), and Wechsler Adult Intelligence Scale–Third Edition (WAIS III), each of which provides composite index scores for verbal conceptual reasoning (Verbal IQ [VIQ] or), nonverbal reasoning (Performance IQ [PIQ] or Perceptual Reasoning Index), and Full Scale IQ (FSIQ). Eighty-three subjects were administered the WASI, 41 subjects were administered the WISC-IV, 8 subjects were administered the WISC-III, and 2 subjects were administered the WAIS-III.

The 4-subtest FSIQ estimate from the WASI correlates with the WISC-IV FSIQ at 0.86. Nevertheless, for children administered the WISC-IV, the General Ability Index (GAI) standard score was used instead of the FSIQ because the GAI is more directly comparable with the WASI VIQ and PIQ scores (i.e., the latter do not include any Working Memory or Processing Speed subtests, and neither does the GAI). As GAI scores are not available for the WISC-III, the FSIQ score was used for the 8 children administered this version; it should be noted, however, that the WISC-III FSIQ is not as heavily influenced by working memory or processing speed skills, as only 1 subtest from each is used in the FSIQ computation.

For 4 participants, IQ results were obtained from outside records. These results were used if the cognitive test was administered by a licensed psychologist within 1 year of their study visit. Two participants were administered the Differential Ability Scales; for these children, we used the Verbal Cluster and Nonverbal Reasoning Cluster standard scores, which are highly correlated to the Wechsler Verbal and PIQ scores (Verbal Cluster and VIQ, $r = .87$;

Nonverbal Reasoning Cluster and PIQ, $r = .78$; General Conceptual Ability and FSIQ, $r = .92$). One participant had been administered the Stanford Binet Scales of Intelligence—Fifth Edition (SB-5), which provides Nonverbal IQ, VIQ, and FSIQ composite scores. The SB-5 composites are also highly correlated with the Wechsler measures (SB-5 FSIQ and WISC-III FSIQ, $r = .84$). Finally, 1 participant had been administered the Woodcock-Johnson—Third Edition Test of Cognitive Ability, whose overall composite is also highly correlated with the Wechsler FSIQ (Pearson $r = .76$).

Adaptive functioning was measured by 1 of 3 standardized measures, including the Vineland Adaptive Behavior Scales-II (n = 50), the Adaptive Behavior Assessment System—Second Edition (ABAS-II) (n = 71), or the Scales of Independent Behavior—Revised (SIB-R) (n = 19). The overall adaptive functioning composite score from each test was used in the statistical analyses. Per the information provided in each of the manuals, these 3 measures have moderate to high intercorrelations (i.e., Vineland II and ABAS-II, $r = .78$; SIB-R and ABAS-II, $r = .66$).

ADHD symptoms were evaluated by using the parent version of the Conners' Rating Scale for 58 participants (35%) or the Swanson, Nolan, and Pelham Questionnaire—Fourth Edition (SNAP-IV) for 109 participants (65%). Both of these questionnaires contain the identical 18 symptom items from the DSM-IV ADHD diagnostic criteria, and these were the only items used from these rating scales. Parent or primary caregiver data were obtained for all participants. Participants were given the option of having a teacher complete an ADHD rating scale about behaviors in the school setting, and we received teacher rating scale results from 45% of participants. Thus, teacher data were only used in secondary analyses.

Both the Conners' Rating Scale and the SNAP-IV use a Likert scale consisting of 4 possible responses for each item: not at all (0); just a little (1); pretty much/quite a bit (2); and very much (3). A score of 2 or 3 on an item was counted as a positive symptom, and the number of items so endorsed out of the 18 that comprise the DSM-IV ADHD criteria were tallied. Based on these data, participants were assigned to 1 of 4 categories based on whether they had positive symptoms in 6 or more items in the inattentive domain and/or the hyperactive/impulsive domain (no ADHD, ADHD—Inattentive subtype, ADHD—Hyperactive/Impulsive subtype, and ADHD—Combined subtype). Three continuous ADHD scores (Inattentive, Hyperactive/Impulsive, and Combined) were also derived by summing the total points across appropriate sets of items. The total possible score for the Inattentive and Hyperactive/Impulsive subsets was 27, while the total possible combined score was 54. It is important to note that these categories were assigned based on the results of the parent-report questionnaires rather than a more comprehensive diagnostic evaluation. However, participants were classified into these categories to quantify the percentage of participants with significant ADHD symptoms noted by their parents/primary caregivers and to allow for further analyses of factors contributing to ADHD symptomatology in children with SCA.

Following participation in the study, a subset of participants sought clinical evaluation and follow-up care in the Developmental-Behavioral Pediatrics clinic by N.R.T. These patients received an initial comprehensive assessment resulting in clinical diagnoses and treatment recommendations in consideration with their SCA condition and follow-up as indicated. If diagnosed with ADHD and treated with medications, medication choice (i.e., stimulant vs nonstimulant) was based on history and consideration of other medical conditions, current medications, and other behavioral or psychological symptoms, per standard clinical practice in developmental pediatrics. For this study, a retrospective chart review of these patient visits was performed to determine whether they were found to meet criteria for a clinical diagnosis of ADHD, whether ADHD symptoms were treated with medications, and their response to medication treatment. Records from follow-up visits were reviewed, with

specific attention paid to (1) subjective descriptions of changes in ADHD symptoms in the home and school settings as reported by the parents, (2) ADHD medication prescription refills, (3) results of updated ADHD rating scales if available, and (4) impressions/recommendations formulated by the treating physician. These factors were considered to develop an impression of whether the response to medication was positive or negative. A positive response was considered to be a clinical improvement in ADHD symptoms following 6 months of treatment. A response was classified as negative if there was no improvement in symptoms or if side effects led to discontinuation of treatment. These data were then combined with data collected by the initial semistructured interview to determine the percentage of participants treated with medications and the general response to medication treatment for ADHD symptoms.

RESULTS

Participants

A total of 167 children and adolescents aged 6 to 20 years with sex chromosome aneuploidy (SCA) participated in the study. The subgroups by diagnosis included XXY (n = 56), XYY (n = 33), XXX (n = 25), and XXYY (n = 53). Table 1 provides demographic, cognitive, and adaptive functioning information by group. There were no significant differences among diagnostic subgroups in terms of age, race, ethnicity, years of maternal education, or years of paternal education.

The timing of ascertainment of SCA diagnosis is important to consider when comparing groups because some previous studies have shown better outcomes for prenatally diagnosed children when compared with postnatally diagnosed children. Previous researchers have hypothesized that this finding is due to the fact that infants with a prenatal diagnosis have the potential to fall anywhere along the full spectrum of involvement for their specific SCA and may have additional advantages of stronger family supports, more favorable background genetics, and early developmental interventions.[11,12] In contrast, individuals ascertained in the postnatal period usually come to clinical attention due to developmental-behavioral or medical problems and, thus, are more likely to represent the more affected end of the spectrum. In this study, there were significant differences among the diagnostic subgroups with regard to when children were diagnosed, and this was primarily driven by the low rate (2%, n = 1) of children with XXYY who were prenatally diagnosed. Due to the more involved cognitive and medical phenotype in XXYY syndrome, fewer cases identified in the prenatal period are carried to term. When the XXYY group was removed from this analysis, the proportion of individuals with a prenatal diagnosis was not significantly different ($\chi^2(2) = 2.60$, not significant) among the 3 trisomy groups.

Analysis of the cognitive assessment tests showed mean Full Scale IQ (FSIQ) scores within the expected range for each subgroup and also showed the characteristic relative strength in Nonverbal IQ as compared with VIQ that has been previously described. An analysis of variance showed significant differences among groups for all 3 cognitive scores (VIQ, Performance IQ [PIQ], FSIQ), with post hoc Tukey analysis indicating that the XXYY (FSIQ mean = 79.4) and XXX (FSIQ mean = 82.7) groups scored significantly lower in terms of overall cognitive ability than the XXY (FSIQ mean = 97.5) and XYY (FSIQ mean = 96.41) groups. For each of the SCA groups, VIQ was significantly lower than PIQ (XXY: $t(44) = -3.56$, $p < .001$; XXYY: $t(41) = -5.46$, $p < .001$; XYY: $t(27) = -3.34$, $p < .001$; XXX: $t(20) = -2.39$, $p < .05$).

Compared with same age peers, mean adaptive functioning skills in the SCA groups ranged from the low average range for the XXY group to significantly below average for the XXYY group. Mean adaptive skills for the XYY and XXX groups were in the borderline

range. Adaptive functioning scores were significantly different among groups, with analysis of variance results indicating that the XXYY and XYY groups scored significantly lower than XXY; there was no pairwise difference between the XXX and the other 3 groups. Furthermore, adaptive functioning scores were significantly lower than FSIQ for all groups except XXX (XXY: $t(34) = 5.34$, $p < .001$; XXYY: $t(38) = 4.17$, $p < .001$; XYY: $t(20) = 6.23$, $p < .001$; XXX: $t(17) = 1.39$, not significant).

Comorbid Conditions

Table 2 provides information regarding the comorbid medical, learning, and psychiatric disorders for each group, regardless of attention-deficit hyperactivity disorder (ADHD) status. Higher rates of intellectual disability were noted in the XXX and XXYY groups, while a previous diagnosis of an autism spectrum disorder was more common in the XYY and XXYY groups. A previous diagnosis of a learning disability was quite common in all groups especially in the XXYY group. Mood disorders, including anxiety and depression, were less frequent in the XXY group than in the other 3 groups, but rates were still higher than in the general population for all 4 groups.

ADHD Symptoms

Of the total study group, 58% of children (96/167) had symptoms meeting DSM-IV criteria for ADHD based on parent-report questionnaires. Table 3 shows the percentage of children who met criteria for each ADHD subtype by SCA group. The XYY and XXYY groups showed the highest rates of symptom scores in the ADHD range overall (76% in XYY and 72% in XXYY), with the Inattentive and Combined subtypes making similar contributions to the total ADHD rate in each group. In contrast, the XXY and XXX groups had lower rates of scores in the ADHD range (36% in XXY and 52% in XXX), with the total ADHD rate in these groups almost entirely due to the Inattentive subtype; only 1 to 2 participants in each of the latter groups exhibited significant hyperactivity or impulsivity. Comparing overall ADHD rates yielded a significant difference between XXY and the rest of the groups, with the XXY group exhibiting a lower rate of scores in the ADHD range (any subtype). The other 3 groups did not differ from one another ($\chi^2(3,167) = 20.057$, $p < .001$; test of column proportions, $p < .05$).

A z-test of column proportions showed that children in the XYY and XXYY groups exhibited higher rates of hyperactive/impulsive symptoms than did children in the XXY group, as seen by the higher rates of ADHD-combined type in the former 2 groups ($p < .05$). The rate of ADHD-combined type in children with XXX did not differ from the rate in any of the other 3 groups. Rates of the ADHD-Inattentive subtype were significantly higher in XXY and XXX compared with XYY and XXYY ($p < .05$).

As cognitive abilities can affect ADHD behaviors, and because there were significant differences in cognitive scores among the SCA subgroups, we wanted to determine whether differences in ADHD symptomatology between SCA subgroups could be accounted for by differences in IQ. Analyses of covariance were performed using the 3 continuous ADHD symptom scores (Inattentive, Hyperactive, and Combined) as dependent measures and FSIQ as a covariate. The results indicated significant differences among groups for all 3 ADHD symptom scores. Specifically, for inattention, the XXY group had fewer symptoms than the XYY group, with XXX and XXYY intermediate, but the XXY, XXX, and XXYY groups did not differ from one another ($F(3,133) = 3.30$, $p < .05$). For hyperactivity/impulsivity and combined scores, the XXY and XXX groups had fewer symptoms than XYY, with XXYY intermediate and not different from XXX and XYY (Hyperactive/Impulsive: $F(3,133) = 6.00$, $p < .001$; Combined: $F(3,133) = 6.01$, $p < .001$).

Teacher-report questionnaires were available for 71 (45%) of the participants overall. Table 3 provides group sizes and symptom counts for the teacher data (XXY = 27, XYY = 12, XXX = 10, and XXYY = 21). When comparing parent and teacher responses, there was agreement of overall classification (ADHD vs no ADHD) in 69% of subjects, and the parent and teacher total scores were within 5 points (with 1 rater just subthreshold for ADHD cutoff) in an additional 14%. The same analyses of covariance were performed on the 3 ADHD continuous scores using teacher data, and a similar pattern of results was found. For Inattentive symptoms ($F(3,55) = 3.66$, $p < .05$), the XXX group had a significantly lower score than the other 3 groups, which did not differ from each other. For Hyperactive/Impulsive symptoms and combined symptoms, the XYY group had a significantly higher score than the other 3 groups, which did not differ from one another (Hyperactive/Impulsive: $F(3,55) = 4.64$, $p < .01$; Combined: $F(3,55) = 4.50$, $p < .01$).

Effect of Prenatal Versus Postnatal SCA Diagnosis on ADHD Symptoms

To evaluate whether ADHD symptoms were more common in the subgroups with a postnatal diagnosis, a Fisher's exact test was conducted in each of the trisomy subgroups comparing ADHD symptom scores of those meeting criteria for ADHD with the scores of those below this range. XXYY was excluded from this analysis because 98% were ascertained postnatally. The results, shown in Table 4, indicate that a disproportionate number of children in the XXY group diagnosed postnatally had total symptom scores in the ADHD range (1-sided exact $p = .026$). In XYY and XXX, there was a trend toward increased incidence of ADHD symptoms in postnatally diagnosed children, but differences were not statistically significant (1-sided exact p values of .23 and .27, respectively). In all 3 trisomy groups with a prenatal diagnosis, rates of symptom scores in the ADHD range were higher than seen in the general population.

Comorbid Conditions and ADHD Symptoms

A secondary cross-tabulation analysis was conducted to see whether rates of learning, mood, or autism spectrum disorders were higher in children with symptom scores in the ADHD range. In the sample as a whole, children with symptoms in the ADHD range were more likely to have learning problems ($\chi^2 = 10.9$, $p = .001$) and autism spectrum disorder ($\chi^2 = 9.96$, $p = .002$) but not mood disorder ($\chi^2 = 0.72$, $p = .396$). Examining rates by SCA type, there was a disproportionately higher rate of learning disorder in children with ADHD in the XXX group ($\chi^2 = 4.81$ $p = .028$), and there was a disproportionately higher rate of autism spectrum disorder in children with ADHD in the XXYY group ($\chi^2 = 3.97$, $p = .046$).

Cognitive and Adaptive Functioning

To evaluate whether there were significant differences between cognitive or adaptive scores in individuals with and without symptoms scores in the ADHD range, we compared VIQ, PIQ, FSIQ, and adaptive functioning scores in the pooled group of trisomy patients (XXY, XYY, and XXX). There were no significant differences between the group of trisomy children with ADHD versus those without ADHD on any of the IQ scales; however, adaptive functioning scores were found to be significantly lower in the group with ADHD compared with the group without ADHD (ADHD mean = 74.82 (16.7); no ADHD mean = 85.76 (15.2); $t(80) = 3.08$, $p < .01$).

Psychopharmacologic Treatment of ADHD in Participants

On presentation to the study, 41% (68/167) of participants had previously been diagnosed with ADHD, and 26% (44/167) were currently receiving medication treatment for ADHD. Of the 24 participants with a previous ADHD diagnosis not receiving medication treatment, 20 had previously been tried on medications, including 9 where medication treatment was

not felt to be effective, and 11 where medication was discontinued due to side effects. Families had deferred medication treatment for the remaining 4 untreated participants. An additional 81 patients were subsequently seen for comprehensive clinical evaluation by N.R.T., with 45 patients receiving a clinical diagnosis of ADHD. Of these 45 diagnosed with ADHD, 37 were started on medication treatment for ADHD.

It is important to note that not all 68 patients with a previous clinical diagnosis of ADHD met full DSM-IV criteria on the Conners' or Swanson, Nolan, and Pelham Questionnaire—Fourth Edition (SNAP-IV) checklists administered in the study. Many of these participants endorsed symptoms that were just subthreshold to DSM-IV criteria (i.e., moderate to severe symptoms in 4 or 5 of the 6 required DSM-IV criteria), and a percentage of participants were on medication treatments that were leading to improved symptoms and lower scores on the ADHD checklists. Similarly, for those seen clinically and started on ADHD medications, some patients did not meet full DSM-IV criteria but had significant symptoms that were impairing functioning based on history obtained from parent and school reports sufficient to warrant recommendation for a medication trial. In combination, a history of medication use for ADHD symptoms was available for a total of 101 study participants (30 XXY, 25 XYY, 10 XXX, and 36 XXYY).

The results of responses to medication use for ADHD symptoms are shown in Table 5. Across all groups, psychopharmacologic treatment of ADHD with stimulants was effective in 78.6% (66/84) of patients, with positive response rates ranging from 73% for XXY to 84% for XXYY. There were no significant differences in response rates to stimulant medications between SCA groups ($p = .74$, Fisher's exact test). Methylphenidate products (59%) were used slightly more frequently than Dexedrine or mixed amphetamine salts (41%); however, there were no differences in response rates between the 2 main types of stimulants. For those who had a negative response to stimulants (n = 18), medication was discontinued due to side effects in 13 patients (9 due to increased irritability and 4 due to appetite or sleep disturbance). Stimulant medication was not felt to be effective in the other 5 patients. These patients had been trialed on 1 (n = 3) or 2 (n = 2) stimulant medication(s) without positive effects, and parents opted not to pursue further medication treatment. A smaller group of patients were started on nonstimulant medications including atomoxetine and alpha-agonists (guanfacine or clonidine), and these results are also shown in Table 5; however, percentages and comparisons were not calculated due to the small sample sizes.

DISCUSSION

This study describes and compares attention-deficit hyperactivity disorder (ADHD) symptoms in a large cohort of children and adolescents with 4 different types of sex chromosome aneuploidy (SCA). Overall, the results show that ADHD symptoms are very common in all SCA groups and that the rates of individuals meeting DSM-IV criteria for ADHD based on parent report rating scales (ranging from 34% in XXY to 76% in XYY) are considerably higher than the 3% to 10% rate of ADHD estimated in the general population. Symptoms seen in the inattentive subtype of ADHD were the most common across all groups; however, males with XYY and XXYY were more likely to also have symptoms of hyperactivity and impulsivity.

It is important to note that current recommendations for establishing a diagnosis of ADHD include obtaining rating scales of a child's behavior from both a parent/primary caregiver and 1 or more other adults familiar with the child's behavior (usually a teacher) to establish that symptoms are present in more than 1 setting.[13] In this study, results of parent report rating scales were used to classify whether patients had scores that met DSM-IV criteria for ADHD. Thus, it is important to recognize that the rates and subtype classifications are based

on parent rating scale results and may overestimate the percentages that would meet criteria based on more comprehensive clinical assessment. Although results of the optional teacher rating scales were available only in 45% of cases, there were high agreement rates and a similar profile of symptoms when comparing parent and teacher responses. Further, consideration of other possible diagnoses or comorbid conditions is important before assigning a clinical ADHD diagnosis.[13] Of the subgroup of 81 patients subsequently seen for clinical diagnostic evaluation, the classification of ADHD versus no ADHD on parent questionnaire was consistent with the final clinical diagnosis in 90% (73/81), although other clinical diagnoses may have also been applied. Thus, in this study group, it seems that classification of ADHD based on parent-report rating scales closely estimated final ADHD diagnosis.

There are only 2 previous studies that have evaluated rates and subtypes of ADHD based on parent-report of DSM-IV criteria in children with XXY/Klinefelter syndrome (KS). In 2009, Bruining et al[6] found ADHD in 63%, which is somewhat higher than the 34% in our XXY group. Their sample had lower cognitive scores (Full Scale IQ [FSIQ] mean = 80) compared with our sample (FSIQ mean = 97) and somewhat higher rates of other psychological disorders such as autism spectrum disorders (14% vs 4%), depression or anxiety (56% vs 29%), and psychotic disorders (12% vs 2%). The more significant cognitive and psychological involvement in the study by Bruining et al[6] might explain the higher rate of ADHD symptoms in their cohort. The second comparison study by Lee et al[7] reported an ADHD rate of 41% in a sample of 27 males with XXY with a mean FSIQ of 101, which is more consistent with our findings. Both the other studies also found an increased likelihood of the inattentive subtype of ADHD in XXY, also similar to our study results.

As this study is the first to directly apply ADHD DSM-IV criteria in XYY, XXX, and XXYY, there are no direct comparison studies for these groups. However, previous case series have described previous ADHD diagnoses in XYY and XXYY at rates higher than those seen in the general population,[5,9] which converges with our findings of significantly increased risk of ADHD in all SCA subgroups.

The most comprehensive studies on the psychological phenotypes of SCA subgroups were a group of studies conducted in the 1970s to 1990s at multiple sites around the world where samples were ascertained by newborn screening and followed closely into adulthood.[8,10,14,15] These longitudinal studies provided information on an unselected sample of individuals with SCA, and the results of these prospective studies identified the elevated rates of language-based learning disabilities and psychosocial difficulties that characterize the behavioral phenotype of the SCA groups.[16–18] When reviewing the findings from these studies, there were few reports of ADHD diagnoses; however, multiple study sites reported descriptions of problems with attention, distractibility, impulsivity, behavioral regulation, and executive function (EF). The discrepancy in rates of ADHD diagnosis between our study and these earlier studies may be due to the difference in time period, as there has been increased awareness about ADHD as a diagnosis and research in ADHD since the 1980s and early 1990s, at which point many of these patients were beyond school age. In addition, the strength of the newborn screening studies was in the ascertainment of an unselected sample followed from birth. In contrast, our sample contains a majority of individuals ascertained in the postnatal period due to developmental delays or cognitive impairments; thus, the ascertainment bias in our sample may also contribute to the elevated rates of ADHD symptoms compared with these previous studies.

Ascertainment bias must be addressed in any study on groups of individuals with SCA due to the large spectrum of involvement in these conditions and the low rate of lifetime diagnosis. It is important to point out that participants in this study were recruited primarily

through advocacy groups and developmental-behavioral pediatrics clinics where patients with learning and behavioral difficulties are more likely to present. Thus, the rates of ADHD reported in this study are not being presented as the prevalence of ADHD in all individuals (diagnosed and/or undiagnosed) with SCA. If all individuals with SCA were ascertained at birth and evaluated for ADHD, the rates would most likely be much lower than in our sample. However, in the subset of the SCA population presenting for clinical care, ADHD is an important diagnostic consideration, and recognition of these symptoms by professionals is critical.

It should be noted that the mean IQ scores for each of the SCA types reported in this study are quite similar to what has been reported previously in the literature. In a meta-analytic review, Leggett et al (2010) reported mean Verbal IQs (VIQs) of 95, 99, and 80 and mean Performance IQs (PIQs) of 100, 106, and 85 for participants with XXY, XYY, and XXX, respectively.[19] A review of XXYY syndrome describes a mean VIQ of 74 and PIQ of 87 in a large cohort.[4] The mean IQs from these studies are quite similar to those reported in this article for each of the SCA types (Table 1), indicating that our samples are representative of patient populations with these disorders with regard to cognitive ability.

To decrease the effect of ascertainment bias on study results and to aid in prenatal genetic counseling of these conditions, previous studies in SCA also compare individuals diagnosed in the prenatal period to those in the postnatal period.[5,11,20] A prenatally diagnosed sample is less biased toward individuals ascertained due to developmental problems, and previous literature supports the finding that those with a prenatal diagnosis have improved outcomes compared with those diagnosed in the postnatal period.[12] The latter is likely due, in part, to higher socioeconomic status and improved opportunities for early intervention therapies. In our sample, those with a prenatal diagnosis of XXY were less likely to meet criteria for ADHD compared with the postnatally diagnosed group, and there was a similar trend in the XXX and XYY groups as well. Overall, the data suggest that genetic counselors should describe that children with SCA diagnosed in the prenatal period are less likely to have ADHD later in life; however, the rates of ADHD in a prenatally diagnosed sample are still higher than in the general population.

When we compared the pooled group of children with trisomy SCA with ADHD to those without ADHD, there were no significant differences in FSIQ scores between groups. However, the group with ADHD had significantly lower adaptive functioning abilities compared with those without ADHD. These results suggest that the effects of ADHD symptoms extend beyond the academic setting and are likely affecting overall functioning across multiple domains of daily functioning.

This study has important clinical implications in that it calls attention to the high rates of ADHD symptoms in the SCA conditions and supports the need for screening for ADHD in all children with SCA. As the hyperactive/impulsive symptoms are not as prominent in the XXY and XXX subgroups, it is sometimes easy to miss problems with attention and distractibility as being significant contributing factors affecting educational performance and daily living skills. Although comorbidities of learning, language, and social-emotional disorders may make the picture more complex, the diagnosis of ADHD is important to establish, if present, because it has implications in the educational setting. Most educational settings do not recognize the specific features and learning profiles of each genetic condition, but an ADHD diagnosis will often lead to additional educational interventions and accommodations via an individualized educational plan or other support plan. Strategies designed for children and adolescents with ADHD can also be implemented in the home setting to support daily living skills and social interactions.

The general approach to ADHD evaluation and treatment in the SCA conditions is not significantly different compared with the general population; however, an understanding of medical and other psychological features of the SCA conditions is important when evaluating the patient and developing a treatment plan. In adolescents with XXY/KS and XXYY, testosterone deficiency can lead to decreased energy levels and may contribute to attentional difficulties. Thus, evaluation of testosterone levels must be considered and treatment optimized. Risks for hypothyroidism, seizure disorders, and sleep apnea are slightly elevated in all SCA groups compared with the general population and should be screened for a possible contribution to attentional and academic difficulties. This study, along with previous SCA literature, shows that ADHD symptoms are often accompanied by other cognitive and psychological difficulties, so a full psychological assessment is recommended before assigning an ADHD diagnosis or starting on medication treatment. A psychological or neuropsychological assessment will help determine whether other learning disabilities, speech/language disorders, or emotional symptoms are present, which may need to be included as part of a comprehensive treatment plan. Patients previously diagnosed with ADHD who do not seem to respond to treatment may have increased rates or severity of these comorbid factors, which may not have been fully appreciated or addressed. Furthermore, comorbid learning and social-emotional symptoms, just like ADHD symptoms, often present differently across the life span, so periodic reevaluation may be necessary.

Finally, the results of the medication review show that more than 70% of children and adolescents with SCA and ADHD responded to standard stimulant medications, with a relatively low rate of significant side effects. Increased irritability was the most common side effect leading to discontinuation of medication, so low starting doses with gradual increases are recommended to decrease impact of irritability symptoms. The response rates to pharmacological intervention for ADHD are included in this article because of the lack of data in the literature on ADHD treatment in SCA beyond a few case reports. It should be noted, however, that the results presented here are based on a retrospective chart review. A more rigorous study design is needed to better understand medication responses in SCA compared with general ADHD. There were no sufficient data to draw firm conclusions about the response rates to nonstimulant medications, although based on this small series of cases, they are generally effective and well tolerated across all SCA subgroups and thus appropriate to try whether other clinical symptoms, parental preferences, or stimulant side effects lead to selection of these medications.

Other weaknesses of this study include the variability in measures used for assessment of cognitive and adaptive functioning. In addition, current best practice in ADHD diagnosis includes obtaining information about symptoms in more than 1 setting, so classification of ADHD diagnosis based on both parent and teacher responses for all subjects would have strengthened study results.

Although it is important to identify ADHD as a clinical diagnosis, additional research is needed to deconstruct the neuropsychological deficits leading to the behavioral symptoms of ADHD in the SCA population. Although FSIQ was not related to ADHD diagnostic rates in this study, it is possible that increased rates of language-based learning disabilities, EF deficits, and social emotional disorders underlie some of the behavioral ADHD symptoms. Specifically, EF impairments have been described in small cohorts of children and adults with XXY/KS, with these studies showing impairment in various EF subdomains, including inhibition, verbal working memory, processing speed, attention, and other frontal-executive deficits.[21–26] The sample sizes, assessments used, and ages of the participants in these studies have varied, and thus more carefully designed prospective studies of EF and how

they relate to ADHD and other neuropsychological features in larger cohorts of individuals with SCA are an important next step for researchers.

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Table 1

Demographic Characteristics of Sample by Sex Chromosome Aneuploidy Group

Descriptives	47, XXY (n = 56), Mean (SD)	47, XYY (n = 33), Mean (SD)	47, XXX (n = 25), Mean (SD)	48, XXYY (n = 53), Mean (SD)	Significance Test
Age (y)	11.96 (4.19)	11.33 (3.68)	12.21 (4.19)	12.51 (3.91)	$F(3, 163) = .606$, ns
Range	5.98–20.06	6.33–20.51	5.4–20.04	6.23–20.19	
Race (% white)	86%	91%	84%	91%	$\chi^2(3, 167) = 1.25$, ns
Ethnicity (% Hispanic)	9%	3%	8%	4%	$\chi^2(3, 167) = 2.01$, ns
Maternal education (y)	15.75 (2.45)	15.44 (1.95)	16.40 (2.10)	15.16 (2.31)	$F(3, 156) = 1.814$, ns
Father education (y)	15.48 (2.69)	14.87 (2.32)	14.96 (2.82)	14.73 (3.43)	$F(3, 149) = .604$, ns
Prenatal diagnosis (%)	45%	33%	56%	2%	$\chi^2(3, 167) = 33.52^{***}$
Verbal IQ[a]	93.02 (18.76)	91.90 (16.02)	81.86 (16.48)	76.45 (13.20)	$F(3, 133) = 9.33^{***}$
Range	53–119	46–129	53–117	59–112	
Nonverbal IQ[b]	99.07 (15.85)	101.79 (16.62)	86.81 (17.67)	86.98 (14.73)	$F(3, 132) = 7.86^{***}$
Range	61–129	73–139	57–116	64–117	
Full Scale IQ[c]	97.53 (19.28)	96.41 (15.47)	82.71 (18.48)	79.37 (14.00)	$F(3, 134) = 11.33^{***}$
Range	46–141	56–127	50–118	57–117	
Adaptive composite[d]	84.82 (14.92)	74.05 (15.54)	77.23 (19.44)	67.97 (15.80)	$F(3, 118) = 7.167^{***}$
Range	45–120	40–102	46–106	27–98	

ns, not significant.

[a,b,c]For Verbal IQ, Nonverbal IQ, and Full Scale IQ, missing data led to the following group sample sizes: XXY = 45, XYY = 29, XXYY = 43, and XXX = 21. Furthermore, Tukey B post hoc tests showed that XXYY and XXX < XXY and XYY.

[d]For Adaptive composite, Tukey B post hoc test showed XXYY and XYY < XXY.

$^{*}p < .05$;

$^{**}p < .01$;

$^{***}p < .001$.

Table 2

Diagnoses Comorbid with Each Sex Chromosome Aneuploidy (Regardless of Attention-Deficit Hyperactivity Disorder Status)

Descriptive	47, XXY (n = 56), n (%)	47, XYY (n = 33), n (%)	47, XXX (n = 25), n (%)	48, XXYY (n = 53), n (%)	Significance Test
Intellectual disability	5 (9)	3 (9)	5 (20)	17 (32)	$\chi^2(3, n = 167) = 12.10^{**}$
Learning disability	35 (63)	23 (70)	14 (56)	51 (96)	$\chi^2(3, n = 167) = 21.79^{***}$
Mood or behavioral disorder	16 (29)	18 (54)	10 (40)	29 (55)	$\chi^2(3, n = 167) = 9.54^{*}$
Autism spectrum disorder	2 (4)	12 (36)	1 (4)	18 (34)	$\chi^2(3, n = 167) = 25.65^{***}$
Tics	6 (11)	13 (39)	5 (20)	13 (25)	$\chi^2(3, n = 167) = 10.18^{*}$
Seizures	3 (5)	4 (12)	6 (24)	7 (13)	$\chi^2(3, n = 167) = 5.83$, ns

ns, not significant.

$^{*}p < .05$;

$^{**}p < .01$;

$^{***}p < .001$.

Table 3

Proportion of Children Meeting DSM-IV Criteria for ADHD Subtypes Based on Parent Ratings and ADHD Symptom Counts Based on Parent and Teacher Ratings

	XXY (Parent: n = 56; Teacher: n = 27)	XYY (Parent: n = 33; Teacher: n = 12)	XXX (Parent: n = 25; Teacher: n = 10)	XXYY (Parent: n = 53; Teacher: n = 21)
Categorical data				
No ADHD diagnosis	36 (64%)	8 (24%)	12 (48%)	15 (28%)
Parent—Inattentive	19 (34%)	16 (49%)	11 (44%)	28 (53%)
Parent—Hyperactive	0	1 (3%)	0	0
Parent—Combined	1 (2%)	8 (24%)	2 (8%)	10 (19%)
Parent—any subtype	20 (36%)	25 (76%)	13 (52%)	38 (72%)
% of children with ADHD with Inattentive subtype	19/20 (95%)	16/25 (64%)	11/13 (85%)	28/38 (74%)
% of children with ADHD with Combined subtype	1/20 (5%)	8/25 (32%)	2/13 (15%)	10/38 (26%)
Continuous data				
Parent—Inattentive total symptom count	12.48 (6.65)[a]	17.42 (5.84)[b]	14.20 (6.20)[b]	16.85 (5.86)[b]
Parent—Hyperactive total symptom count	4.54 (4.79)[a]	11.15 (6.76)[b]	6.76 (5.76)[a, c]	9.58 (6.51)[b, c]
Parent—Combined total symptom count	17.02 (9.96)[a]	28.58 (10.76)[b]	20.96 (10.71)[a, c]	26.43 (10.76)[b, c]
Teacher—Inattentive total symptom count	14.52 (7.30)[b]	15.92 (5.53)[b]	10.30 (6.96)[a]	15.48 (5.78)[b]
Teacher—Hyperactive total symptom count	4.41 (4.05)[b]	12.92 (9.57)[a]	5.40 (6.64)[b]	6.86 (4.39)[b]
Teacher—Combined total symptom count	18.93 (9.66)[b]	28.83 (12.99)[a]	15.70 (12.15)[b]	22.33 (9.17)[b]

ADHD, attention-deficit hyperactive disorder. For continuous data, total symptom counts for parents and teachers are raw means (marginal means not shown). If 2 group means share a letter superscript, then they were not significantly different from each other; in contrast, group means that do not share a letter superscript differed at the 0.05 level or better in analyses of covariance with Full Scale IQ as a covariate.

Table 4

Proportion of Children Within Each Trisomy Group Diagnosed with ADHD (Any Subtype) by Prenatal vs Postnatal Diagnostic Status

	47, XXY	47, XYY	47, XXX
Prenatal diagnosis	n = 25	n = 11	n = 14
No. with ADHD	5 (20%)	7 (64%)	6 (43%)
Postnatal Diagnosis	n = 31	n = 22	n = 11
No. with ADHD	15 (48%)	18 (82%)	7 (64%)

ADHD, attention-deficit hyperactive disorder.

Table 5

Psychopharmacologic Medication Treatment of Attention-Deficit Hyperactivity Disorder by Sex Chromosome Aneuploidy Group

	47, XXY	47, XYY	47, XXX	48, XXYY
N	30	25	10	36
Stimulants				
Positive response	73% (19/26)	79% (15/19)	75% (6/8)	84% (26/31)
Negative response	27% (7/26)	21% (4/19)	25% (2/8)	16% (5/31)
Nonstimulants (guanfacine, clonidine, and atomoxetine)				
Positive response	3/4	5/6	2/2	5/5
Negative response	1/4	1/6	0/2	0/5