DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *15: 328–332 (2009)*

# Social Function in Multiple X and Y Chromosome Disorders: XXY, XYY, XXYY, XXXY

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Klinefelter syndrome (47,XXY) was initially described in the context of its endocrinologic and physical features; however, subsequent studies have revealed specific impairments in verbal skills and social functioning. Males with sex chromosomal aneuploidies are known to have variability in their developmental profile with the majority presenting with expressive language deficits. As a consequence of language delays, they have an increased likelihood of language-based learning disabilities and social-emotional problems that may persist through adulthood. Studies on males with 47,XXY have revealed unique behavioral and social profiles with possible vulnerability to autistic traits. The prevalence of males with more than one extra sex chromosome (e.g., 48,XXYY and 48,XXXY) and an additional Y (e.g., 47,XYY) is less common, but it is important to understand their social functioning as it provides insight into treatment implications. 
Dev Disabil Res Rev 2009;15:328–332.

**Key Words:** sex chromosomal aneuploidies; Klinefelter syndrome; 47,XXY; 48,XXYY; 48,XXXY; 47,XYY

In 1942, Harry Klinefelter, an adult endocrinologist, described nine postpubertal males with infertility, hypogonadism, gynecomastia, lack of pubertal virilization, small, firm testes, and increased gonadotropin levels [Klinefelter et al., 1942]. It was not until 1959 that these males were noted to have an extra X chromosome resulting in the karyotype of 47,XXY [Jacobs and Strong, 1959]. Although 47,XXY is the most common sex chromosomal condition, mosaic patterns (46,XY/47,XXY) and additional X's and/or Y such as 48,XXYY; 48,XXXY; and 47,XYY can occur although less frequently than 47,XXY.

The prevalence of Klinefelter syndrome or 47,XXY is estimated to be between 1 in 581 to 1 in 917 males, making it the most common disorder of sex chromosomes in humans [Morris et al., 2008]. Although it is the most common sex chromosomal aneuploidy (SCA), 64% of males with 47,XXY are never diagnosed, 10% of these cases are diagnosed prenatally by amniocentesis, and 26% are diagnosed postnatally during childhood and adulthood when they present with developmental delay, behavioral problems, hypogonadism, gynecomastia, or infertility [Abramsky and Chapple, 1997]. Since the physical gestalt of males with 47,XXY is often subtle and may become apparent postpubertally, it is important to recognize their social behavioral phenotype that may prompt chromosomal testing.

The original description of Klinefelter syndrome focused on endocrinologic and physical characteristics; however, subsequent studies of captive populations in mental and penal settings suggested a risk for mental retardation, criminality, and psychiatric issues [Pasqualini et al., 1957; Maclean and Mitchell, 1962]. These studies were obviously biased and incorrect as subjects were recruited from institutions, prisons, and psychiatric hospitals where large numbers of male subjects could be screened. Beginning in the 60s and 70s, it was recognized that there was a need to obtain accurate information about the developmental and behavioral trajectories of males with SCA; hence, prospective, unbiased studies were initiated with the utilization of newborn screening for SCA. Findings from these prospective studies predominantly focused on academic achievement, occupation, marital status rather than social behavioral phenotype. Furthermore, studies on SCA are often limited by small sample size, role of androgen deficiency, lack of control groups from individuals within the general population, or lack of standardized behavioral measurements [van Rijn et al., 2008]. As an example, studies may categorically describe these males as social, passive, or shy without comparing to controls and/or assessing these features using standardized instruments. Additionally, since the majority of

Grant sponsor: NIH/NICHD; Grant number: 1K23HD058043-01A1; Grant sponsor: NIH/NCRR; Grant number: K12 RR017643; Grant sponsor: NIH Clinical Research LRP Award; Grant number: L32MD000625-01; Grant sponsor: Medical Genetics NIH/NIGMS Training Program; Grant number: 5-T32-GM08243; Grant sponsor: NIH/NICHD Program Project; Grant number: HD22657; Grant sponsors: Emory Egleston Children's Research Center; Hoffmann-LaRoche Pharmaceuticals; SHARE's Childhood Disability Center, the Steven Spielberg Pediatric Research Center.
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Received 22 June 2009; Accepted 2 September 2009
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ddrr.76

males with 47,XXY remain undiagnosed [Abramsky and Chapple, 1997], subjects may not be completely representative.

Despite these general concerns, the early language deficits in males with SCA have been well-described, and we continue to appreciate their impact on social and behavioral functioning. Research on SCA has previously been limited to childhood and adolescence, but has now shifted to adulthood, which provides a deeper understanding of psychopathology across the life course. In this review, we will focus on the social functioning of males with the following SCA: 47,XXY; 48,XXYY; 48,XXXY; and 47,XYY. Interestingly, recent studies have revealed specific social functioning profile of males with SCA with suggestions of vulnerability to autism. Hence, males with an additional X and/or Y chromosomes may serve as a model in understanding social behavioral functioning and autism spectrum disorder.

**Social Functioning in 47,XXY**

Samango-Sprouse examined the developmental differences within the first year of life in 73 boys with 47,XXY who were diagnosed prenatally based on advanced maternal age. Sixty-two percent had truncal hypotonia and 20% had pseudo-torticollis with flattening of the occipital area and decreased range of motion on the contralateral side of the pseudotorticollis [Samango-Sprouse, 2001]. Expressive language delay was noted by 12 months of age with deficits in phonemic development, motor imitation, and decreased vocalizations. It has been hypothesized that decreased muscle tone, psychomotor delay, decreased motor activity, and atypical movement patterns may contribute to being passive, clumsy, and awkward in motor function, with expressionless facial appearance in infants with 47,XXY [Ross et al., 2005].

Previous studies have also confirmed that males with 47,XXY have a high rate of early speech/language delays, which can lead to language-based learning disabilities. Problems with word retrieval, syntax, and narrative construction are characteristics of males with 47,XXY [Graham et al., 1988]. As a result of the language-based learning deficits, lower Verbal IQ (VIQ) than Performance IQ (PIQ) is noted with normal Full-Scale IQ (FSIQ). Additionally, males with 47,XXY have deficits in social interactions possibly contributed by language-based learning difficulties, social cognition impairments, and language delay [van Rijn et al., 2006b]. These males may also encounter self-image struggles as their physical stigma includes tall stature, thin frame, and lack of pubertal development [Visootsak et al., 2001]. They may have weak upper-extremity strength and poor coordination with decreased energy level, especially during the period of testosterone deficiency. These factors make them an easy target for teasing from peers, which can result in avoidance of social interactions and participation in extracurricular activities.

The behavioral characteristics of males with 47,XXY are variable. They are described as friendly, kind, helpful, and relate well with other people [Leonard, 1991], whereas other studies indicate that they are timid, immature, reserved, with challenges in interacting with their peers and a tendency to withdraw from social interactions [Bancroft et al., 1982; Ratcliffe et al., 1982]. During childhood, most are quiet, shy, hypoactive, and unassertive with a dislike for rough games and easy crying when bullied by other children [Ratcliffe, 1999]. Most males with 47,XXY also rate themselves as more sensitive, apprehensive, and insecure compared to their peers [Ratcliffe et al., 1982]. Of note, the majority of these studies did not consider the possible factor of testosterone deficiency. In adults with 47,XXY, testosterone replacement therapy has been shown to have positive impact on self-esteem and general well-being, as well as energy level and mood [Nielsen et al., 1988; Wang et al., 2000].

***Interestingly, recent studies have revealed specific social functioning profile of males with SCA with suggestions of vulnerability to autism.***

In a study comparing 47,XXY males who were diagnosed at birth to 47,XXY boys diagnosed postnatally because of physical and/or emotional problems, it was noted that latter group demonstrated problems with emotional adjustment with poor relationships with peers and high likelihood of anger and depression [Salbenblatt et al., 1981]. Individuals who received the diagnosis of 47,XXY at birth or prenatally may have fewer behavioral issues when early diagnosis results in early interventional therapy, greater attention and educational support, as well as understanding of the associated problems that can result from language delay.

A recent study suggested that social difficulties and vulnerability for autistic traits exist in adults with 47,XXY [van Rijn et al., 2008]. A study conducted by van Rijn et al. compared males with 47,XXY (mean age 41.3 years) to males recruited from the general population (mean age 35.7 years). Since both groups measured in the normal range for VIQ and PIQ, intellectual functioning should not confound the outcome results. When compared to men from the general population, the 47,XXY group was reported to have increased levels of distress during social interactions. For instance, the 47,XXY group had greater difficulties in expressing negative emotions to others, expressing and dealing with personal limitations, and initiating contact with others. Notably, the overall frequency of participating in social interactions was similar in both groups, but the 47,XXY group had fewer interactions dealing with expression of negative emotions, such as refusing a request or standing up for one's rights in a public situation. These findings in adults with 47,XXY are consistent with previous reports of social anxiety, social withdrawal, and shyness in children and adolescents with 47,XXY [Salbenblatt et al., 1981; Ratcliffe et al., 1982]. Thus, challenges in social function persist from childhood to adulthood.

In this same cohort of adults with 47,XXY, levels of autistic traits on the Autism Spectrum Quotient were higher in the 47,XXY group compared to men from the general population [van Rijn et al., 2008]. When compared to males from the general population, males with 47,XXY displayed more autistic traits in all domains including social skills, attention switching, attention to detail, communication, and imagination. Interestingly, males with 47,XXY were not restricted to deficits in the social behavior and communication domains, but displayed impairment in all domains. For these reasons, males with 47,XXY may be at higher risk for autism and other psychiatric disorders.

These findings suggest that individuals with 47,XXY have social difficulties through adulthood, and may have a propensity for autism traits. Further studies are needed using standardized autism testing instruments (e.g., Autism Diagnostic Observation Schedule (ADOS)) as subjects may under/over estimate their social functioning based on self-report measures.

In a study of social cognitive processing and emotion recognition, 32 males with 47,XXY (mean age 38.8 years) were matched for age, educational level, and IQ to 26 males from the general population (mean age 35.2 years) [van Rijn et al., 2006b]. In the 47,XXY group, 28 men were treated with testosterone supplements beginning at a mean age of 26.2 years. Males with 47,XXY have deficits in perception of social-emotional cues as revealed by their impairment in recognizing facial expressions of anger. As a result of their misperception of nonverbal signals and/or facial affect recognition, problems in social functioning may emerge. Furthermore, males with 47,XXY experience increased levels of emotional arousal, yet they are less able to identify and verbalize their own emotions, in comparison to the general population. Importantly, deficits in social cognition may contribute to the social difficulties noted in 47,XXY. Among the individuals with 47,XXY studied longitudinally after ascertainment through newborn chromosome surveys, Robinson et al. [1979] found 32% to have delayed emotional development, compared with 9% of their siblings [Robinson et al., 1979].

It has been hypothesized that social communication difficulties in 47,XXY males may be largely attributed to deficits in left hemisphere-mediated language functions, social cognitive impairments, and verbal disabilities [Rovet et al., 1996]. As explained above, males with 47,XXY demonstrate problems in reading, articulation, phonemic processing, spelling, language expression, verbal memory, language comprehension, understanding words, finding words, and verbally expressing their thoughts, which result in VIQ being lower than PIQ. However, a recent study examined the ability of 47,XXY men to decode emotions from tone of voice, a pragmatic aspect of social communication that may be associated with right hemisphere functioning [van Rijn et al., 2007]. In this study, 26 men with 47,XXY men and 20 men from the general population completed tasks involving emotion discrimination in speech, based on verbal content or tone of voice. The results revealed that the 47,XXY group displayed relative difficulties in discriminating emotions in verbal content of speech, and even more so, in tone of voice. This finding suggests that the males with 47,XXY have difficulties in semantic aspects (e.g., meaning of words) of language and with prosodic aspects (e.g., intonation) as well. Difficulties in pragmatic communicative cues in conversation can lead to impaired ability in coping with social situations.

Furthermore, high levels of schizotypal traits and schizophrenia symptoms have been identified in males with 47,XXY; however, these studies have been limited to psychiatric samples [DeLisi et al., 1994]. A recent study by van Rijn et al. compared 32 males with 47,XXY (mean age 38.8 years) to 26 healthy control males (mean age 35.0), and further matched for education and intellectual functioning [van Rijn et al., 2006a]. In the 47,XXY group, the mean level of schizotypal traits on the Schizotypal Personality Questionnaire and the Positive and Negative Syndrome Scale were significantly higher than in the control group ($P < 0.0001$). The possible vulnerability to schizophrenia-spectrum disorders in 47,XXY may suggest a link between X chromosomal abnormality and schizophrenia. In addition, decreased size of the amygdala is a potential anatomic basis for the emotional differences and schizophrenia-spectrum pathology with 47,XXY [Patwardhan et al., 2002; van Rijn et al., 2005].

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**Social Functioning in 48,XXYY**

The physical features of males with 48,XXYY are similar to 47,XXY; however, 48,XXYY is associated with more significant neurodevelopmental and psychological features. In most cases, IQ ranges from 70 to 80, with VIQ significantly lower than PIQ [Borgaonkar and Mules, 1970]. Early developmental delays are noted in 48,XXYY males, with mean full-scale IQ of 77.8, and a significantly lower mean verbal IQ of 74.0 relative to the performance IQ of 87.4 [Tartaglia et al., 2008]. The verbal IQ decreased with advancing age, despite the performance IQ remaining unchanged. Similar to the 47,XXY group, early language deficits increase the risk for language-based learning disabilities and maladaptive behavior. Based on the Vineland Adaptive Behavior Scales, males with 48,XXYY have higher overall adaptive functioning in daily living skills, socialization, and communication compared to 48,XXXY and 49, XXXXY [Visootsak et al., 2007].

Behavior is often shy and reserved [Linden et al., 1995], and can include hyperactivity, attention problems, impulsivity, aggression, mood instability, and "autistic-like" behaviors [Sorensen et al., 1978; Fryns et al., 1995]. Based on the Reiss Personality Profiles, 48,XXYY males revealed elevated scores in anxiety, frustration, order, and vengeance domains [Visootsak et al., 2007]. Furthermore, they have a higher likelihood of internalizing (e.g., anxiety, withdrawal, somatic, and attention problems) and externalizing (e.g., aggressive and delinquent behaviors) when compared to cohorts with 48, XXXY and 49,XXXXY.

The largest case report to date on 48,XXYY consists of 95 subjects ranging from 1 to 55 years of age, 92% with speech/language delays and 100% received special education for learning disabilities [Tartaglia et al., 2008]. The most common diagnoses in this group included 72% with attention deficit/hyperactivity disorder, 28% with autism spectrum disorder (ASD), and 47% mood disorders (e.g., generalized anxiety disorder, obsessive-compulsive disorder, depression, bipolar). Two individuals had been diagnosed with paranoid delusions and auditory hallucinations. In a study of 20 males with 48,XXYY [Tartaglia et al., 2005], 10 had a diagnosis of autism spectrum disorder based on the Social Communication Questionnaire and the Autism Diagnostic Observation Schedule (ADOS-G). In the group that met the criteria for ASD, three had autistic disorder and seven PDD-NOS. In those without the diagnosis of ASD, three males with 48,XXYY met ADOS criteria in at least one domain. Thus, ASD is an important clinical consideration in the 48,

XXYY group. Irrespectively, males with 48,XXYY have greater impairment in cognitive, verbal, and social functioning when compared to 47, XXY.

### Social Functioning in 48,XXXY

Our knowledge of the cognitive and social phenotype in 48,XXXY has been limited since it is uncommon with the prevalence of 1:50,000 [Linden et al., 1995]. Males with 48,XXXY present with significant cognitive and behavioral problems as each extra X reduces the overall IQ by 15 points, with language most affected [Linden et al., 1995]. Of note, there is great variability in cognitive and social functioning within each SCA group. Additionally, height decreases, and radioulnar synostosis becomes common when the number of X chromosomes increases. IQs generally range between 40 and 60, with greater deficits in daily living skills, communication, and socialization when compared to 48,XXYY [Visootsak et al., 2007].

Males with 48,XXXY have lower risk of internalizing and externalizing maladaptive behavior problems when compared to males with 48,XXYY [Visootsak et al., 2007]; however, they are not completely problem-free. Behavioral characteristics consisting of immaturity, passivity, and irritability with temper tantrums and outbursts. Similarities are noted to the 48,XXYY group in areas of activity level, help others, pain tolerance, morality, and rejection based on the Reiss Personality Profile [Visootsak et al., 2007].

### Social Functioning in 47,XYY

The 47,XYY occurs in 1 in 1,000 male births and it is not associated with the same endocrine and infertility problems described in 47,XXY [Robinson and Jacobs, 1999]. Earlier studies described a high numbers of males with 47,XYY in prison and institution for individuals with mental retardation [Price and Whatmore 1967a,b]. These males were identified to be aggressive, antisocial, and violent. These earlier studies were biased and are considered controversial. Subsequent longitudinal studies of males identified at birth with 47,XYY have not revealed an increased risk of incarceration [Nielsen and Wohlert, 1990].

The majority of males with 47,XYY have a wide range of IQs, with the majority being in the normal range with learning disability [Nicolson et al., 1998]. Similar to males with 47,XXY, language delay is common despite having IQs in the normal range.

Approximately 82% of boys with 47,XYY have symptoms of ADHD, which greatly interfere with academic performance and may lead to aggression, though they are not at increased risk for incarceration as suggested by earlier studies with biased ascertainment [Walzer et al., 1990]. Interestingly, the distractibility in boys with 47,XYY typically emerges between 2 and 3 years of age, prior to receiving the diagnosis of learning disability, whereas in boys with 47,XXY, the learning problem is followed by distractibility. Despite having fewer learning and language problems than the 47,XXY group, males with 47,XYY have been reported to be more disruptive and impulsive, which greatly interferes with their learning skills. Males with 47,XXY are typically shy and withdrawn compared to 47,XYY.

Parents have also reported concerns for antisocial behavior, with a significantly increased factor score for "uncontrolled, follows own urges, careless of social rules" when compared to sibling controls [Ratcliffe et al., 1990]. Psychiatric referrals occurred in 47% of 47,XYY cases compared with 9% of male controls, with persistent tantrums present in all cases [Ratcliffe and Field, 1982]. Additionally, other problems included difficult and defiant behavior, temper tantrums beginning in early childhood, stealing, and school related enuresis. Most males with 47,XYY were diagnosed with conduct disorder, and depressive reactions to environmental stressors, such as family dysfunction, were also noted. In a study comparing males with 47,XYY and 46,XY controls who were matched on IQ and socioeconomic status, the 47,XYY group displayed aggressiveness, with emotional outbursts, and impulsivity when they were frustrated [Schiavi et al., 1984]. Individuals with lower IQ appeared to have less control of their aggressive behavior.

In a study assessing the risk of ASD in 62 males with SCA (20 XXY, 22 XYY, 20 XXYY), none of 47,XXY, 36% of 47,XYY, and 50% of 48,XXYY had a diagnosis of ASD based on administration of the Social Communication Questionnaire (SCQ) and the Autism Diagnostic Observation Schedule (ADOS-G) [Tartaglia et al., 2005]. In those without ASD, 7 of 14 males with 47,XYY met ADOS criteria in at least one domain. The estimates appear high as these studies are limited by ascertainment design (e.g., clinical referrals).

## SUMMARY

Although progress has been made toward understanding the unique cognitive and social behavioral phenotypes of SCA, much work needs to be done, especially other forms of SCA (e.g., 48,XXYY; 48,XXXY; 47,XYY). The molecular mechanism for how extra sex chromosomes may lead to cognitive disabilities is not known. It is suspected that extra copies of genes that escape X-inactivation may contribute to such problems in a dose-related fashion, but the specific genes causing these effects are not known.

We initially recognized that males with SCA have early language delays, which increased their likelihood of language-based learning disabilities and social-emotional problems. Recent investigations have now revealed social-emotional impairment that may persist through adulthood. Indeed, we are beginning to learn that males with SCA may have increased vulnerability for autistic features as evidenced in their social behavior and communication impairment. Furthermore, the patterns of anxiety, shyness, and distress specifically during social situations may appear similar to ASD symptoms. Thus, it is difficult to tease apart the cause of the social-emotional problems seen in SCA, but we speculate that their early communication deficits and age-related changes in testosterone level may contribute to these problems. Irrespectively, these findings emphasize the potential influence of an extra X and/or Y chromosome for development of autism-like features. It is important to continue to identify the social and behavioral phenotypes in SCA, as this will enhance our clinical treatment, anticipatory guidance, and care throughout the lifespan for individuals with SCA. ■

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