UNRAVELING AUTISM SPECTRUM DISORDER THROUGH GENETICALLY DEFINED SYNDROMES

Autistic traits and social cognition in Klinefelter syndrome and Triple X syndrome

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Preface

This thesis would not have been possible without the inspiration and guidance from my supervisor Sophie. With your enthusiasm, valuable advice and the freedom you gave me in writing this thesis, I have been able to grow and learn. I also want to thank the children and their parents for taking the time to participate in this study. I feel privileged that I received the opportunity to work with all these wonderful children.

I wish to warmly thank my parents, Lia and Taco for your unconditional support in so many ways, and my brother Wouter for teaching me what it means to work hard and how to dream big. I also want to thank the most special group of friends someone could ever ask for. You girls inspire me every day and made me see that I could do so much more than I thought. Next, I want to thank Anne and Lisette – my 'research buddies'. The many coffee breaks, our intellectual sense of humor, and our shared drive to make the most out of everything, made the hard work so much fun. Finally, I want to thank Arne for providing me with a perspective on things, for making me calm and for always putting a smile on my face.

Gemma Zantinge

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"The key to realizing a dream is to focus not on success but significance – and then even the small steps and little victories along your path will take on greater meaning"

- Oprah Winfrey -

Abstract

The main objective of this study was to unravel characteristics of Autism Spectrum Disorder (ASD) by studying autism traits, social cognition, and gender differences in Klinefelter Syndrome (KS) and Triple X syndrome. ASD traits were assessed with the parent-report Autism Spectrum Quotient. Social cognition was measured with the Social Cognitive Skills Test. Participants included 17 KS boys and 16 Triple X girls (M_{age} = 12.0 years, *SD* = 2.6), and 85 control children (M_{age} = 10.6 years, *SD* = 1.1). Our results showed that both boys and girls with an extra X chromosome show substantially elevated rates of ASD traits compared to controls. In addition, our study is the first to show that KS boys and Triple X girls have overall impaired social cognitive skills and function at a lower social cognitive level than typically developing children. Our study provides guidelines for the design and enhancement of screening instruments and treatment programs, which will benefit the development of these children. Future studies should focus on identifying risk factors endangering the development of children with ASD and those that are born with an extra X chromosome.

Key words: Autism Spectrum Disorders, Social cognition, Klinefelter syndrome, Triple X syndrome, gender differences.

Introduction

In the development of a child, from the early beginning to adulthood, various complex mechanisms interact in shaping the behavior that can be observed on the outside. Consensus on when a child's normal development has gone awry has been documented in classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) and the Classification of Mental and Behavioral Disorders in Children and Adolescents (ICD-10; World Health Organization, 1996). In these manuals definitions of childhood disorders are listed on the basis of the co-occurrence of certain symptoms and traits. These guidelines, however, not only serve the purpose of assigning a certain diagnosis to a child but also mention implications for causative factors and consequences. In other words, they offer insight into the prognosis, point to starting points for treatment, and are of help in exploring the etiology of disorders.

The question of etiology is often addressed in scientific research (Caronna, Milunsky, & Tager-Flusberg, 2011; Freitag, 2007; Geschwind, 2009). Why do some children develop normally and are others at risk of developing psychopathology? Studying risk factors in child development is hampered by the complexity and diversity of disorders in clinical practice and the overlap between the diagnostic criteria. Moreover, besides the clinical diversity, decades of research into the risk factors for development of psychopathology have also revealed great genetic and biological heterogeneity. For example in Autism Spectrum Disorders, for which no substantive, unifying, replicable neuropathological features have been conclusively identified (Geschwind, 2009; Skuse, 2007). Over the last two decades the issue of heterogeneity has led to an increasing interest in studying risk factors in child development in genetically defined syndromes (Bruining, De Sonneville, Swaab, De Jonge, Kas, Van Engeland, & Vorstman, 2010; Van Rijn & Swaab, 2011). By

studying the phenotypes of these children researchers are able to gain more understanding of the etiological risk factors for neurodevelopmental disorders. This two-way approach on the part of behavioral neurogenetics, as stated by Van Rijn and Swaab (2011), "allows the study of bottom-up effects of a developmental condition of prenatal origin on behavioral phenotypes and complements top-down studies where behavioral phenotypes are studied to identify developmental origins" (p. 908).

Two of such genetically defined syndromes of prenatal origin that are associated with elevated risks of cognitive and behavioral dysfunction are Klinefelter syndrome (KS; 47,XXY) and Triple X syndrome (47,XXX), both defined by the presence of an extra X chromosome. Klinefelter syndrome affects approximately 1 in 500 to 600 live-born boys, making it the most common human sex chromosome aneuploidy (Bojesen, Juul, & Højbjerg Gravholt, 2003; Boyd, Loane, Garne, Khoshnood, & Dolk, 2011; Lanfranco, Kamischke, Zitzmann, & Nieschlag, 2004). Triple X syndrome has an estimated prevalence of 1 in 1000 live-born girls (Boyd et al., 2011; Nielsen & Wohlert, 1991) but is recognized relatively more rarely than KS which among other factors could be due to the mildness of physical phenotypic characteristics (Lenroot, Lee, & Giedd, 2009). Since KS and Triple X syndrome were first reported most studies have focused on medical and physical abnormalities in these children, such as infertility problems and specific physical features (Jacobs et al., 1959; Klinefelter, Reifenstein, & Albright, 1942). In the last decades research has began to focus more on the social (Van Rijn, Swaab, Aleman, & Kahn, 2006; Van Rijn, Swaab, Aleman, & Kahn, 2008; Visootsak & Graham, 2009), neuropsychological (Bender, Linden, & Harmon, 2001; Boone et al., 2001; Fales et al., 2003) and cognitive profiles (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009; Bruining et al., 2011; Otter, Schrander-Stumpel, & Curfs, 2010; Ross et al., 2008),

with an emphasis on language and speech development (Bender, Linden, & Robinson, 1993; Bender, Harmon, Linden, & Robinson, 1995; Bishop & Scerif, 2011; Boada et al., 2009). These studies show that there are differences in general development between boys with KS on the one hand and girls with Triple X syndrome on the other. For example, overall intelligence scores are significantly lower for Triple X girls than for KS boys, below average and average to low average, respectively (Boada et al., 2009; Otter et al., 2010). Both groups also show generally impaired communication, but pragmatic skills appear to be less affected in Triple X girls, suggesting that they use language more appropriately in social situations than KS boys (Bishop & Scerif, 2011). Besides these subtle differences, both KS boys and Triple X girls show clear correspondences in speech, language, and communication development, and exhibit similar fine and gross motor impairments (Bishop & Scerif, 2011). In addition, the most striking resemblance reported between KS and Triple X syndrome is that on difficulties with overall social functioning (Bender, Harmon, Linden, Bucher-Bartelson, & Robinson, 1999; Geschwind, Boone, Miller, & Swerdloff, 2000; Geschwind & Dykens, 2004; Harmon, Bender, Linden, & Robinson, 1998; Otter et al., 2010; Ratcliffe, 1999; Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010; Van Rijn et al., 2008).

Social functioning is a broad construct encompassing many levels, mechanisms, and skills that are all of vital importance for interacting with other individuals and for participating in social situations. In general, impairments in social functioning are visible to the outside world, where knowledge of social rules and manners are essential to appropriate social behavior. Disturbances or delays in the development of socially adaptive behavior and difficulties with adequately regulating behavior can become so severe that they could lead to serious impairments in

communication skills, social perception, and interaction. A childhood developmental disorder that is highly associated with delays and impairments in social behavior is Autism Spectrum Disorder (ASD; DSM-IV; American Psychiatric Association, 1994). This is a very common disorder (prevalence between 1/200 and 1/500; Geschwind, 2009) that entails a spectrum of subtypes including autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified. Since it was reported by Leo Kanner (Kanner, 1943) it has become one of the most intensively studied neurodevelopmental disorders. Individuals affected by ASD are not only defined by the presence of a continuum of qualitative impairments in social interaction and communication, but also show repetitive and stereotyped patterns of behavior, interests, and activities (American Psychiatric Association, 1994).

Interestingly, given the fact that social difficulties have been reported in children with an extra X chromosome it does not come as a surprise that several studies have revealed elevated rates of ASD in children with an extra X chromosome (Kielinen, Reifenstein, & Albright, 2004; Tartaglia et al., 2010; Van Rijn & Swaab, 2011). A study by Bruining, Swaab, Kas, and Van Engeland (2009) explored the incidence of psychiatric characteristics in a self-selected sample of boys with KS. Subjects were 51 KS boys from 6 to 19 years old (mean age 12.2). The presence of an ASD was assessed by means of structured interviews and analyses controlled for intelligence scores. Results revealed that 27% of the KS boys met the threshold for an ASD, which is markedly higher than the reported prevalence in the normal population. In addition, all subjects that met ASD criteria displayed noticeable behavior impairment before the age of five years old. Furthermore, another recent study addressed ASD, language, and communication in children with sex trisomies (Bishop et al., 2010). The sample included 58 Triple X girls, 19 KS boys (ages 4 to

15), and their siblings (ages 4 to 16). For this sample ASD was diagnosed in 11% of the KS boys, which indicates a substantially elevated risk and a ten- to twenty-fold increase compared to the normal population. For Triple X girls, even though none of them had received an ASD diagnosis, the authors did find milder communicative difficulties similar to those seen in ASD.

The studies mentioned above looked into ASD traits, i.e., observable behavior (phenotype, the expression of a genotype) in children with an extra X chromosome. However, in addition to studying the phenotype in these children, it is of equal importance to look more closely into the underlying mechanisms (i.e., the endophenotype) that form and shape this social behavior. In order to function adequately in social situations that are complex, dynamic, and often happen in split seconds, humans need numerous neurocognitive skills. A general term that covers these neurocognitive skills is ‘social cognition’. Social cognition consists of several mental sub-processes within social information processing, which can be represented by the following steps: perception, interpretation, and reaction (Van Rijn, Van ‘t Wout, & Spikman, 2011). The first step refers to individuals being able to perceive crucial social stimuli, which can reach them through verbal signals: for example, when somebody talks to them, and provides them with information. These social signals can also be non-verbal, for example body posture, the direction of view, tone of voice (i.e., prosody), or facial expressions. The second step is to interpret and give meaning to what is observed. This includes, being able to empathize with someone, to understand what the other is expecting of you, and to be aware of social rules in particular situations. The third and final step is to react and regulate one’s own behavior appropriately in responding to a social situation. It goes without saying that these processes are highly interdependent. For example, when tone of voice or facial

expression is interpreted incorrectly, a joke could be misunderstood. Conversely, when behavior is not adequately adapted to the social context, a specific joke may be considered impertinent by others.

Studying social behavior and social cognition, i.e., phenotypes and endophenotypes, respectively, of boys and girls with a genetically defined syndrome, could provide more insight into psychopathologies that are associated with difficulties in these areas such as ASD. Regarding girls with Triple X syndrome nevertheless, there are no studies available to this date that assess the development and quality of their social cognitive skills (Otter et al., 2010). As for social behavior of these girls there are some studies available, however, often outdated and lacking standardized methods. In the studies that are available, overall difficulties in social functioning are reported. In a longitudinal study by Harmon et al. (1998) eleven Triple X girls and their siblings were compared in their transition from adolescence to early adulthood via semi-structured interviews. This study revealed that Triple X girls were less well adapted, had more relationship problems in general, and showed more psychopathology than female sibling control. In a study by Bender et al. (1999), comparisons of 36 KS boys, Triple X girls, and their chromosomally normal sibling controls revealed that both KS and Triple X syndrome groups showed more social problems than their siblings. Furthermore, a review article by Otter et al. (2010) provides an overview of the few studies on social skills of Triple X girls. This overview shows that between the ages of 6 through 13 years Triple X girls have difficulties in forming good interpersonal relationships, show a lack of self-confidence, are shy, and report feelings of inferiority as compared to siblings or female controls. In the period from adolescence to early adulthood, again poor interpersonal relationships are reported.

Studies on the behavioral phenotype of boys and men with KS are less rare than those on Triple X girls, particularly studies that focus on social cognition (for reviews see Geschwind et al., 2000; Visootsak & Graham, 2009). In a study by Van Rijn et al. (2006) social cognitive processing and emotion regulation was assessed in 32 KS men (mean age 38.8 years) and 26 matched controls from the normal population (mean age 35.2). Standardized instruments were included reflecting aspects of social emotional information processing on the levels of perception, experience, and expression. Results revealed that KS men were less accurate than controls in their perception of socio-emotional cues, with specific deficits in the perception of angry facial expressions. Also, they were found to be less able to identify or verbalize their emotions than controls. Interestingly, KS men showed higher levels of emotional arousal than the general population, which indicates a clear discrepancy between cognitive appraisal of emotions and emotional arousal (Van Rijn et al., 2006). In a different study by Eisenberg, Hofer, and Vaughan (2009) the relevance of this discrepancy is highlighted. They showed that children who become emotionally aroused are less likely to focus on relevant information about emotions in social interaction than children who are able to adaptively regulate emotional arousal. These results reveal the struggle that KS men experience in daily life, not being able to accurately understand and label their social surroundings, which may lead to problems in social interaction, and at the same time experiencing feelings of confusion and emotional arousal. In another study by Van Rijn et al. (2008) specific social behavior and autistic traits were studied in 31 KS men (mean age 41.3) and two control groups of 24 and 20 men (mean ages 35.7 and 39.2, respectively). All participants had average scores on cognitive functioning, which was therefore assumed not to be of influence on the results. This study confirmed previous findings

concerning emotional arousal, with KS men reporting increased distress during social interactions, for example when expressing negative emotions towards others. In addition, KS men showed less engagement in specific social situations, for example when dealing with expression of negative emotions or refusing a request. Finally, KS men displayed more autistic traits than the control group when measured with the Autism Spectrum Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley 2001) on all domains including social skills, communication, attention to detail, attention switching, and imagination (Van Rijn et al., 2008). In addition to the previous two studies, which included adult men with KS, Tartaglia et al. (2010) described the behavioral phenotype of 42 KS children and adolescents from 6 to 20 years old (mean age 12.26). To assess the behavioral features, parents filled out the Social Responsiveness Scale (Constantino & Gruber, 2005), which revealed an increased risk of social difficulties in the domains of social cognition, social communication, social motivation, and autistic preoccupations. In addition, a subset of 20 participants took part in a structured interview to further assess specific autistic traits. Even though only 5% of the participants met the criteria of ASD, this rate is still high compared to the normal population (Tartaglia et al., 2010). Their study replicated previous results found in adults, in a sample containing children and adolescents aged 6-20, suggesting that impaired social functioning and social cognition is present in the KS population, independent of age.

In sum, research has shown that children with an extra X chromosome experience difficulties in general social functioning throughout their development into adulthood. With respect to social cognitive skills, studies have revealed that KS boys experience more problems than typically developing boys, showing a poorer perception of social-emotional cues, more difficulties with verbalizing emotions, and

a discrepancy between cognitive appraisal of emotions and emotional arousal. For Triple X girls, as said before, to this date no studies are available that assess the strengths and weaknesses of their social cognitive skills. Furthermore, previous studies have suggested an increased risk of ASD in children with an extra X chromosome. Looking more closely into the mechanism of social cognition, a core deficit of ASD, in boys with KS and girls with Triple X syndrome can teach us more about the risk factors involved in developing ASD. A question that needs to be answered in this respect is whether or not poor social cognitive skills in children with an extra X chromosome are related to a possible elevated risk of ASD traits. In addition, considering the fact that the prevalence of ASD is four times higher in boys than in girls, it is even more interesting to investigate gender differences a population with an extra sex chromosome that is associated with elevated rates of ASD traits. The previously mentioned study by Bishop et al. (2010) reported that Triple X girls in their sample did not receive an ASD diagnosis. However, the authors did find milder associated difficulties similar to those seen in ASD. This finding is in concordance with current knowledge that ASD is indeed more prevalent in boys, with boys outnumbering girls by at least four to one (Lord, Rutter, & LeCouteur, 1994; Skuse, 2000; Volkmar, Szatmari, & Sparrow, 1993). Mis- or under-diagnosing of ASD in girls might explain some of the bias in prevalence rates. However, biological factors should also be taken into account, such as X and Y chromosome influences. Therefore, studying gender differences with respect to ASD traits in boys and girls with an extra sex chromosome might offer insight into the causes of this bias in prevalence and consequently, into the etiology of this neurodevelopmental disorder.

The aim of this study is to unravel characteristics of ASD by studying autism traits and social cognition in children with a genetically defined syndrome. The

hypothesized elevated risk for ASD traits in children with an extra X chromosome is assessed, with a specific focus on social cognitive skills as a core deficit in ASD. In addition, possible underlying mechanisms of ASD in a genetically defined syndrome might be revealed by looking at gender differences between KS boys and Triple X girls, both groups defined by the presence of an extra X chromosome. These issues are addressed by answering the following research questions: 1. Do KS boys and Triple X girls have an elevated risk of developing ASD traits compared to typically developing children, and are there differences between boys with KS and girls with Triple X? 2. Do KS boys and Triple X girls have impaired social cognitive skills compared to typically developing children, and are there differences between boys with KS and girls with Triple X? 3. Do specific impaired social cognitive skills contribute to the probability of finding ASD traits in children with an extra X chromosome?

Method

Participants

The total sample included 118 children. The control group consisted of 51 girls and 34 boys (M_{age} = 10.6 years, SD = 1.1). The extra X chromosome group consisted of 17 boys with KS and 16 girls with Triple X syndrome (M_{age} = 12.0 years, SD = 2.6). Participants from the control group were significantly younger than the children from the extra X chromosome group. The recruitment of children from the control group was done between November 2009 and June 2010 at nine elementary schools located in nine different suburban cities in the west of the Netherlands. KS boys and Triple X girls were recruited between April 2009 and March 2011 through clinical genetics clinics in the Netherlands. KS boys were also recruited from the Dutch Klinefelter Association and Triple X girls from the Contact Group Triple-X

Syndrome. The children with an extra X chromosome received their diagnosis prenatally as well as postnatally. Five out of the 17 KS boys used testosterone supplements at time of testing.

Procedure

After an elaborate explanation of the study through a letter with information as well as an oral explanation on the first day of testing, written informed consent was obtained from all participants. In case children were younger than 12 years the parent or caretaker signed the informed consent, if they were older than 12, both the child and the parent or caretaker signed. All tests were conducted and supervised by trained administrators who were experienced with psychological testing of children. Participants from the control group completed the tests either at school or at home in a stimulus-free room. KS boys and Triple X girls completed the tests at the Faculty of Social and Behavioral Sciences at Leiden University in a quiet room designed for psychological testing. All tests were administered during two separate mornings that lasted approximately two and a half hours, including a 15 minute break. Parents and caretakers were asked to complete a set of behavioral questionnaires. All participants received a small reward for participating in the study at the end of the second day. A report with the individual results on the cognitive tests was sent to the parents or caretakers. Tests and questionnaires were scored and processed according to the appropriate standardized procedures.

Instruments

Intelligence. General intellectual abilities (TIQ) were screened using two subtests of the Dutch version of the WISC-III for children, vocabulary and block design. These subtests have a strong correlation (r = .90) with full scale IQ and have shown to provide an adequate estimation for general intelligence (Sattler, 1992;

Watkins, 1986). The vocabulary subtest assesses general verbal abilities whereas block design taps the visuospatial abilities (Wechsler, 1991).

Autism traits. Autism traits were assessed with the Autism-Spectrum Quotient (AQ) which is a 50-item questionnaire that detects and quantifies autistic traits in individuals. In this study the AQ child version was used, which is a parent-report questionnaire for children aged 4-12. The child version of the AQ was adapted from the widely used self-administered AQ-Adult and the parent-administered AQ-Adolescent. Psychometric properties of the AQ are excellent, with high internal consistency, construct validity, and test-retest reliability for the test as a whole as well as for each of the subscales (Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008). The AQ consists of 50 descriptive statements with a four-point Likert response scale. Parents indicated to what extent they agreed with the statements about their child, choosing between the following categories: *definitely agree* (1), *slightly agree* (2), *slightly disagree* (3), or *definitely disagree* (4). Scoring of the AQ child was done according to the scoring system of Baron-Cohen et al. (2001). Total scores on the AQ ranged from zero to 50, higher scores corresponded to more 'autistic-like' behavior. A cut-off score of 26 in a clinical population has shown to provide high sensitivity (.95) and specificity (.95). The AQ assesses the following five different domains that are highly associated with autism: social skills, attention switching, attention to detail, communication, and imagination. Each of these domains is represented by ten items (for examples of statements belonging to the five domains see Table 1).

Table 1

Examples of statements for each of the five domains

Domain	Statement
Social skills	"S/he is drawn more strongly to people than to things"
	"S/he finds it difficult to work out people's intentions"
Attention switching	"S/he prefers to do things the same way over and over again"
	"S/he finds it easy to go back and forth between different activities"
Attention to detail	"S/he notices patterns in things all the time"
	"S/he does not usually notice small changes in a situation, or a person's appearance"
Communication	"When s/he talks, it is not always easy for others to get a word in edgeways"
	"S/he is good at social chit-chat"
Imagination	"S/he finds it difficult to imagine what it would be like to be someone else"
	"S/he finds making up stories easy"

Social cognition. All participants completed the Social Cognitive Skills Test (SCST; Van Manen, Prins, & Emmelkamp, 2007) to assess social cognitive skills at an age-related developmental level. Psychometric properties of the SCST have been rated by the COTAN (Dutch Committee on Tests and Testing) as satisfactory for reliability and validity values (NJI, 2011). The SCST comprises of seven different short stories, each of the stories supported by a set of illustrations that depict varying social situations. The stories are read to the child in a neutral manner while pointing at the accompanying illustrations. For each story eight different questions are formulated that correspond with the social cognitive skills (Gerris, 1981) (see Figure 1 for an example of a cartoon and related question); 1. Identifying refers to the ability to identify and label perspectives of others and oneself. 2. Discriminating requires the ability to judge whether two or more observable perspectives are similar or dissimilar, without having to label them verbally. 3. Differentiating taps into the ability to understand that two or more persons in similar or dissimilar situations do not

necessarily have identical perspectives. 4. Comparing requires the child to determine and label discrepancies and similarities between observable perspectives of different persons in the same situation. 5. Perspective taking involves the ability to take the position of another person and to infer the perspective of that person. 6. Relating taps into the skill of relating to at least two other perspectives (Figure 1). 7. Coordinating refers to the ability to take a third person's position. 8. Taking into account requires that the child takes its own perspective and that of others into account at the same time. The eight social cognitive skills together represent four age-related social cognitive levels that increase in complexity (Selman, 1980). For an overview of the skills and corresponding social cognitive levels see Table 2. Scoring of the SCST was done according to the standardized scoring method described in the manual by Van Manen et al. (2007). The maximum score that could be obtained for one story of the SCST was 24 points. The total scores for each of the social skills could reach a maximum of 21 points (with eight questions tapping into a single cognitive skill). Subsequently, raw scores were calculated into standardized scores using separate norms for boys and girls.

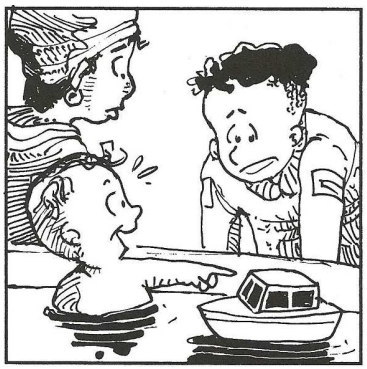

Figure 1 Relating: "Why is the boy not feeling happy like his brother?"
(Van Manen, et al., 2007)

Table 2

Age-related social cognitive levels and corresponding social cognitive skills

Social cognitive level	Social cognitive skill	Age
1. Egocentric role-taking	1. Identifying 2. Discriminating	Around 4 years
2. Subjective role-taking	3. Differentiating 4. Comparing	Around 6 years
3. Self-reflective role-taking	5. Perspective-taking 6. Relating	Around 8 years
4. Mutual role-taking	7. Coordinating 8. Taking into account	Around 10 years

Source: Van Manen et al. (2001)

Statistical Analyses

Data were analyzed using SPSS for Windows (Statistical Package for Social Sciences; version 19.0, 2011). Preliminary data analyses were performed to decide whether parametric or non-parametric tests were required by checking if the data fulfilled the necessary assumptions (Field, 2009). This included performing a missing value analysis to check whether or not data was missing and if these missing values concerned random or systematically missing data. In case participants had multiple missing values on dependent variables, they were excluded from further analyses. The assumption of normal distributed data was checked with the Kolmogorov-Smirnov test. The homogeneity of variance was tested with Levene's test. In addition, boxplots and *z*-scores were inspected to detect significant outliers. Outliers defined as scores that deviate more than two standard deviations. Multivariate analyses of co-variance (MANCOVAs) based on Pillai-Bertlett's trace were carried out to assess multivariate effects of group. Age was added as a covariate in the analyses that concerned the AQ questionnaire taking into account possible age-related ASD features. For the analyses that concerned the SCST, in addition to controlling for age, IQ estimates and language comprehension scores were also added as covariates to the analyses. This was done to

control for effects that intelligence and comprehension of language might have on the performance on the social cognitive task. Gender (boys, girls) and group (clinical, control) were set as fixed factors. In the MANCOVAs, all five subscales of the AQ and the eight social cognitive skills of the SCST were added as dependent variables. Effect sizes were calculated with Cohen's *d* which represents the standardized difference between the means of both groups. Effect sizes up to .40 were considered a small effect, up to .70 medium, and from .80 and above a large effect. Next, Spearman's Rho correlations were computed to assess whether or not certain aspects of social cognitive skills contribute to ASD traits in children with an extra X chromosome. *P* values of .05 or lower were considered to be statistically significant.

Results

Background variables

Background variables of the participants are presented in Table 3. Total IQ estimate scores for participants from the control group (M_{TIQ} = 103, *SD* = 14) were significantly higher than for boys with KS and girls with Triple X syndrome (M_{TIQ} = 84, *SD* = 15), F(1,114) = 41.32, p <.001. Sample sizes for the two dependent variables ASD traits, and social cognition are presented in Table 4.

Table 3
Sample characteristics of the independent variables in Means and SDs (N = 118)

	Controls (*n* = 85)		XXY and XXX (*n* = 33)	
	Boys (*n* = 34)	Girls (*n* = 51)	XXY (*n* = 17)	XXX (*n* = 16)
Age	10.7 (1.0)	10.5 (1.2)	12.5 (2.6)	11.5 (2.6)
IQ estimate	102 (13)	104 (15)	84 (13)	83 (18)

Table 4

Sample sizes of the dependent variables (N = 118)

	Controls (*n* = 85)			XXY and XXX (*n* = 33)		
	Boys	Girls	Total	XXY	XXX	Total
AQ	33	51	84	16	15	31
SCVT	34	51	85	13	13	26

ASD traits

Results showed that in the control group, 5% of the children scored above the cut-off score for an ASD classification in the clinical population (i.e., ≥26) whereas 27% of the children with an extra X chromosome scored above this cut-off point. Mean total AQ score in the control group was 12.6 (*SD* = 6.0), and for the extra X chromosome group the mean total AQ score was 21.2 (*SD* = 8.5). For ASD traits, the MANCOVA revealed a significant multivariate effect of Group ($F(5, 106) = 8.91$, $p < .001$) and Gender ($F(5, 106) = 2.76$, $p = .022$). The univariate results for the individual subscales revealed that for the AQ, the Group effect was significant for four out of the five subscales. Children with an extra X chromosome scored higher (i.e., showed more 'autistic-like' behavior) than controls on the four following subscales: Social skills, $F(1, 110) = 17.49$, $p < .001$ (effect size, $d = .98$), Attention switching, $F(1, 110) = 33.55$, $p < .001$ (effect size, $d = 1.38$), Communication, $F(1, 110) = 23.91$, $p < .001$ (effect size, $d = 1.08$), and lastly Imagination, $F(1, 110) = 17.98$, $p < .001$ (effect size, $d = .94$). Effect sizes for all four subscales indicated a large effect. See Figure 2 for means and *SD*s of the five subscales on the AQ in both groups. For Gender, univariate results for the individual subscales showed that this main effect loaded on a single significant subscale, namely, Imagination ($F(1, 110) = 7.58$, $p = .007$). Overall, boys with KS as well as boys from the control group scored higher on this scale ($M = 3.2$, $SD = 2.1$) compared to Triple X girls and girls from the

control group (*M* = 2.1, *SD* = 1.8). There was no significant main effect of Age as covariate and no multivariate Group by Gender interaction.

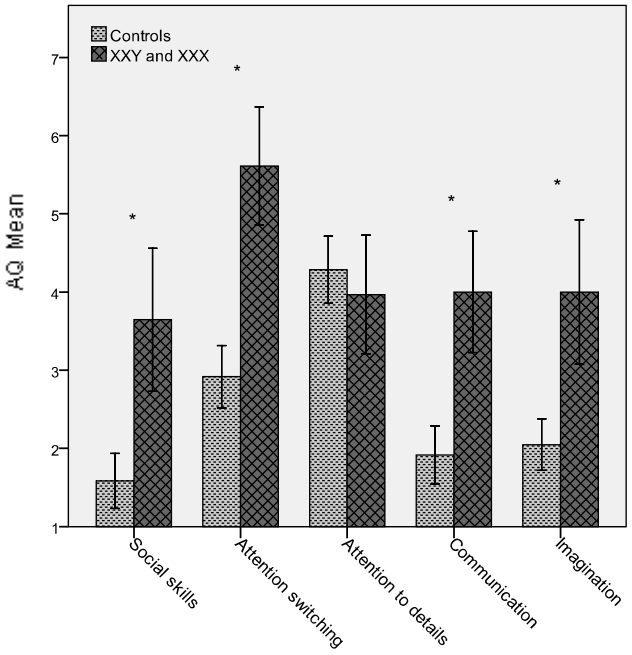

Figure 2. Means and *SD*s on the subscales of the AQ in controls and children with an extra X chromosome * *p* <.001.

Social cognition

For social cognitive skills, the MANCOVA revealed a significant multivariate effect of Group ($F(8, 97) = 10.95$, $p < .001$), and a significant main effect of the covariates IQ estimate ($F(8, 97) = 2.29$, $p = .028$), and Language comprehension ($F(8, 97) = 2.25$, $p = .030$). The univariate results for the individual domains of the social cognitive skills task revealed that the Group effect was significant for all skills. Children with an extra X chromosome scored lower than controls on all of the following domains: Identifying, $F(1, 104) = 36.26$, $p < .001$ (effect size, $d = 1.19$), Discriminating, $F(1, 104) = 26.73$, $p < .001$ (effect size, $d = 1.29$), Differentiating, $F(1, 104) = 62.51$, $p < .001$ (effect size, $d = 1.88$), Comparing, $F(1, 104) = 28.79$, $p < .001$ (effect size, $d = 1.47$), Perspective-taking, $F(1, 104) = 19.94$, $p < .001$ (effect size, $d =$

1.24), Relating, $F(1, 104) = 25.22$, $p < .001$ (effect size, $d = 1.49$), Coordinating, $F(1, 104) = 22.59$, $p < .001$ (effect size, $d = 1.54$) and finally, Taking into account, $F(1, 104) = 20.23$, $p < .001$ (effect size, $d = 1.52$). Effect sizes for all domains indicating a large effect. See Figure 3 for means and *SD*s of the social cognitive skills in both groups. For the covariate IQ estimate, univariate results for the individual domains revealed that this main effect was significant for six out of eight domains ($p < .05$), all belonging to the higher level, more complex social cognitive skills. For the covariate Language comprehension, the univariate results showed that this effect loaded on a single significant skill, Taking into account ($F(1, 104) = 4.99$, $p = .028$), which is the most complex social cognitive skill of the SCST. No main effect of Age or Gender as covariates was found. Finally, there was also no multivariate Group by Gender interaction.

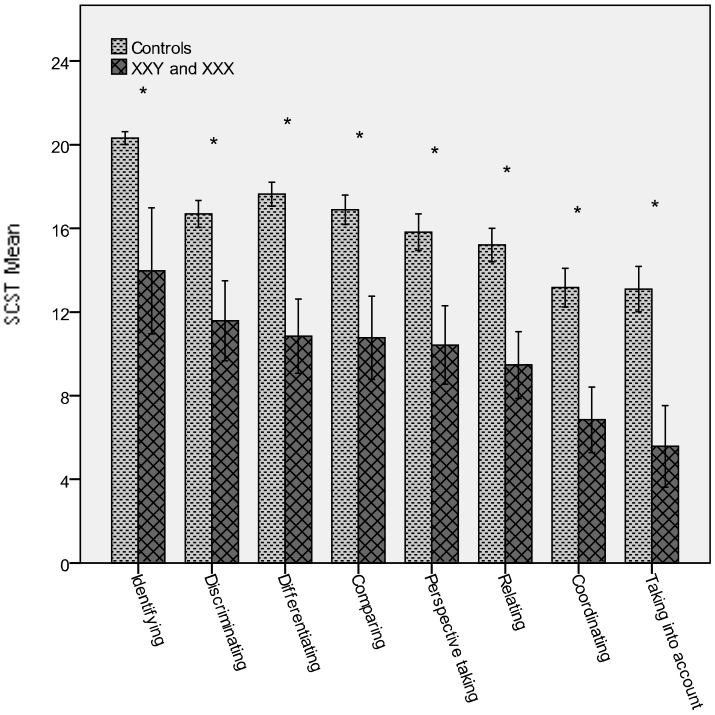

Figure 3. Means and *SD*s of the social cognitive skills in controls and children with an extra X chromosome * $p < .001$.

The social cognitive skills are represented by four age-related social cognitive levels that increase in complexity. Mean scores on these social cognitive levels revealed a decreasing trend in scores for both groups as the social cognitive levels increased in complexity (Figure 4). Furthermore, results showed that children with an extra X chromosome perform poorer on all social cognitive levels compared to children from the control group. On the Egocentric role-taking level, children with an extra X chromosome had lower scores (M = 12.8, SD = 5.8) than control children (M = 18.5, SD = 1.7), indicating that the extra X chromosome children experienced more difficulties with differentiating other people's points of view. On the second level, Subjective role-taking, boys and girls with an extra X chromosome performed poorer (M = 10.8, SD = 4.2) than control children (M = 17.3, SD = 2.4), suggesting that children with an extra X chromosome are able to think about other people in various situations, but experience difficulties when it comes to thinking about other people's thoughts. Children with an extra X chromosome also scored lower (M = 9.9, SD = 3.9) on the Self-reflective role-taking level compared to control children (M = 15.5, SD = 3.3), indicating that the extra X chromosome children experience difficulties with reflecting on their own behavior as seen from the eyes of others. On the highest and most complex level, Mutual role-taking, children with an extra X chromosome also performed poorer (M = 6.2, SD = 3.8) compared to control children (M = 13.1, SD = 4.2), suggesting that children with an extra X chromosome have more trouble with recognizing the point of view of someone else.

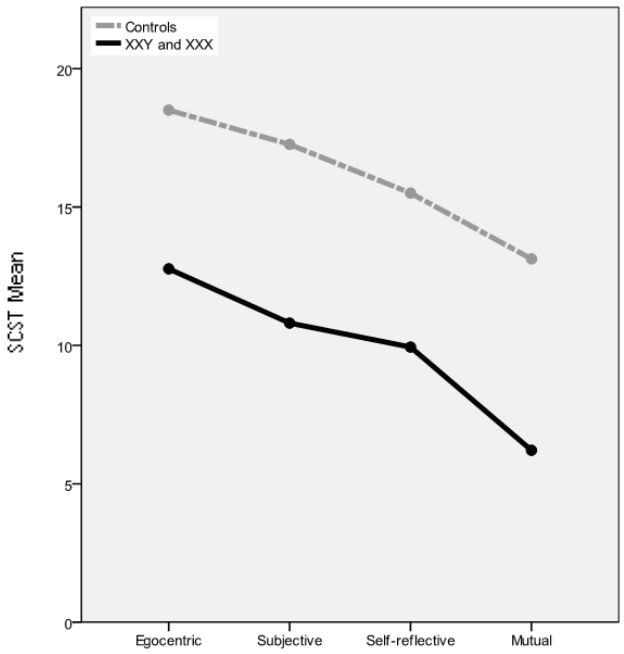

Figure 4. Means scores of social cognitive levels in controls and children with an extra X chromosome.

Social cognitive skills and ASD traits in KS and Triple X syndrome

The final analysis was performed to assess whether or not specific social cognitive skills contribute to the presence of ASD traits in children with an extra X chromosome. Correlations between the eight domains of the social cognitive skills task, and the total score on the AQ were computed. Spearman's Rho revealed that the domain Comparing was significantly and inversely related to ASD traits ($r(22) = -.41$, $p = .049$, $R^2 = .16$). In other words, children with an extra X chromosome that have low scores on Comparing, show higher total scores on the AQ (i.e., show more ASD traits) and vice versa.

Discussion

The goal of this study was to unravel characteristics of Autism Spectrum Disorder by investigating autism traits and social cognition in children with a genetically defined syndrome. The hypothesized elevated risk of ASD in children with an extra X chromosome was assessed, with a specific focus on social cognitive skills as a core deficit of this neurodevelopmental disorder. Furthermore, underlying mechanisms of ASD were addressed by analyzing gender differences between boys with KS on the one hand and girls with Triple X syndrome on the other.

Our results reveal that children with an extra X chromosome overall show more autistic-like behavior than typically developing children. Only 5% of the children from the control group score above the cut-off point (i.e., ≥26), which is in accordance with ASD rates in the general population (2-5%; Geschwind, 2009). As much as 27% of the extra X chromosome children score above this cut-off point, which is a five- to thirteen-fold increase compared to ASD rates in the general population. These increased levels of ASD traits are the same for KS boys and Triple X girls. More specifically, boys as well as girls with an extra X chromosome have poorer social skills, are less able to switch their attention, and have poorer communicative skills than typically developing children, irrespective of their age. These results replicate earlier studies in which equally elevated rates of ASD traits were found in boys with KS. Bruining et al. (2009) reported that in their sample 27% of KS boys and adolescents met the criteria for an ASD classification. Furthermore, Van Rijn and colleagues (2008) found that as much as 48% of their KS men scored above the cuff-off point for Asperger syndrome in a clinical population, suggesting that these impairments also persist into adulthood. Only one study into the presence of autism in girls with an extra X chromosome has been carried out (Bishop et al., 2010); the authors found that none of the Triple X girls in their sample had received an ASD

diagnosis. However, they asked parents to report psychiatric diagnostic information about their child, so that only the severe cases of autism were reported. This means that their study does not provide information on the more subtle ASD traits that might be present in these girls. Hence, ours is the first study to reveal that Triple X girls show equally elevated levels of ASD traits as KS boys. Next, regarding the level of attention to detail we found that there is no difference between children with an extra X chromosome and children from the control group. This result is consistent with an earlier study on ASD traits in boys and men with KS, in which the same measure for ASD traits was used (Van Rijn & Swaab, 2011). Increased levels of attention to detail were only found in adults with KS, not in younger boys with KS, which provides evidence for the idea that differentiation of this particular aspect of ASD only becomes apparent later in the developmental stage. And finally, for imagination skills, results reveal that boys with KS as well as boys from the control group have poorer imagination skills than Triple X girls and girls from the control group. This suggests that this specific skill could generally be more impaired in boys than in girls. To sum up, we found that boys as well as girls with an extra X chromosome show highly increased levels of ASD traits. In other words, our results provide evidence that being born with an extra X chromosome is associated with an increased genetic vulnerability for developing ASD traits. Replication of these results with more extensive and thorough diagnostic measures is necessary to confirm this conclusion.

Our findings are of importance for various theoretical models of neurodevelopment disorders, as well as research into possible risk factors in child development. For example, the clinical heterogeneity of ASD is large, which means that symptoms of children with ASD vary greatly in severity and incidence. This leads to the question whether this clinical heterogeneity could be explained by genetic

heterogeneity. This is a complicated question, since the search for causal relationships between genes and behavior is fraught with difficulties. Therefore, genetically defined syndromes pose a solution because they are defined by the same X chromosomal abnormality. An attempt to dissect the clinical heterogeneity of ASD in genetically defined syndromes was made by Bruining and colleagues (2010). They studied KS boys and children with 22q11 deletion syndrome and found that both genetic disorders showed substantial symptom homogeneity. In addition, a robust discrimination between both disorders could be made, suggesting that these children have specific ASD profiles. Another example is provided by Van Rijn and Swaab (2011) who studied cognitive-specific risk profiles with respect to levels of autism traits and schizotypal traits in boys and men with KS. They report that elevated levels of autistic traits seemed to be more strongly associated with relative deficits in verbal abilities, whereas increased levels of schizotypal traits were more strongly associated with relative deficits in visuospatial abilities. These results suggest that the risk of developing psychopathology in individuals with KS might be related to specific cognitive profiles.

Studies such as these highlight the theoretical importance of studying neurodevelopmental disorders in children with a genetically defined syndrome. Since boys with KS and girls with Triple X syndrome share the same X chromosomal background and appear to have an equally high risk of ASD traits, we may hypothesize that an X chromosomal abnormality is one of many genetic factors that is associated with the etiology of autistic-like behaviors. Evidence for this hypothesis comes from studies on another X chromosomal disorder, Turner syndrome (defined by a partial or complete absence of one of the X chromosomes; 45,XO). These girls also show elevated rates of ASD traits and impaired social functioning (Skuse, 2000).

With respect to the genetic mechanisms involved in the presence of an extra X chromosome, evidence is inconclusive. Some studies emphasize the role of genomic imprinting, which refers to the differential expression of a gene depending on the parental origin of the gene, and the impact this has on the development of social behavior (Skuse, 2000). However, the effects of the imprinted locus are wide-ranging and no causal evidence has been conclusively identified (Skuse, 2000). Other studies stress the importance of looking more closely into the role of abnormal X-inactivation and the overexpression of genes on the X chromosome (Samango-Sprouse, 2001; Vawter, Harvey, & DeLisi, 2007). Furthermore, hormonal influences such as the effect of testosterone deficits are also hypothesized to be of importance in behavioral impairments (Baron-Cohen et al., 2011). However, this hypothesis is not supported by evidence from studies on Triple X girls. These girls generally show average androgen levels, but do have impairments in overall social functioning (Bender et al., 1999; Harmon et al., 1998). The exact impact of an extra X chromosome on the genetic mechanisms that influence social behavior and ASD traits is being intensively studied, but remains unclear. Our results show for the first time that boys as well as girls with an extra X chromosome exhibit high levels of ASD traits. This stresses the importance of looking more closely into possible gender similarities in addition to focusing on gender differences between boys and girls with an extra X chromosome. In the general population, ASD is much more prevalent in boys, with boys outnumbering girls by at least four to one (Lord et al., 1994; Skuse, 2000; Volkmar et al., 1993). Therefore, theories on the etiology of ASD try to use gender differences as an explanatory factor. An example of a highly discussed theory is the Extreme Male Brain theory (Baron-Cohen, 2010). This theory hypothesizes that females in general have a stronger drive to empathize, and males in general have a stronger drive to

systemize (Baron-Cohen, 2010). Even though this theory is supported by a lot of research, it does not seem to apply to girls and boys with an extra X chromosome, since they do not exhibit the same clear gender differences with respect to ASD traits. This could indicate that the X chromosome is of particular influence regarding the mechanisms that are involved in the expression of gender dependent behavioral differences. Future genetic studies should therefore focus on the possible explanations for the reported gender similarities between KS and Triple X syndrome as a tool for explaining the role of the X chromosome on the etiological risk factors of ASD.

In addition to the theoretical relevance discussed above there are also clinical implications with respect to interventions regarding and treatment of boys with KS on the one hand, and girls with Triple X syndrome on the other. Our results reveal that girls with Triple X syndrome experience difficulties with switching their attention, and have poor communication skills and impaired social skills. In comparison to KS boys, their imagination skills seem to be less impaired. Knowing not only which skills are impaired, but also realizing which stronger skills should be used for compensation is important for possible intervention and treatment. For example, treatment could make good use of imaginations skills by asking children to think of difficult social situations and to come up with possible ways to handle these when interacting with others. Since Triple X girls have trouble with communication and social interaction, prepared schemes for particular social situations might help them in interacting with others. As for KS boys, who do show impaired imagination skills, it is important that treatment should not rely exclusively on these skills. For KS boys it would be more useful to act out certain social situations, thus relying less on their imagination skills. These may seem small and irrelevant details, but could be of crucial importance in determining whether or not treatment will be effective for these children.

Our study is the first to date to address social cognitive skills in girls with Triple X syndrome and boys with KS. The results reveal that children with an extra X chromosome show overall impairments in social cognitive skills, regardless of age, gender, intelligence, and language comprehension. Boys with KS as well as girls with Triple X syndrome experience more difficulties than controls in various domains of social cognition, such as theory of mind (for an extensive review on theory of mind see Baron-Cohen, 2001). In addition to assessing the individual social cognitive skills, looking more closely into cognitive levels reveals a decreasing trend in scores for both groups as the social cognitive skills increase in complexity. More specifically, at every developmental stage children with an extra X chromosome perform at a lower social cognitive level than control children. These results are in agreement with a study by Coleman et al. (2008), who used the same measure we used in this study to investigated social cognitive skills in children with ASD compared to control children. The authors found a similar decreasing trend in scores, with a significant difference between the two groups. Social cognitive skills in children from the ASD group were significantly more impaired than in control children. This result is comparable to the discrepancy we found between controls and extra X chromosome children, which indicates that the impaired social cognitive skills in KS boys and Triple X girls are generally similar to those in children with ASD. It is proposed that impairments in social cognition in KS boys and Triple X girls could be interpreted as a direct consequence of language problems and delays, or impaired intellectual abilities (Visootsak & Graham, 2009). This would constitute a limitation of our study, since the social cognitive task we used required the child to think abstractly and tapped heavily into verbal abilities. However, our study provides evidence that even though intelligence scores and language comprehension influence the quality of social

cognitive skills, the discrepancy between children with an extra X chromosome and typically developing children cannot be fully explained by these factors. After correction for intelligence and language deficits the differences remained large (effect sizes between 1 and 2). This suggests that social cognition can be considered a mechanism that is of great importance, besides other aspects of cognition such as language comprehension and general intellectual abilities. Additional support for this hypothesis comes from studies on children with high-functioning autism and Asperger's syndrome, who show specific impairments in social cognitive skills irrespective of cognitive abilities (Pinkham et al., 2003).

Another question that needs to be answered is whether or not specific social cognitive skills contribute to the presence of ASD traits in children with an extra X chromosome. Our results show that in boys with KS and girls with Triple X syndrome the social cognitive skill of 'comparing' is inversely related to the risk of having more ASD traits. In other words, children with an extra X chromosome that experience difficulties with comparing show more ASD traits, and vice versa. This skill belongs to the subjective level of social cognition, i.e., theory of mind, which starts to develop around the age of 6 and is a core deficit in children with ASD. This result confirms conclusions mentioned above, that children with an extra X chromosome are associated with more autistic-like behaviors and show similar key impairments.

Our study is the first to show that Triple X girls have severe difficulties with overall social information processing. For these girls perception and interpretation of, and reaction to social information is substantially more difficult than for typically developing girls. For KS boys, this study adds substantially to the existing knowledge that these boys experience difficulties in various domains of social cognitive functioning (Van Rijn et al., 2006; Van Rijn et al., 2008; Visootsak & Graham, 2009).

Earlier studies have already found that KS boys have a poorer perception of social-emotional cues, more difficulties with verbalizing emotions, and show a discrepancy between cognitive appraisal of emotions and emotional arousal. Although our results provide strong evidence for impaired social cognitive skills, more research is needed to replicate these findings, especially for Triple X syndrome, which so far has been scarcely studied. The realization that social functioning is a challenge for children born with an extra X chromosome is important for the practitioners who work with these children. Early intervention, directed not only at specific social cognitive impairments but also at the strengths that these children show, could reduce the difficulties they are likely to experience in later life. Treatment programs that are being developed for these children could profit from information on their functioning, in order to improve their effectiveness and enable boys with KS and girls with Triple X syndrome to derive maximum benefit. In addition, the detailed and extensive information that is provided with our study is important for practitioners in health care settings with respect to the detection of and screening for syndromes such as KS and Triple X. Recent figures indicate that up to 65% of boys with KS remain undiagnosed throughout their lives (Bojesen et al., 2003). For Triple X syndrome there are no exact percentages, but research has shown that the majority of Triple X girls go through life undiagnosed (Gustavson, 1999). One could argue that because these children do not encounter substantial problems in their lives they are not in need of treatment. However, prospective studies do show that children with an extra X chromosome experience physical as well as psychosocial difficulties which can be prevented and reduced, if recognized. This indicates the importance of more recognition and understanding for children and adults with KS and Triple X syndrome (Bojesen et al., 2003).

In conclusion, our study has shown that girls with Triple X as well as boys with KS show substantially elevated rates of ASD-like behavior. In addition, we are the first to show that children with an extra X chromosome have overall impaired social cognitive skills, and function at a lower social cognitive level than typically developing children, even when intelligence and language comprehension are taken into account. Furthermore, no evidence was found for gender differences in the mechanisms underlying ASD traits in boys with KS and girls with Triple X syndrome, which suggests that the impairments these children exhibit can be attributed at least partly to having been born with an extra X chromosome. Furthermore, the specific impairments shown by children with an extra X chromosome are not exclusively related to ASD. Therefore, future research should focus on other psychopathologies associated with impaired social cognitive skills, such as schizophrenia. These future studies should aim to identify risk factors endangering the development of children with ASD and those that are born with an extra X chromosome. Our study on the behavioral phenotypes of genetic syndromes of prenatal origin and their underlying mechanisms provides guidelines for future studies so that screening instruments and treatment programs may be designed and further enhanced which will benefit the development of these children.

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