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Original article

Autism, language and communication in children with sex chromosome trisomies

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ABSTRACT

Purpose Sex chromosome trisomies (SCTs) are found on amniocentesis in 2.3–3.7 per 1000 same-sex births, yet there is a limited database on which to base a prognosis. Autism has been described in postnatally diagnosed cases of Klinefelter syndrome (XXY karyotype), but the prevalence in non-referred samples, and in other trisomies, is unclear. The authors recruited the largest sample including all three SCTs to be reported to date, including children identified on prenatal screening, to clarify this issue.

Design Parents of children with a SCT were recruited either via prenatal screening or via a parental support group, to give a sample of 58 XXX, 19 XXY and 58 XYY cases. Parents were interviewed using the Vineland Adaptive Behavior Scales and completed questionnaires about the communicative development of children with SCTs and their siblings (42 brothers and 26 sisters).

Results Rates of language and communication problems were high in all three trisomies. Diagnoses of autism spectrum disorder (ASD) were found in 2/19 cases of XXY (11%) and 11/58 XYY (19%). After excluding those with an ASD diagnosis, communicative profiles indicative of mild autistic features were common, although there was wide individual variation.

Conclusions Autistic features have not previously been remarked upon in studies of non-referred samples with SCTs, yet the rate is substantially above population levels in this sample, even when attention is restricted to early-identified cases. The authors hypothesise that X-linked and Y-linked neuroligins may play a significant role in the aetiology of communication impairments and ASD.

What is already known on this topic

► Children with sex chromosome trisomies (SCTs) are at increased risk for neurodevelopmental disorders, especially those affecting language, but many children develop normally.

► It has been difficult to specify risks precisely because the database is very sparse.

► Autism has been described as a correlate of Klinefelter syndrome, but it is unclear how far this reflects ascertainment bias, or whether children with other trisomies have increased risk.

What this study adds

► This is the largest study to date that encompasses all three SCTs (XXX, XXY and XYY), and includes cases identified on prenatal screening.

► We confirm a high risk of language impairment in all three trisomies, and an increased risk of autistic spectrum disorder in XXY and XYY karyotypes.

► Our study will inform practice in clinical genetics and also supports a role of neuroligin genes in the aetiology of communication disorders.

Errors in meiosis can lead to duplication of an entire chromosome, so that the individual has three rather than the usual two copies, that is, trisomy. Trisomies affecting the sex chromosomes are relatively common: in newborn surveys, XXX and XYY karyotypes are found in around 1 in 1000 live female and male births respectively, with XXY karyotype (Klinefelter syndrome) showing a recent rise in frequency to 1.72 per 1000 male births.[1] The impact of sex chromosome trisomies (SCTs) on brain function is typically mild, in contrast to duplication of an autosome, which is typically lethal or associated with major cognitive impairments. This difference in outcomes is explained by X-chromosome inactivation, a process that ensures that the amount of gene product from X-chromosomes is comparable in normal males and females.[2] The presence of an extra chromosome often goes undetected in childhood, unless chromosome studies are undertaken to establish the aetiology of educational or behavioural difficulties. Studies based on such cases will be biased as they exclude those whose development is not giving cause for concern. In the 1960s, several studies were initiated to investigate development in unbiased samples of children with SCTs, identified on neonatal screening. These confirmed that there was an increased risk of educational difficulties, especially those affecting language, in all three types of SCT, though with some differences in cognitive profile.[3] However, cognitive deficits were generally mild, most children attended mainstream schools and some performed in the normal or superior range.[4] For

those seen in adolescence and adulthood, results were again mixed, but major psychopathology was rare.[5] [6] Neonatal screening for SCTs is no longer regarded as ethically justifiable, so there is a dearth of up-to-date information on non-referred samples. More recent literature on brain-related outcomes has focused predominantly on cases of Klinefelter syndrome identified either through endocrinological clinics or support groups. Two such studies,[7] [8] together with some case reports,[9] [10] have drawn attention to autistic features in Klinefelter syndrome, something that was not reported by the earlier literature from unbiased samples. A key question is whether this association is an artefact of ascertainment bias. In addition, we need to know whether any association is specific to the XXY karyotype or whether it is seen in the other SCTs.

METHODS
Sample
We studied families recruited because they had a child identified with a SCT on prenatal screening. Such a sample is not unbiased for two reasons: first, mothers who are offered prenatal screening are on average older than other mothers, and in some cases amniocentesis is prompted by abnormal results of ultrasound or serum screening or presence of genetic abnormalities in the family. Prevalence of SCTs on prenatal screening is higher than found in newborn surveys.[1] Second, where a SCT is identified on prenatal screening, some parents may opt to terminate the pregnancy. Nevertheless, a sample recruited this way is not identified because of any developmental concerns during childhood, and so gives a better estimate of prevalence of neurodevelopmental disorders than samples recruited because of medical concerns or through a support group.

Because children with SCTs may not be told of the diagnosis, we collected data only from parents, using standardised interviews and questionnaires. Siblings of the study sample provided a comparison group of the same social background. The study had the backing of the parent support group Unique, and was approved by Oxfordshire Research Ethics Committee B (ref: MREC 07/Q1605/49); all parents gave written informed consent.

Live born cases of SCT aged from 4 to 16 years, identified on prenatal screening, were identified from six regional genetics services in England and from regional congenital anomaly registers. Additional cases of 4–16-year-old XXX and XYY trisomies were recruited via Unique, a parent support organisation for children with rare genetic disorders. We divided our sample into two groups. Group I consisted of the prenatal referrals from the regional centres, augmented by 10 cases (all prenatally diagnosed) whose parents had joined Unique prior to their first birthday. Group II consisted of those with XXX and XYY karyotypes (either prenatally or postnatally diagnosed) whose parents had joined Unique after their first birthday. We thus kept separate those cases where the child's characteristics could have affected their identification for this study. We did not recruit from a support group catering for Klinefelter syndrome, so there were no XXY cases in Group II. Parents were mailed information about the study, yielding a response rate of 70%. Table 1 shows the characteristics of children in the two groups. Where feasible, parents also provided information about a sibling of the child with a SCT in the same age range. Siblings were grouped together by gender, regardless of the karyotype of the proband.

Background information
Parents reported the type of school their child attended (regular mainstream, special class in mainstream, or special school); the latter two categories were grouped together. In addition, parents indicated whether the child was identified by the educational system as having special educational needs (SEN), whether the child had contact with a professional such as speech and language therapist, and whether any diagnosis had been given to the child by a medical professional or psychologist. Diagnostic information was coded into mutually exclusive categories of (1) autism spectrum disorder (ASD)/ Asperger syndrome; (2) language or literacy problems; (3) other neurodevelopmental disorder (eg, dyspraxia, attention deficit hyperactivity disorder (ADHD)).

Assessments
Vineland Adaptive Behaviour Scales (VABS-II).[11] This is a semi-structured interview, covering the domains of communication, daily living skills and socialisation, standardised on a representative US population.
Children's Communication Checklist-2 (CCC-2).[12] For this checklist, parents rate the frequency with which specific communicative behaviours are observed. The CCC-2 has been standardised on a large, representative sample of British children aged from 4 to 16 years. There are 10 subscales: four scales assess areas that are often impaired in children with specific language impairment (SLI). The next six scales cover aspects

Table 1 Number of children according to karyotype and method of ascertainment, with age and mean parental educational level

	N	Mean (SD) age (years)	Range (years)	Mean (SD) parental educational level*
Group I				
XXX	30	9.2 (3.88)	4–15	3.02 (1.06)
XXY	19	9.4 (4.10)	4–15	2.79 (1.13)
XYY	21	8.7 (3.48)	4–15	2.57 (0.93)
Group II				
XXX	28	10.4 (4.25)	4–17	2.72 (0.89)
XYY	37	10.0 (3.36)	4–16	2.29 (0.89)
Siblings				
Girls	26	11.0 (3.38)	4–16	2.56 (1.07)
Boys	42	11.4 (3.24)	4–16	2.71 (1.01)

*Coded as follows: 1, no academic qualifications; 2, CSE/O-level or equivalent; 3, A-level or equivalent; 4, degree; 5, postgraduate.

of communication and behaviour that are often impaired in autistic disorder.[13]

DATA ANALYSIS

Categorical diagnostic information was evaluated using ORs indicating likelihood of problems in each SCT group relative to same-sex controls (siblings of all SCT groups combined), after confirming that these groups did not differ in mean parental educational level; for boys, $F_{(3, 115)}=1.57$, $p=0.201$; for girls, $F_{(2, 81)}=1.45$, $p=0.241$. Where appropriate, rates of impairment were also compared with national statistics.[14] The national statistics are provided by gender for specific categories, but not for total sample, so the latter is estimated as 50% male. Group means on quantitative data from questionnaires were compared separately for each sex using multivariate analysis of variance.

RESULTS

Table 2 shows type of school provision, frequency of registration of SEN and speech therapy, and diagnoses in girls. Among Group I XXX girls, 14% were identified as having SEN, compared to a national prevalence rate of 5%,[14] and 24% had had speech and language therapy. In Group II girls, rates of educational difficulties were higher, but no girl in either Group I or Group II was diagnosed with an ASD. The 'other' diagnoses in this group were mainly dyspraxia and ADHD. Overall, 55% of girls with XXX karyotype had no indication of neurodevelopmental problems.

Table 3 shows analogous data for boys. Among boys with XXY karyotype rates of educational difficulty were significantly higher than in the male controls, with 28% in special classes or schools, 32% having SEN and 47% having received speech and language therapy. The commonest diagnosis was ASD, seen in 2/19 cases. We did not have information on the criteria used to make this diagnosis: the term 'ASD' is often applied to children with mild autistic features who do not meet full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition or International Statistical Classification of Diseases and Related Health Problems 10th Revision criteria. Nevertheless, this is a substantially elevated risk compared to general population prevalence estimates for broadly defined ASD.[14] [15] For XXY boys in Group I, 37% had no evidence of any problems on the measures in table 3.

For the XYY boys, an ASD diagnosis was found in four of 21 (20%) in Group I and seven of 37 (19%) in Group II. Around half the Group I cases had a statement of SEN and 71% had received speech and language therapy. Only 14% of those in Group I and eight per cent of those in Group II had no evidence of any problems.

Quantitative assessments

We considered first the 13 children with a diagnosis of ASD. The VABS-II (table 4) confirmed substantial impairment in these children, with mean scores more than 2 SD below average.

Multivariate analysis of variance was conducted separately for each sex to compare the remainder of the sample with same-sex siblings. The group effect was highly significant (p<0.001) for males and females. CIs for difference scores are shown in the online supplementary table 1.

Table 2 N (%) girls receiving special schooling, registered with special educational needs (SEN), with speech and language therapy (SALT) or a given diagnosis

| | Group I | | Group II | | Siblings | National data[14] |
	XXX	OR	XXX	OR	Sisters	Girls
N	30		28		26	3992857
Special schooling	3 (12%)	2.78 (0.3 to 28.5)	3 (12%)	3.00 (0.3 to 30.8)	**1 (4%)**	
SEN	5 (14%)	3.80 (1.5 to 10.0)	14 (50%)	19.10 (9.1 to 40.0)	**0 (0%)**	**199150 (5%)**
SALT	7 (24%)	7.61 (0.9 to 66.7)	17 (61%)	38.64 (4.6 to 327.7)	**1 (4%)**	
ASD*	0 (0%)	–	0 (0%)	–	**0 (0%)**	**6680 (0.2%)**
Language/literacy problems	0 (0%)	–	2 (7%)	6.00 (1.4 to 25.3)	**0 (0%)**	**50520 (1%)**
Other*	2 (7%)	–	5 (18%)	–	**1 (4%)**	
No special needs or diagnosis	16 (55%)	0.39 (0.1 to 1.3)	5 (18%)	0.07 (0.02 to 0.3)	**20 (77%)**	

ORs shown with 95% CI relative to comparison group shown in bold.
*Diagnoses coded as mutually exclusive.
ASD, autism spectrum disorder.

Table 3 N (%) boys receiving special schooling, registered with special educational needs (SEN), with speech and language therapy (SALT) or a given diagnosis

| | Group I | | Group I | | Group II | | Siblings | National data[14] |
	XXY	OR	XYY	OR	XYY	OR	Boys	Boys
N	19		21		37		41	3992857
Special schooling	5 (28%)	3.30 (0.8 to 14.1)	9 (47%)	6.94 (1.8 to 26.7)	16 (46%)	7.05 (2.1 to 23.9)	**4 (10%)**	
SEN	6 (32%)	3.60 (1.4 to 9.4)	10 (48%)	7.10 (3.0 to 16.6)	29 (78%)	28.0 (12.8 to 61.5)	**4 (10%)**	**456350 (11%)**
SALT	9 (47%)	4.37 (1.3 to 14.7)	15 (71%)	12.14 (3.5 to 42.3)	27 (73%)	13.11 (4.4 to 39.0)	**7 (18%)**	
ASD*	2 (11%)	19.60 (4.5 to 85.1)	4 (20%)	39.30 (13.8 to 116.8)	7 (19%)	38.90 (17.1 to 88.7)	**0 (0%)**	**23760 (0.6%)**
Language/literacy problems	1 (5%)	1.80 (0.2 to 13.1)	1 (5%)	1.60 (0.2 to 11.8)	0 (0%)	–	**2 (5%)**	**122490 (3%)**
Other*	0 (0%)	–	1 (5%)	–	1 (3%)		**1 (3%)**	
No special needs or diagnosis	7 (37%)	0.24 (0.1 to 0.8)	3 (14%)	0.07 (0.02 to 0.3)	3 (8%)	0.04 (0.01 to 0.2)	**27 (68%)**	

ORs shown with 95% CI relative to comparison group shown in bold.
*Diagnoses coded as mutually exclusive.

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Table 4 Mean and SD age-scaled scores (mean 100, SD 15) on the Vineland Adaptive Behavior Scales for cases with and without a diagnosis of ASD, with latter group subdivided by karyotype

	N	Communication Mean	Communication SD	Daily living Mean	Daily living SD	Social Mean	Social SD
Subset with ASD							
Diagnosis (XXY/XYY)	13	65.2*	14.48	69.3*	11.29	63.4*	10.33
Children without ASD							
Group I							
XXX	29	91.8	13.87	90.8	12.56	92.9*	10.67
XXY	17	83.4*	15.40	88.2	13.09	89.7	13.20
XYY	17	89.0	16.39	82.8	15.20	87.1*	14.32
Group II							
XXX	28	79.5*	17.00	82.9*	14.89	86.6*	13.37
XYY	30	76.3*	11.24	80.4*	14.58	81.9*	13.72
Siblings							
Girls	26	101.0	12.51	98.0	14.47	104.7	13.06
Boys	40	98.0	13.70	92.4	11.75	100.1	11.94

*Score is significantly lower than same-sex siblings, $p < 0.05$, on Scheffé test.
ASD, autism spectrum disorder.

The General Communication Composite index of the CCC-2 was severely impaired for those with a diagnosis of ASD, and was significantly below control levels for the remaining children from all three karyotypes (table 5 and the online supplementary table 1). As can be seen in figure 1 and the online supplementary table 2, and was confirmed by lack of interaction between group and subscale on repeated measures analysis of variance, the profile of impairment is similar in all SCT groups, but there is a trend for greater overall severity of impairment in boys than girls, and in Group II compared with Group I. When categorised according to whether one or more scores fell below the 10th centile (scaled score of 6) in domains of structure (scales A–D) or pragmatics (E–H), 41% of XXX, 25% of XXY and 31% of XYY from Group I had no impairment, compared with 16% of XXX and 7% of Group II. Fifteen per cent of XXX, 25% XXY and 31% of XYY in Group I had structural problems only, plus 16% of XXX and seven per cent of XYY in Group II. Children with this profile do not say unusual things or show over-literal misunderstandings, but have difficulty with expression or understanding of complex language. Nearly all the remaining cases had problems in both structural and pragmatic domains: 44% of XXX, 50% of XXY and 38% of XYY from Group I, 68% XXX and 85% of XYY in Group II.
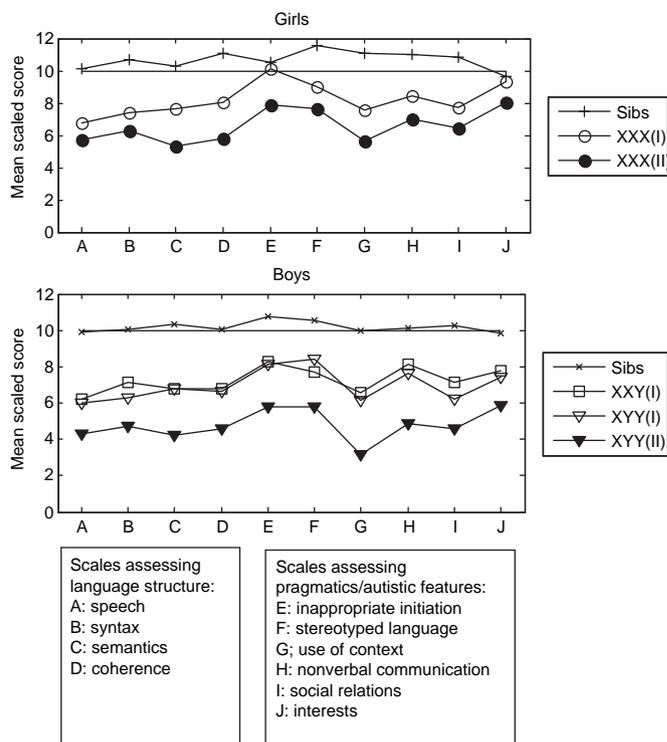
DISCUSSION

This study revealed an association with autistic features in males with an extra sex chromosome. Around 20% of XYY males and 11% of XXY males had received a diagnosis of ASD, which is a 10–20-fold increase over even the most liberal prevalence estimate for autism in the general population.[15] Furthermore, among those who did not have an ASD diagnosis, there was evidence of milder communicative difficulties similar to those seen in autism. It is noteworthy that a significant increase in ASD was seen in males from Group I, who were identified prenatally, before there was any concern about the child's development. Although girls with XXX karyotype also had a high rate of educational difficulties and frequently had received speech and language therapy, none had an ASD diagnosis, and the CCC-2 profile suggested few had major communicative problems.

Table 5 Mean and SD age-scaled scores on the GCC index of CCC-2 for cases with and without a diagnosis of ASD, with latter group subdivided by karyotype: normative mean is 82, 10th centile cut-off is 54

	GCC N*	Mean	SD
Subset with ASD			
Diagnosis (XXY/XYY)	11	26.2†	20.52
Children without ASD			
Group I			
XXX	27	65.0†	28.88
XXY	16	57.5†	25.64
XYY	16	55.9†	23.68
Group II			
XXX	24	51.3†	27.07
XYY	28	37.4†	23.18
Siblings			
Girls	22	86.2	13.58
Boys	40	81.7	17.53

*Where N is lower than for full sample, data were excluded because the respondent failed the consistency check (suggestive of failure to understand the instructions), or did not complete the CCC-2.
†Score is significantly lower than same-sex siblings, $p < 0.05$, on Scheffé test.
ASD, autism spectrum disorder; CCC-2, Children's Communication Checklist-2; GCC, .

Scales assessing language structure:
A: speech
B: syntax
C: semantics
D: coherence

Scales assessing pragmatics/autistic features:
E: inappropriate initiation
F: stereotyped language
G: use of context
H: nonverbal communication
I: social relations
J: interests

Figure 1 Profile plots for boys and girls on Children's Communication Checklist—2 subscales.

Despite these associations with impairment, when attention is focused on Group I, 14% of XYY boys, 37% of XXY boys and just over half the XXX girls had not been noted as requiring support services nor received any educationally relevant diagnosis. These results confirm previous reports from studies of samples identified by newborn screening, in revealing an increased prevalence of educational difficulties and speech-language problems in children with SCTs, but

with many nevertheless coping in mainstream schools, and some children performing within the normal range.[3] ASD, however, was not mentioned in those earlier studies, where the emphasis was more on language and literacy problems, as well as a general reduction in IQ. A possible explanation for this mismatch is a change in diagnostic practices which means that children who in previous years would have been identified as cases of language disorder may now be diagnosed with ASD.[16]

The association between autistic features and SCTs is of both clinical and theoretical significance. Parents whose child is diagnosed with an SCT often feel they do not get adequate information about the implications of the diagnosis. It is important not to give an unduly negative prognosis and to keep in mind that not all children with SCTs will have educational difficulties. Nevertheless, if a child does experience problems, parents need to be directed to the most appropriate sources of help, and this will be facilitated if clinicians are alerted to the fact that ASD may be implicated.

As research on genetics of neurodevelopmental disorders proceeds, it has become increasingly clear that the phenotypes of autism and SLI can be a common result of perturbation of a wide range of different mechanisms.[17] Although our data indicate an increase in the relative risk of ASD and language difficulties with SCTs, most children with communication disorders have a normal karyotype,[18 19] and these trisomies cannot provide any general explanation for these neurodevelopmental disorders. Nevertheless these findings point to a possible role for genes on both the X-chromosome and Y-chromosome, and the neuroligin genes (NLGN) are attractive candidates as they code for cell adhesion molecules involved in the formation of functional synapses, and have been implicated in autism.[20 27] There are two NLGN genes on the X-chromosome: NLGN3 and NLGN4X, the latter located on Xp22 where the majority of genes are expressed from both the active and the inactive X.[25] There are very few genes on the Y-chromosome, but NLGN4Y is located on the male-specific region of the Y and is highly homologous with NLGN4X.[28] It is expressed in brain, and all other tested tissues.

Our data suggest a triple dose of such genes is a strong risk factor for language difficulties, with additional social impairments being found when it occurs in a male, leading to autistic features. This account is, however, complicated by evidence that in Turner syndrome, where there is 45, X karyotype, the prevalence of autism is around 3%—lower than that seen in males with SCTs, but substantially higher than in the general population of females.[29] Language, however, is not usually impaired in 45, X females. We therefore hypothesise that risk of autism is increased when there is either deficit or over-expression of X-linked and Y-linked NLGNs; this kind of mechanism, where autism is associated with too much or too little gene product, has been demonstrated for CNVs on 16p11.2.[30] Thus, aberrant gene dosage of NLGNs may provide a common mechanism underpinning the excess of ASD in XYY and XXY males, and in 45, X females.

An alternative hypothesis would maintain that the social impairments seen in 45, X, 47, XXY and 47, XYY karyotypes are less similar than they seem on the surface, with social anxiety being at the root of the difficulties of some children and lack of empathy characterising others.[31] More detailed investigations of the phenotype are now needed to clarify these issues.

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