

CHAPTER 2

SOCIAL BEHAVIOR AND AUTISM TRAITS IN A SEX CHROMOSOMAL DISORDER: KLINEFELTER (47XXY) SYNDROME

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Abstract

The XXY chromosomal pattern has been associated with difficulties in psychosocial functioning. Our aim was to examine frequency of participation in social interactions, distress during social interactions and autism traits in Klinefelter syndrome.

Scores of 31 XXY men on the Scale for Interpersonal Behavior and the Autism Spectrum Questionnaire were compared to 24 and 20 control men respectively.

XXY men reported increased distress during social interactions and less engagement of specific social behaviors. Overall rates of autism traits were significantly higher in XXY men.

These findings call for a clinical investigation of vulnerability to autism in Klinefelter syndrome. Klinefelter syndrome might serve as a model for studying a role of the X chromosome in social behavioral dysfunction and autism-like behavior.

Introduction

Klinefelter syndrome affects approximately 1 in 700 men and is the most common sex chromosomal disorder. Men with this syndrome have an extra X chromosome, giving rise to the XXY chromosomal pattern. This sex chromosomal aneuploidy results in a variety of phenotypes including hypogonadism, androgen deficiency and infertility (Lanfranco et al., 2004). Cognitive and behavioral dysfunctions in Klinefelter syndrome have generally been under-appreciated relative to endocrinological and physical features. However, there is an awareness of behavioral and cognitive abnormalities (Boone et al., 2001; Geschwind et al., 2000b). Prominent behavioral problems in men with Klinefelter syndrome are found in the social domain, such as social withdrawal, social anxiety, shyness, impulsivity and inappropriate social behavior (Bender et al., 1999; Geschwind et al., 2000a; Geschwind et al., 2004; Ratcliffe, 1999). In early adulthood XXY men report having few or no friends, poor relations with siblings and parents, little energy and initiative, and few or no sparetime interests (Nielsen et al., 1980). Difficulties in social functioning have been attributed to language based learning difficulties (Geschwind et al., 2000a), social cognitive impairments (van Rijn et al., 2006) and verbal disabilities (Rovet et al., 1996) that have been observed in Klinefelter syndrome.

In previous studies, social adjustment in Klinefelter syndrome has primarily been described from a psychosocial perspective. Psychosocial competence has been measured using psychiatric interviews or parental questionnaires focused at, for example, the quality of relationships with family members, self-esteem and coping with stressors (Bender et al., 1995; Ratcliffe, 1999). Impairments in social adjustment, communication and social cognition might reflect an increased liability for neurodevelopmental disorders such as autism. Therefore, a refinement of the social behavioral phenotype in individuals with the XXY karyotype is warranted.

In this study, we measured frequency of participation in social interactions and distress during social behavior in adult XXY men. To explore the extent to which social disabilities reflect increased levels of features that belong to the autism phenotype, we included quantitative measures of autism traits. We used this dimensional, rather than categorical, approach as it has been proposed that autism is a disorder of social behavior that reflects the extreme of a bell-shaped distribution of variation in autism traits, including social competence, in the population (Baron-Cohen et al., 2001; Constantino et al., 2003; Spiker et al., 2002).

Methods

Subjects

We included 31 men with Klinefelter syndrome (mean age 41.3, SD 10.0) with help from the Dutch Klinefelter Association. Diagnosis of Klinefelter syndrome was confirmed by karyotyping, using standard procedures. Twenty-four men were treated with testosterone supplements, with a mean age of treatment onset of 26.9 years (SD 7.6).

We compared autism traits in XXY men with 20 men from the general population (control group I), who were recruited using advertisements in local newspapers. Mean age in this group was 39.2 years (SD 13.1). Social behavior in XXY men was compared with 24 men from the general population (control group II). Mean age in this group was 35.7 (SD 8.5). There were no significant differences in age between the three groups, as indicated by a multivariate ANOVA as well as post-hoc tests ($F(2,72)=1.8$, $p=0.16$). None of the control subjects had a history of psychiatric illness as confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan *et al.*, 1998). The study was approved by the local ethics committee and written informed consent was obtained according to the declaration of Helsinki.

Intellectual ability

Raven's Advanced Progressive Matrices (short form)

This test is commonly accepted as a measure of general intelligence and has been shown to correlate with a number of other standardized intelligence tests (Lezak, 1995; Raven *et al.*, 1993). Subjects are shown 12 pictures of matrices (i.e., related patterns), each of which is a figural design with a part removed. The subject must choose the correct missing part from eight options.

National Adult Reading Test (NART)

The Dutch translation of the NART (Nelson, 1982; Schmand *et al.*, 1991) provides an estimate of verbal IQ and is based on the high correlation between reading ability, specifically of irregular words, with intelligence in the normal population. Subjects are required to read 50 irregular words aloud, and, on the basis of the number of errors made in pronunciation a reliable estimate of WAIS-R IQ can be calculated (Willshire *et al.*, 1991).

Social behavior

Social behavior was evaluated using the Scale for Interpersonal Behavior (SIB) (Arrindell, 1985). The SIB is a reliable and valid self-report measure of the frequency of engagement in specific social behaviors as well as the experienced distress it is accompanied by (Arrindell et al., 2001). Besides an overall measure of *frequency* of social behavior and *distress* during social behavior, there are four factorially-derived subscales: (I) Display of negative feelings (negative assertion), such as refusing a request or standing up for one's rights in a public situation, (II) Expression of and dealing with personal limitations, such as ability to deal with criticism or requesting attention/help, (III) Initiating assertiveness, such as starting a conversation with strangers or expressing one's own opinion and (IV) Praising others and the ability to deal with compliments/praise of others (positive assertion), such as giving and receiving compliments. Scores that are obtained with the SIB represent mean item-scores for each dimension of social behavior, on a scale from one (high frequency or low distress) to five (low frequency or high distress).

Autism traits

The Autism-spectrum Quotient (ASQ) (Baron-Cohen *et al.*, 2001) is a self-administered questionnaire for adults that assesses the degree to which any individual adult of normal intelligence might have features of the core autistic phenotype. It has good test-retest reliability and good discriminative validity for Asperger syndrome at a cut-off score of 26 (Woodbury-Smith *et al.*, 2005). Scores on the ASQ have shown to be normally distributed in the general population. Five subscales cover personality traits associated with the autistic spectrum; social skills, communication, imagination, attention to detail, and attention switching.

Results

Intellectual ability

Mean score on the Raven's Advanced Progressive Matrices was not significantly different between the groups ($F(2.72)=1.3$, $p=0.27$) as indicated by a multivariate ANOVA. Post-hoc tests also showed no significant differences between XXY men and the control groups ($p=0.18$ and $p=0.16$). Mean scores were 105.2 (SD 9.1), 109.4 (SD 8.8) and 109.6 (SD 14.6) for the Klinefelter group and control group I and II respectively.

On the NART, mean score of the Klinefelter men did not significantly differ from the control groups ($F(2,72)=0.7$, $p=0.48$). Post-hoc tests also showed no significant differences between XXY men and the control groups ($p=0.46$ and $p=0.58$). Mean score in de Klinefelter group was 108.6 (SD 13.5), for the control group I and II it was 110.0 (SD 5.3) and 107.1 (SD 7.8) respectively.

Social behavior

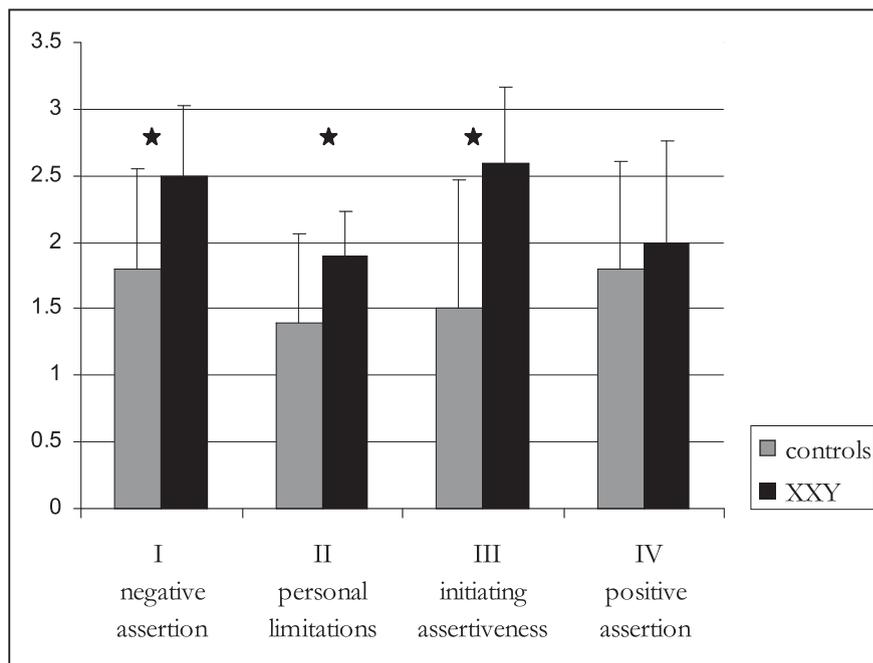
Overall distress during social interactions was significantly higher in the XXY group as compared to men from the general population. Mean score in the XXY group was 2.2 (SD 0.67) and in the control group 1.6 (SD 0.49), which was significantly different ($F(1,52)=13.2$, $p=0.001$). Significantly higher scores, i.e. more distress, in XXY men were observed in the subscales ‘negative assertion’ ($F(1,52)=13.9$, $p<0.001$), ‘personal limitations’ ($F(1,52)=12.1$, $p=0.001$) and ‘initiation assertiveness’ ($F(1,52)=20.5$, $p<0.001$). Mean item scores for distress in each dimension of social behavior are presented in figure 1.

Although overall frequency score of social behavior was not significantly different between XXY men and control men, the XXY group reported to less frequently display negative assertion, such as refusing a request or standing up for one’s rights in a public situation. Mean frequency score in this domain of social behavior was 2.9 (SD 0.66) in the XXY group and 3.5 (SD 1.1) in the control group, which was significantly different ($F(1,52)=6.2$, $p=0.01$).

Figure 1

Self reported distress in XXY men and men from the general population during social interactions in four domains of social behavior: (I) Display of negative feelings (negative assertion), (II) Expression of and dealing with personal limitations, (III) Initiating assertiveness and (IV) Praising others and the ability to deal with compliments/praise of others (positive assertion).

* significantly different at $p \leq 0.001$

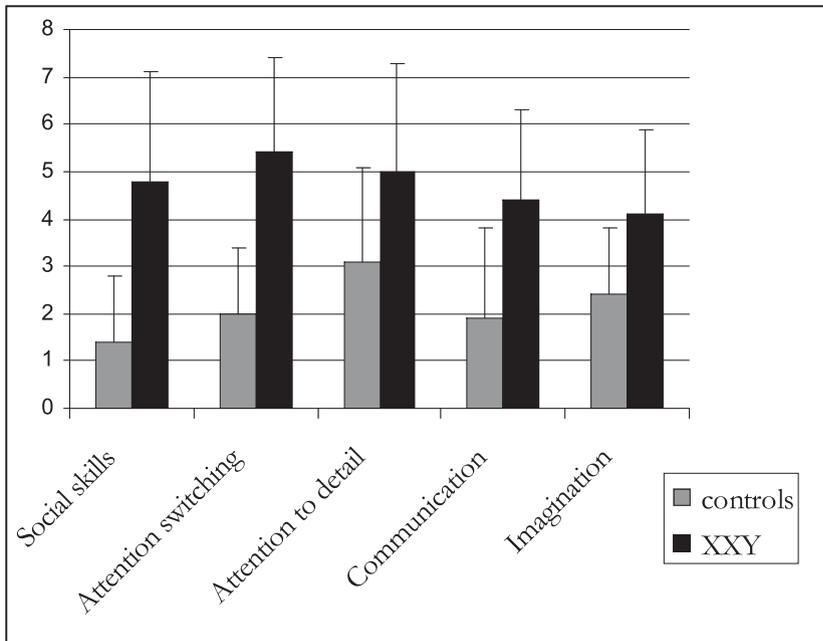


Autism traits

Mean total ASQ score and all subscales separately were significantly higher in Klinefelter men as compared to controls. Total score in the XXY group was 23.8 (SD 6.6) and in the control group 11.0 (SD 5.1), $F(1,57)=57.8$, $p < 0.001$. As compared to men from the general population, XXY men displayed more autism traits in all domains; social skills ($F(1,57)=32.3$, $p < 0.001$), attention switching ($F(1,57)=38.9$, $p < 0.001$), attention to detail ($F(1,57)=8.3$, $p = 0.006$), communication ($F(1,57)=19.6$, $p < 0.001$) and imagination ($F(1,57)=12.7$, $p = 0.001$). See figure 2 for mean scores and SD's on the five subscales of the ASQ.

Figure 2

Levels of autism traits in XXY men and men from the general population as measured with the Autism Spectrum Questionnaire. Scores in all individual dimensions were significantly higher in XXY men.



Discussion

The aim of this study was to refine the social behavioral phenotype in Klinefelter syndrome (47, XXY), a sex chromosomal disorder. We measured frequency of social behavior and distress during social interactions in adult men with the XXY karyotype. In addition, this study was the first exploration of features of the autism phenotype in Klinefelter syndrome.

As compared to men from the general population, XXY men reported increased levels of distress during social interactions in various domains of social behavior, namely: expressing of negative emotions to others, expressing and dealing with personal limitations and initiating contact with others. Although overall frequency of social behavior in XXY men was not different from men from the general population, significant differences in specific domains of social behavior were observed. XXY men reported to less often

engage in social behavior dealing with expression of negative emotions, such as refusing a request or standing up for one's rights in a public situation. In addition, high rates of autistic-like traits were observed in XXY men, across all dimensions of the autism phenotype, namely: difficulties in social skills, attention switching, imagination, communication and increased attention to details.

Our findings of difficulties in coping with social situations in XXY men, especially high levels of distress during social interactions, are consistent with reports of social anxiety, social withdrawal and shyness in individuals with the XXY karyotype (Bender et al., 1999; Ratcliffe, 1999). Difficulties in social adjustment have primarily been reported for children or adolescents with Klinefelter syndrome. Our data suggest that social difficulties may persist into adulthood, with social distress more prominent than a general reduction in engagement of social behavior. The use of self-report measures might have biased the degree of social disabilities in Klinefelter syndrome. However, studies showing that XXY men tend to overrate, rather than underrate, their own social adjustment (Bender et al., 1999) suggest that our findings might rather be an underestimation than overestimation of social disabilities in Klinefelter syndrome.

The high levels of autism traits in XXY men that were observed across all dimensions of the autism phenotype, suggest that the impairments in social interactions and communication parallel autism-like features that characterizes individuals at increased risk for autism. Increased levels of autism traits have also been found in biological relatives of subject with autism (Bishop et al., 2004). Our findings fit with the concept of a 'broad phenotype' of autism, which refers to the mild autistic-like features that are seen in individuals that are genetically related to an individual with autism (Bailey et al., 1998; Bishop et al., 2004). Similar to biological relatives of individuals with autism, autism-like features in XXY men were observed in the face of spared verbal- and general intellectual abilities (Bishop et al., 2004).

Based on twin studies, it has been suggested that the typical clinical phenotype of autism as seen in subjects with the disorder and the broader subclinical phenotype of autism as seen in biological relatives may share a genetic origin (Rutter, 2000). Although speculative, this might suggest that the X chromosome might be one of many genetic factors that play a role in the etiology of autism-like behaviors. Our findings are in line with studies in Turner syndrome, another X chromosomal disorder characterized by a partial or complete absence of one of the X chromosomes in females (45,XO). Turner

females also display difficulties in the social domain and the estimated risk of autism spectrum disorders may be several times higher as compared to women from the general population (Creswell et al., 1999; Mazzocco et al., 1998; McCauley et al., 2006; Skuse, 2000).

A hypothesized role of genetic mechanisms involving the X chromosome in social behavior fits with the notion that several genetic factors in autism might operate on components of the disorder, rather than the syndrome as a whole (Rutter, 2000). Influence of genes on the X chromosome on the development of autism-like features would fit with the male preponderance in autism spectrum disorders (Volkmar et al., 1993).

Taken together, as compared to men from the general population, XXY men reported increased levels of distress during social interactions and less engagement in those aspects of social behavior that deal with display of negative emotions. The increased levels of autism traits that we observed in XXY men call for a more thorough clinical investigation of vulnerability to autism in Klinefelter syndrome in a larger and more representative sample in epidemiological terms. Although our findings require replication, Klinefelter syndrome might prove to serve as a useful model for studying a role of the X chromosome in social behavioral dysfunction and autism-like behavior.

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