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Social deficits in male children and adolescents with sex chromosome aneuploidy: A comparison of XXY, XYY, and XXYY syndromes

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ABSTRACT

We compare social skills in three groups of males with sex chromosome aneuploidies (SCAs) using the Social Responsiveness Scale (SRS). Participants included males with XXY ($N = 102$, $M = 10.08$ years), XYY ($N = 40$, $M = 9.93$ years), and XXYY ($N = 32$, $M = 11.57$ years). XXY had lower (better) SRS scores compared to XYY and XXYY. Scores were not significantly different between XYY and XXYY. In all groups, there were significantly more with SRS scores in the severe range compared to the SRS normative sample. All groups scored lowest (better) on Social Motivation. Relationships between SRS scores and demographic and clinical variables were examined. Results describe the social skills in males with SCA, and suggest that an additional Y chromosome may contribute to increased risk of autistic behaviors.

1. Introduction

Sex chromosome aneuploidy (SCA) describes a group of conditions in which individuals have an atypical number of sex chromosomes. The three most common SCA variations in males include 47, XXY (Klinefelter syndrome), 47, XYY, and 48, XXYY. Klinefelter syndrome (KS) is the most prevalent, occurring in 1 in 650 males, while XYY occurs in 1 in 1000 males (Nielsen, 1990). XXYY is less common, occurring in approximately 1 in 18,000 males (Sorensen, Nielsen, Jacobsen, & Rolle, 1978). There are shared features in the phenotypes of all three conditions, but there are typically more significant medical problems and psychological features among males with XXYY.

1.1. Medical/physical features

The addition of the extra sex chromosome(s) in all three conditions leads to tall stature (Ottesen et al., 2010) and long legs, and features of clinodactyly and pes planus are commonly described. There is not a distinct set of dysmorphic facial features among males with SCA, although hypertelorism has been reported in both KS and in XXYY (Ross et al., 2008; Tartaglia et al.,

Abbreviations: SCA, sex chromosome aneuploidy; KS, Klinefelter syndrome; ASD, autism spectrum disorder; SRS, Social Responsiveness Scale; DAS-2, Differential Ability Scales – 2nd edition.

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2008). The extra X chromosome in KS and XXYY leads to testicular hyalinization that most often becomes apparent in adolescence with findings of microorchidism, lack of pubertal progression due to testosterone deficiency, and decreased fertility. Testosterone replacement therapy is necessary in most individuals with KS and XXYY. In comparison, testicular size, pubertal progression, and testosterone levels are usually normal in males with XYY. In XXYY syndrome, there are increased risks for additional medical problems such as seizures and other congenital malformations such as cleft palate or congenital heart malformations (Tartaglia et al., 2008).

1.2. Developmental and behavioral features

In all three of these SCA conditions, there is an increased risk for developmental delays, speech-language disorders, social–emotional difficulties, and cognitive impairments. In both Klinefelter and XYY syndromes, cognitive abilities are typically in the average to low average range with strengths in visual–perceptual skills and weaknesses in verbal skills (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009). In XXYY syndrome, cognitive abilities are typically lower due to the additional gene dosage effect of having 2 extra sex chromosomes, with mean scores in the borderline range and more significant weaknesses in the verbal domain (Tartaglia et al., 2008). Males with XXYY are also more likely to have complex behavioral or social–emotional difficulties (Tartaglia, Ayari, Howell, D'Epagnier, & Zeitler, 2011).

1.3. Social-behavioral phenotype and autism

There has been increasing interest in the social development of individuals with SCA over the past decade as research in genetic etiologies of ASDs has grown. Previous studies of children and adolescents with SCA describe a social-behavioral phenotype that includes shyness, social difficulties, and social withdrawal (Bancroft, Axworthy, & Ratcliffe, 1982; Ratcliffe, Butler, & Jones, 1990; Walzer, Bashir, & Silbert, 1990). Case reports of autism spectrum disorders (ASDs) and autistic behaviors in Klinefelter syndrome, XYY, and XXYY have also been reported (Jha, Sheth, & Ghaziuddin, 2007; Merhar & Manning-Courtney, 2007; Nicolson, Bhalerao, & Sloman, 1998).

There has been more systematic study of ASD in KS than XYY or XXYY. Bruining et al. administered the Autism Diagnostic Interview-Revised (ADI-R) while evaluating psychiatric characteristics in a group of 51 boys with KS between the ages of 6 and 19, and results showed that 27% met criteria for an ASD (Bruining, Swaab, Kas, & van Engeland, 2009). In comparison, Tartaglia et al. administered the Autism Diagnostic Observation Scales (ADOS) and ADI-R to a group of 20 children and adolescents age 6–21 with XXY, and found that only 1 of 20 (5%) met criteria for ASD. Of the remaining 19 participants in this study who did not reach diagnostic criteria for ASD, 42% were found to have significant deficits in either communication or reciprocal social interactions (Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010). In another study of KS, van Rijn, Swaab, Aleman, and Kahn (2008) evaluated social abilities and autistic traits in a group of 31 adult males and controls using two standardized self-report questionnaires, the Scale for Interpersonal Behavior (SIB) and Autism Spectrum Quotient (ASQ). Results showed that the KS group reported increased distress during social interactions, and total scores on the ASQ were significantly higher than the control group with 48% scoring above the cut-off for Asperger syndrome (van Rijn et al., 2008).

A study of 26 males diagnosed with XYY syndrome in the postnatal period found that 19% had been previously diagnosed with ASD (Geerts, Steyaert, & Fryns, 2003). In the largest descriptive study of XXYY syndrome to date, 28.3% of males six and older had been clinically diagnosed with an ASD (Tartaglia et al., 2008), of which 76.9% had received a diagnosis of PDD-NOS. In one of the few comparison studies of KS and XYY, Bishop et al. (2010) compared autism and language abilities in 19 children with KS (4–15 years) and 58 children (4–16 years) with XYY. In this sample, 11% of the Klinefelter group and 19% of the XYY group had been previously diagnosed with ASD. Even when those with a previous diagnosis of ASD were excluded, children with KS and XYY showed an increased risk for communication deficits similar to those seen in children with ASD (Bishop et al., 2010).

While these studies have described an increased rate of social difficulties and autistic behaviors in individual SCA conditions, previous research has not characterized the range of autistic symptoms nor compared the social profiles between individuals with different sex chromosome combinations (i.e. XXY vs. XYY) or with an increasing number of sex chromosomes (i.e. XYY vs. XXYY) using a common standardized measure. In this study, we sought to describe and compare social skills and autistic symptomatology in males with Klinefelter, XYY, and XXYY syndromes by administering the Social Responsiveness Scale (SRS), a parent-report questionnaire that measures 5 domains of social skills including social communication, social cognition, social awareness, social motivation, and autistic mannerisms. We also examined the relationships between SRS scores and factors such as age, socioeconomic status (SES), verbal and nonverbal cognitive abilities, previous clinical diagnosis of ASD, and timing of SCA diagnosis (prenatal vs. postnatal).

2. Methods

2.1. Design

Participants ages 4–18 years were recruited from national SCA advocacy organizations, and clinics in endocrinology, genetics, and developmental pediatrics for a study of health and development in SCA. Participants were enrolled in the study at either Children's Hospital Colorado (Denver) ($n = 102$) or Thomas Jefferson University – Philadelphia (TJU) ($n = 72$) and all