Mental health and behavioural problems in children with XXYY: a comparison with intellectual disabilities

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Abstract
Background The phenotype of children with XXYY has predominantly been defined by comparison to other sex chromosome aneuploidies trisomies affecting male children; however, the intellectual ability of children with XXYY is lower than children with other sex chromosome aneuploidies trisomies. It is not known to what extent the phenotype identified to date is specific to XXYY, rather than a reflection of lower IQ. This study evaluates the mental health and behaviour of children with XXYY, in comparison to children with intellectual disabilities of heterogeneous genetic origin.

Methods Fifteen children with XXYY and 30 controls matched for age (4–14 years), sex and intellectual ability were ascertained from the IMAGINE ID study. IMAGINE ID participants have intellectual disabilities due to genetic anomalies confirmed by National Health Service Regional Genetic Centre laboratories. The mental health and behaviour of participants was examined with the Development and Well-being Assessment and the Strengths and Difficulties Questionnaire.

Results Children with XXYY experienced significantly more frequent and intense temper outbursts than the control group.

Conclusion Our results suggest that temper outbursts may be specifically associated with the XXYY phenotype. These problems have a significant impacton the daily lives of boys with XXYY and their families. It is crucial to ensure that families are well supported to manage these difficulties.

Keywords behaviour, conduct, genetics, mental health, sex chromosomes

Introduction

XXYY is a rare genetic sex chromosome aneuploidy (SCA) which is associated with intellectual disabilities (ID). It caused by a double nondisjunction during meiosis, resulting in the affected individual inheriting two additional sex chromosomes. The syndrome affects 1 in 18 000 to 40 000 male children (Sørensen *et al*., 1978), and over two thirds of diagnoses are made by genetic testing obtained following evaluation for developmental delays or behavioural difficulties (Tartaglia *et al*. 2008). XXYY is also associated with a distinct physical phenotype and range of medical problems (Box 1).

Box 1: Physical characteristics and medical problems in XXYY

XXYY is commonly associated with physical characteristics such as tall stature, long legs, clinodactyly and pes planus. The most common facial features are hypertelorism with epicanthal folds and narrow upslanting palpebral fissures (Tartaglia *et al*. 2008). The syndrome also carries an increased risk of seizures, cleft palate or congenital heart malformations (Tartaglia *et al*. 2008). XXYY individuals have testicular hyalinization which leads to testosterone deficiency, microorchidism, lack of pubertal progression and infertility (Borgaonkar *et al*. 1970). Testosterone replacement therapy is usually recommended for those with XXYY (Tartaglia *et al*. 2008).

Developmental delay is common in XXYY; over 90% of children present with speech and language delay and over 75% have motor development delay in early childhood (Tartaglia *et al*. 2008). Nearly all children with XXYY require special education for learning disabilities and language difficulties, which can persist into adulthood (Tartaglia *et al*. 2008).

The intellectual ability of individuals with XXYY varies significantly (Tartaglia *et al*. 2008). The majority of XXYY adults score within the borderline (IQ 70–79) to intellectually disabled (IQ <70) range on full scale IQ tests (Borgaonkar *et al*. 1970; Tartaglia *et al*. 2008; Visootsak & Graham 2009). As in many other SCAs (e.g. XYY and XXY) visuo-spatial IQ is a relative strength compared to verbal IQ. More recent findings also indicate that verbal IQ is lower in adults than in children, whereas there are no significant differences in visuo-spatial IQ (Tartaglia *et al*. 2008).

XXYY is linked to an increased risk of mental health disorders; most notably attention deficit hyperactivity disorder (ADHD) which is reported in nearly three out of four patients (Tartaglia *et al*. 2008; Tartaglia *et al*. 2012); autism spectrum disorder (ASD) which is reported in up to half of cases (Tartaglia *et al*. 2017) and behavioural problems such as impulsivity, aggression and mood instability (Tartaglia *et al*. 2008; Tartaglia *et al*. 2012). Many studies report broad difficulties with social skills (Tartaglia *et al*. 2008; Visootsak & Graham 2009; Cordeiro *et al*. 2012). Cordeiro *et al*. (2012) found that 37.5% of XXYY children had a prior diagnosis of ASD and 43.8% had severe scores on a measure of autistic traits [the social responsiveness scale (SRS)]. Whilst analysis of the SRS subscales showed significant difficulties in all areas, scores on the social motivation subscale were only just outside the normal range, suggesting that social motivation is the least impaired domain (Cordeiro *et al*. 2012). There was a significant but weak correlation between verbal abilities and SRS scores, and the authors suggest that poor language skills may contribute to social difficulties in children with XXYY.

Anxiety and depression are common and affect about half of individuals with XXYY by adulthood (Tartaglia *et al*. 2008; Tartaglia *et al*. 2012). In a small study of children (n = 24), 46% were found to meet criteria for a diagnosis of oppositional defiant disorder (ODD) (Tartaglia *et al*. 2006), but in a larger study including children and adults (age range: 6–55), 10% were diagnosed with ODD (Tartaglia *et al*. 2008). Individuals with XXYY have been found to have more problems with hyperactivity, aggression and conduct than those with XXY (Tartaglia *et al*. 2006; Tartaglia *et al*. 2008), and these symptoms were not associated

with IQ. The prevalence and characteristics of eating and sleeping difficulties have not been systematically reviewed, but sleep disturbances, feeding difficulties and sugar cravings have been commonly reported by parents (Tartaglia *et al*. 2008).

To date, the XXYY phenotype has predominantly been defined by comparison to other SCAs affecting male children (Visootsak *et al*. 2007), without being matched for intellectual ability. Children with XXYY have a lower intellectual ability than those with XYY and XXXXY (Printzlau *et al*. 2017). It is not known to what extent the phenotype identified thus far is specific to XXYY, rather than a reflection of their intellectual ability. Children with ID are more likely to have psychiatric diagnoses than children without ID; a national survey that compared the well-being of children with and without an ID showed that 39% of those with ID had psychiatric disorders compared to 8.1% of those without ID (Emerson 2003).

XXYY is typically identified due to concerns about the associated developmental delay. Given the rarity of the condition, most children will be managed in non-specialist settings that manage children with ID of all causes. The clinical phenotype of XXYY therefore needs to be further differentiated from that of ID in general, in order to ensure that the specific needs of children with XXYY are met within such non-specialist settings.

This study aims to compare the phenotypes of children with XXYY to matched controls that have an equivalent level of ID, of known genetic origin. We investigate the extent to which the XXYY phenotype is distinct.

Methods

Data source

Data were obtained from the IMAGINE ID project. This is a large multicentre Medical Research Council and Medical Research Foundation funded study of psychiatric risk and developmental delay in children with genetic disorders.

The IMAGINE ID cohort comprises children with developmental delay due to a genetic anomaly. In the UK, children with developmental delay undergo genetic testing by National Health Service (NHS) Regional Genetic Centres (RGCs) following an initial evaluation by paediatricians. Children who are found to have a genetic anomaly that contributes to developmental delay following genetic testing are recruited into IMAGINE ID via NHS RGCs or support groups including Unique (www.rarechromo. co.uk) and XXYY UK (www.xxyy.co.uk). Genetic diagnosis was confirmed by RGCs for all participants including those recruited via parental support groups. The majority of participants in the IMAGINE ID study have been ascertained as having structural chromosomal anomalies, for example, pathogenic copy number variants.

The IMAGINE ID sample is representative of the English population. This has been confirmed by analysis of UK Office for National Statistics 2011 census data. Index of Multiple Deprivation scores are available for the sample and are also representative of the English population. Detailed information on the cohort has been collected online via caregiver report measures (see succeeding texts). Ethical approval for the study was obtained from the London – Queen Square Research Ethics Committee.

Sample

Fifteen children with XXYY were identified. Two controls were then selected from the IMAGINE ID cohort for each XXYY case; this was to improve statistical power given the rarity of XXYY (Coggon *et al*. 2009). Controls were matched with cases for age, sex, parental estimates of mental age and language impairment. Controls were selected to be heterogeneous with regard to genetic condition (Table 1) in order to reduce bias caused by the overrepresentation of conditions which may reduce risk for age, sex, parental estimates of mental age and language impairment. Controls were selected to be heterogeneous with regard to genetic condition (Table 1) in order to reduce bias caused by the overrepresentation of conditions which may reduce risk for emotional and behavioural problems.

Table 1 Genetic disorders present in the control group

Participant	Genetic disorder
1	1p36.33 duplication
2	1q21.1-21.2 duplication
3	2p16.3 deletion + SNV
4	2p16.3 deletion
5	4q26-28.1 deletion
6	6p25.3 deletion
7	6q27 duplication
8	6p25.3 duplication + 6q27 deletion + 15q11.2 duplication
9	7p22.1 deletion
10	7q11.23 duplication
11	7q11.23 duplication
12	8q21.11tripliction + 16p13.2 duplication + 5q15 deletion
13	8p23.1 deletion
14	10q26.2-qter deletion
15	15q11.2 deletion
16	15q13 DIC/IDIC
17	15q26 translocation + 18p11 translocation
18	16p11.2 deletion
19	16p11.2 duplication
20	16p11.2 duplication
21	16p12.1 deletion
22	16p11.2 deletion
23	16p11.2 deletion
24	16p13.1-12.3 duplication
25	17q22 duplication
26	18p11.2 deletion
27	20p13-q13.3 ring
28	22q11.21 deletion
29	Xp21.2 deletion
30	Xp21.2 duplication

SNV, Single Nucleotide Variant. DIC/IDIC, Dicentric/Isodicentric.

Measures

The Development and Well-being Assessment (DAWBA)

The DAWBA is a validated and widely used research instrument (Goodman *et al*. 2000; Goodman *et al*. 2011). It collects information on a wide range of behaviours and specific mental health difficulties and generates probability scores for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnoses based on population norms which are then confirmed by a clinician. This study used the caregiver-report measure of the DAWBA which was administered online or by telephone. Respondents complete detailed sections which are organised into modules. A background section that covers the child's general physical health, development, education and family was also administered. The DAWBA incorporates both structured and semi-structured items. Each module is composed

of screening questions, followed by questions regarding specific symptomatology and an estimate of functional impairment. This includes questions on parental estimates of mental age and language impairment. Questions pertaining to mental age from the DAWBA have been validated in a subset of the IMAGINE ID cohort by comparison with the Functional Academics Subscale of the Adaptive Behaviour Assessment Schedule, Second Edition (parent form, 5–21 years). This showed high correlation between the two measures (Pearson correlation coefficient 0.74; 95% CI [0.64, 0.81]).

Strengths and Difficulties Questionnaire (SDQ)

This study used a caregiver report version of the SDQ. The SDQ is a widely used and validated measure (Goodman 2001; Goodman & Goodman 2009; Bøe *et al*. 2014); it is a brief behavioural screening questionnaire that can be administered to the primary caregivers of 4–18 year olds. The SDQ scores have been validated in the general population. The SDQ covers common areas of emotional and behavioural difficulties as well as positive attributes; it can be divided into five subscales of five items each: emotional symptoms, conduct problems, hyperactivity-inattention, peer problems and prosocial behaviour. Each subscale is scored out of 10, and each item is scored according to a 3 point scale (0 = *not true*, 1 = *somewhat true* and 2 = *certainly true*). A total difficulties score (maximum score 40) can be calculated using the emotional problems, conduct problems, hyperactivity-inattention and peer problems subscales. The SDQ also includes an impact supplement which captures information on the parent's perception of the severity of their child's problems and reflects the impairment caused by their child's difficulties.

Everyday Feelings Questionnaire (EFQ)

The EFQ was administered to the parents of participants, who reported on themselves. The EFQ is a validated 10-item self-report measure of psychological distress and well-being which is designed to be used in non-clinical samples of adults (Uher & Goodman 2010; Mann *et al*. 2013; Bøe *et al*. 2014). This was administered to parents to assess their well being. The EFQ covers symptoms relating to anxiety and depression as well as items pertaining to psychological well-being such as optimism, self-esteem and coping. Respondents are asked to answer questions based on their experiences over the prior 4 weeks. Each item is scored according to a 5-point scale (none of the time, a little of the time, some of the time, most of the time and all of the time). Scores between 0 and 12 are considered 'close to average', scores between 13 and 17 are 'slightly raised', scores between 18 and 22 are regarded as 'high' and those above 23 are 'very high'.

Analysis

Analyses were conducted using Stata 13. Fisher's exact or chi-squared test and the Mann–Whitney *U* test were used to assess for difference between the two groups across a range of baseline variables as well as mental health and behavioural problems. Fisher's exact test was used in preference to the chi-squared test when expected cell values were below 5. These were used in the analysis of the DAWBA data which are categorical. The Mann–Whitney *U* test was used for the SDQ data which are continuous. The Mann–Whitney *U* test was used as data were non-normally distributed.

Results

Baseline characteristics

Fifteen participants with XXYY were identified and matched with 30 controls. The mean age of combined participant groups was 8.89 years (SD = 3.13, range 4–14 years), and the estimated developmental delay was 3.02 years (e.g. 3 years behind peers, SD = 1.30, range 0–6 years). The mean estimated language delay was 2.95 years (SD = 1.26, range 1–7 years). There were no significant differences in age, estimated developmental delay or language delay between the two groups. No participants with XXYY were receiving testosterone therapy at the time of completion of the assessments. Children with XXYY of school age were more likely to be educated in special schools than controls (XXYY 71%, Control 29%; *P* = 0.02). All participants lived in the UK or dependent territories. There were no differences in demographics or social deprivation between the two groups; however, all children with XXYY had been recruited into IMAGINE ID from the UK XXYY society whereas control participants were more likely to have been recruited from NHS RGCs (XXYY: 100% support group, Control: 67% support group, 33% RGC, *P* = 0.000). For further information about the genetic disorders present in the control group please refer to Table 1.

Strengths and Difficulties Questionnaire

There were significant differences between the two groups on the 'total difficulties' score and the emotional and conduct problems subscales, to which the emotional and conduct subscales make the major contribution. The mean total difficulties score for both the XXYY and control groups were classified as 'very high' according to the established SDQ norms (Table 2).

Further analysis of the conduct problems subscale showed significant differences between the two groups on three out of five items: children with XXYY were more often reported as engaging in stealing (XXYY 50%, Control 11%; *P* = 0.008) and fighting (XXYY 64%, Control 21%; *P* = 0.017) and were less likely to be obedient (XXYY 60%, Control 90%; *P* = 0.042). There were no significant differences between both groups with regard to tantrums (XXYY 93%, Control 77%; *P* = 0.24) and lying (XXYY 71%, Control 43%; *P* = 0.11).

Table 2 A comparison of SDQ scores between XXYY cases and controls using the Mann–Whitney *U* test

	XXYY		Control		
SDQ score[†]	Mean	SD	Mean	SD	*P*-value
Total difficulties	**25.1**	**8.3**	**21.5**	**5.1**	**0.03***
Conduct	**5.6**	**2.9**	**3.1**	**1.2**	**0.004***
Hyperactivity	7.1	2.7	7.9	1.8	0.39
Emotional	**6.3**	**2.1**	**5.1**	**1.8**	**0.04***
Peer problems	6.1	2.5	5.4	2.4	0.43
Prosocial	4.6	2.4	5.5	3.3	0.33
Impact	6.5	3.0	5.9	2.5	0.14

[†]Mann–Whitney *U* test.
*Significant.
SDQ, Strengths and Difficulties Questionnaire.

Further analysis of the emotional difficulties subscale suggested that boys with XXYY were more likely to experience somatic symptoms of anxiety (XXYY 87%, Control 43%; *P* = 0.045). Although boys with XXYY experienced high levels of other emotional symptoms, there were no significant differences between groups on these items: unhappiness (XXYY 67%, Control 43%; *P* = 0.07), worrying (XXYY 80%, Control 73%; *P* = 0.57), clinginess (XXYY 100%, Control 93%; *P* = 0.88) and being afraid (XXYY 100%, Control 80%; *P* = 0.66).

Development and Well-being Assessment

Analysis of DAWBA psychiatric diagnoses revealed that a higher proportion of the XXYY group met criteria for ODD compared to controls (Table 3). A higher proportion of the XXYY group met diagnostic criteria for social phobia, generalised anxiety, ADHD and tics than controls; however, these results were not statistically significant. A lower proportion of children in the XXYY group met criteria for specific phobia and ASD than controls; these results were not significant (Table 3). No participants in either group met criteria for major depression.

Children in the XXYY group were reported as being more likely to display frequent significant temper outbursts (XXYY 47%, Control 10%; *P* = 0.01) and irritability (XXYY 53%, Control 20%; *P* = 0.03). Review of free text responses from semi-structured components of the DAWBA revealed the intensity of the outbursts often experienced by children with XXYY. They were reported to experience angry outbursts which could involve lashing out, throwing objects impulsively and engaging in destructive behaviour. Outbursts were emotionally distressing to the child and involve self-injurious behaviour or threats to self-harm. These incidents could take place on a daily basis and were often perceived by caregivers to be unpredictable (Box 2).

Table 3 A comparison of DAWBA diagnoses between XXYY cases and controls

	XXYY		Control		
DAWBA diagnosis	***n***	**(%)**	***n***	**(%)**	***P*-value**
Separation anxiety ‡	3	20	6	20	1.00
Specific phobia ‡	2	13.3	8	26.7	0.46
Social Phobia ‡	1	6.7	0	0	0.33
Generalised anxiety ‡	1	6.7	1	3.3	1.00
ADHD †	9	60	14	46.7	0.40
ASD †	5	33	16	53	0.27
Tics ‡	0	0	5	16.7	0.15
ODD †	**9**	**60**	8	**26.7**	**0.03** *

†Chi-squared test.
‡Fishers exact test.
*Significant.
DAWBA, Development and Well-being Assessment.

Box 2: Primary caregiver descriptions of aggression, irritability and conduct problems in children with XXYY

"Is always very frustrated (…) [He] drops to the floor a lot when upset and overwhelmed. Does not want anyone near him will hit himself and throw anything which is near him. It's a very frustrated cry … can be ongoing process for hours."
5 years old
"He is very strong and his outbursts come from nowhere. He will have a least one outburst at home a day. They look like the outbursts of a 2 year old toddler (…). He suffers very badly from remorse after the event and this affects his self-esteem, which is always fragile and low."
13 years old "I cannot leave him unsupervised at my friend'shouse as he will wreck and break stuff. [He makes] threats to hit with a hockey stick, brick and wreck people's things … [He] shouts at her [a 3 year old child] and has tried to lash out [at] her with a hockey stick and throws mud at her and one awful day he tried to drop a brick on her head. Recently at a party he jumped up [and] down on this girl's lovely party shoes shouting 'she's bad'." **5 years old**
"[He] has thrown most of the contents of his bedroom down the stairs before. He has slammed doors, thrown whatever he is holding. He has threatened to kill himself or run away**.** When [he] becomes cross he becomes physical, hitting and lashing out (…) He seems out of control and it can be potentially dangerous as he does things impulsively without thinking about the consequences. He has bitten his arm in frustration and also hit his own head repeatedly saying he's stupid. Afterwards he becomes incredibly low and frustrated with himself. Daily. [It] seems to have got worse since he was 7/8." **10 years old**
"He completely loses it. He shouts, screams, swears, slams doors, throws things, threatens to hit me (but never has)." **11 years old**

"He is more able to control is outbursts as he gets older but at home he still explodes regularly. I worry that he may hurt himself or someone else. Once he blows you just have to ride it out and comfort him after but he is less angry since getting into special education." **12 years old**

Review of free text responses in the section of the DAWBA that inquired about eating behaviours identified that problematic sugar cravings were reported more often in the XXYY group than controls (XXYY 40%, Control 6%; *P* = 0.01). These were often described as being so intense that they were associated with stealing behaviours (Box 3).

Box 3: Primary caregiver descriptions of sugar cravings

"He binges on sugary products and steals them from the cupboard." **13 years old**
"He also will 'steal' sugar, icing sugar, honey, biscuits, mints, sweets etc. and eat them secretly in his room." **10 years old** "He does not know when he's full. He will eat and eat and eat and sneak food. He tries to raid the cupboard when I am not looking. I try to not keep naughty food in the house because he will find them and then his wrappers are hidden under his bed." **11 years old**
"He has the strange phase, twice or three times a year, lasting 2 to 8 weeks, the "sugar craving period"; he becomes the "sugar addict". In this phase, like other the substance abusers, his eyes are glaring, searching for the sugary food is the main focus for him. I am not able to leave any sweets in the reachable place. (…) You can clearly see the difference, as he does not do consuming the vast amount of sweets (two/three family pack kit-kat in one go for example) at all most of the time." **11 years old**
"He would eat far too much sweet food if given the chance. He can sometimes take sweet items such as biscuits, chocolate when adults are not present. He can also become very angry if told he cannot have these items of food." **11 years old**

Review of the strengths section of the DAWBA highlighted that children with XXYY were generous (100%), lively (87%), caring (93%), affectionate (87%), grateful (80%), polite (93%), good fun (93%) and able to bounce back from setbacks (73%). They were also reported as getting on well with their family (100%) and as enjoying family activities (80%).

Everyday Feelings Questionnaire

For both the XXYY and control groups, caregiver EFQ scores fell into the 'slightly raised' range (mean = 17.6; SD = 6.7; range: 4–34) based on the norms described earlier. There were no significant differences in EFQ scores between the two groups (XXYY mean = 17.8, SD = 4.95; Control mean = 17.4, SD = 7.54; *P* = 0.68).

Discussion

This is the first study to systematically assess the mental health and behaviour of children with XXYY to controls matched for age as well as intellectual and language ability. Whilst previous reports have identified behavioural problems such as aggression, impulsivity and

mood instability in children with XXYY, this study is the first to include a detailed assessment of conduct problems alongside other psychopathology. The main differences between the XXYY and control groups were a greater frequency and intensity of temper outbursts and irritability in children with XXYY. These difficulties were not highlighted in our short behavioural screening questionnaire (the SDQ), as the level of conduct problems was high in both groups; however, a detailed examination of the conduct of children with the DAWBA questionnaire revealed significant differences.

Our assessments have shown the substantial impact these conduct problems have on the daily lives of boys with XXYY and their families. These findings support qualitative descriptions of behaviour, where boys are typically described as sweet and loving but also as easily frustrated and impulsive and prone to mood swings and temper outbursts (http://www. rarechromo.co.uk/html/DisorderGuides.asp).

Children with XXYY are significantly more intellectually impaired than children with common SCAs (such as XXY, XYY, XXX or XO) (Visootsak & Graham 2009). Children with ID are more likely to experience emotional and behavioural problems (Emerson 2003; Emerson & Hatton 2007). As a result, a comparison of XXYY with other SCAs may have led to a misattribution of difficulties with social communication and attention/concentration to the XXYY phenotype rather than their intellectual impairment. The results of this study indicate that temper outbursts are specifically associated with the XXYY phenotype but that difficulties with social communication and attention/concentration may relate to intellectual impairment. This is in keeping with the findings of previous studies which found elevated rates of conduct problems in XXYY in comparison to XXY (Davis *et al*. 2006; Tartaglia *et al*. 2006) but not in comparison to XXXY/XXXXY (Visootsak *et al*. 2007).

Comments from parents indicate that the intensity of the temper outbursts seen in XXYY can be distressing for the child and their family (see Box 2). These difficulties have a substantial impact. It is crucial to ensure that families are well supported to manage these difficulties. In the general population, children from socially disadvantaged areas have higher levels of conduct disorders (Bywater *et al*. 2009); however, conduct problems were present in the majority of the sample with XXYY despite coming from diverse socio-economic backgrounds. This suggests that the causes of conduct problems in those with XXYY may be different to the causes of conduct problems in the general population. Conduct problems in the general population have been associated with specific parenting styles (Brestan & Eyberg 1998; Vostanis *et al*. 2006) which has led parents to be considered responsible for their child's difficulties. It is important that parents of children with conduct disorders are not stigmatised for their children's behaviour. For children with XXYY, these problems may, at least partially, be explained by them being a feature of the XXYY behavioural phenotype. In addition, boys with XXYY were noted to experience high levels of emotional difficulties, particularly somatic symptoms. It may be that their outbursts reflect anxiety and frustration that they are not able to verbalise.

Awareness of the higher levels of conduct problems in children with XXYY indicates the need for more intensive behavioural support utilising specialist techniques, given that these problems may be related to the XXYY behavioural phenotype. Anecdotally, parents report an increase in severity of behavioural outbursts at around the age of 8 to 9 years (Tartaglia

et al. 2008), which incidentally is the mean age of our sample. It may be that the increased intensity of outbursts is linked to developmental changes occurring at this age. It would be important to investigate whether pre-existing interventions for conduct problems are effective in those with XXYY; in particular, optimising the timing of intervention is crucial to better manage severe outbursts at 8 to 9 years. Improving the management of conduct problems in children with XXYY may also mean that they could be supported to remain in mainstream educational settings; this requires further investigation.

Whilst information from our participants suggested that children and families with XXYY receive support from a range of services (including specialist education, paediatrics, educational psychology, speech and language therapy, occupational therapy, social care and mental health), the nature of the specific interventions being offered was not clear. Evidence-based parenting interventions such as the Incredible Years/Triple P (Bywater *et al*. 2009) or conceptualisation of outbursts with the well-established ABC behavioural model (Ellis 1991) may be useful in understanding the triggers for such behaviours and in developing a suitable management strategy.

Longitudinal studies of conduct problems in children with XXYY would be beneficial to determine the developmental trajectory of these problems across the lifespan. Epidemiological study of conduct problems has identified different developmental subtypes. In childhood, two subtypes with distinct longer term outcomes have been delineated: the life course persistent subtype and the childhood limited subtype (Odgers *et al*. 2007). The life course persistent subtype is associated with poor longer term outcomes including mental health, physical health, victimisation and offending behaviour, whereas the outcomes of those with the childhood limited conduct problems are similar to those with low levels of conduct problems in childhood. Indeed, within the IMAGINE ID cohort, there are five adults with XXYY syndrome, none of whom appear to have significant difficulties with such behaviour. This highlights the importance of a developmental approach to the presentation of these difficulties.

In other SCAs such as Turner syndrome, problems with attention and concentration are significant in childhood but resolve during adolescence without intervention (Skuse 2009). Some behaviours follow a specific developmental course in SCAs, which may be linked to the genetic anomaly. Understanding the developmental trajectory of conduct problems in XXYY will provide important prognostic information that will be valuable for both clinicians and families.

Previous studies in XXYY have identified a relative preservation in social motivation (Cordeiro *et al*. 2012). In our sample, social motivation in children with XXYY was not explored in detail, but participants were described as being caring, affectionate and generous in the strengths section of the assessment, reflecting their interest in others. This warrants further investigation as the interest in social interaction may be utilised in developing interventions. In addition, it may be that preservation of social motivation as well as relative weakness of language skills predisposes children with XXYY to emotional distress and outbursts as well as subsequent guilt and remorse (Box 2). This may in turn lead to low self-esteem and increase vulnerability to future mental health problems. Therefore, a focus on improving self-esteem or resilience may be of benefit. An increased desire to ‘fit in’

may mean that children with XXYY are more susceptible to negative peer influences, that is, encouragement by peers to engage in problematic behaviour.

Children with XXYY were more likely to be educated in a specialist setting than controls. Based upon previous research findings, this might have been attributed to intellectual impairment and language difficulties, but this is not the case in our sample given that we matched for age and cognitive ability. It would be interesting to explore whether the differences in educational setting are due to higher levels of conduct problems in children with XXYY, which are more difficult to manage in mainstream educational settings. However, this may mean that the social and educational advantages that mainstream education may confer (Department of Education and Skills 2004) (EDUCATION, 2004) are lost. Despite reports of higher levels of conduct problems in children with XXYY, there were no differences in caregiver accounts of their own emotional well-being which is encouraging.

Previous studies have found high rates of ASD and ADHD in those with XXYY. Our study confirmed this finding; however, there were no significant differences in social communication or attention/activity problems. This suggests that the higher rates of these disorders in children with XXYY may be linked to their intellectual and language impairment rather than being a specific feature of XXYY. However, it is important to note the high levels of ASD and ADHD diagnoses in our control group, which comprised children who were ascertained by NHS RGCs as a result of a confirmed diagnosis of ID of known genetic origin. The majority of participants in the control group had been ascertained as having pathogenic copy number variants that were the cause of their developmental difficulties. Over 50% of our control group met criteria for ASD and 46% met criteria for ADHD, whereas national UK studies using the DAWBA have reported point prevalences of ASD in 8% and ADHD in 8.3% of children with ID (Emerson & Hatton 2007). The discrepancy between IMAGINE ID and previous national surveys of children with ID could simply be related to different modes of ascertainment. But it is more likely that the genetic origin of the ID influences the range, severity and complexity of difficulties within the IMAGINE ID cohort. It is possible that ID related to common polygenic variation is less likely to predispose individuals to mental health and behavioural problems than pathogenic variants. As such, it will also be important to compare children with XXYY to children with ID of other causes, in order to fully delineate the mental health and behavioural phenotype.

None of the children with XXYY in our study were receiving testosterone replacement therapy at the time of participation. Endocrine evaluation for testosterone therapy should commence in early adolescence. Testosterone therapy has beneficial effects on physical health (Tartaglia *et al*. 2008).

However, the effect of testosterone therapy on mental health and behaviour has not been clear until more recently (Sourial & Fenton 1988; Lee 1996; Heuser *et al*. 1999; Tartaglia *et al*. 2008; Tartaglia *et al*. 2011).
Overall, testosterone therapy appears to have a positive effect on conduct, behaviour and aggression but should be monitored carefully in patients with mental health problems such as bipolar or psychiatric disorders due to a previous case report suggesting possible increased aggression in an individual with schizophrenia (Lee 1996). There has previously

been debate in the literature regarding the optimal timing of testosterone therapy and its association with behavioural problems in XXYY (Sourial & Fenton 1988; Lee 1996; Heuser *et al*. 1999; Tartaglia *et al*. 2008). This suggests that the conduct problems arise prior to testosterone therapy. It is unclear whether testosterone therapy would exacerbate pre-existing conduct problems; this would benefit from further research.

Consistent with previous anecdotal reports, noticeable sugar craving in children with XXYY was also reported by caregivers in our study (see Box 3). This would benefit from further exploration as XXYY has been associated with dental problems and peripheral vascular disease (Tartaglia *et al*. 2008).

Strengths and limitations

The strengths of this study are that it is the first research to explore the XXYY phenotype in relation to those with ID of genetic origin who have been matched for language ability and developmental delay. The sample consists entirely of children, whereas previous studies have been made up of both children and adults. It is important to delineate presentation according to age, as the symptoms of psychopathology can manifest themselves differently across the lifespan. It is one of the few studies to have simultaneously assessed a broad range of behaviours and mental health symptoms, rather than historical diagnoses. Due to the overlap in symptomatology between psychiatric diagnoses, collecting information of such depth and breadth improves diagnostic accuracy. For example, impulsive behaviour may be observed in children with conduct problems and/or ADHD; in order to avoid misattribution, both of these areas need to be assessed. The children in our cohort come from a nationally representative mix of urban and rural areas across the UK, so the results are generalisable to the UK and Europe.

XXYY is a rare condition; it is one of the rarest SCAs, and our study only examined behaviour in children. This limits the sample size and the power of the study. In addition, our participants were recruited from a support group which introduces recruitment bias as participants recruited via support groups maybe different from those recruited via other pathways.

XXYY is a heterogeneous condition; therefore, our participants may represent a more extreme developmental phenotype limited to childhood. It is important that the results of this study are interpreted in a developmental context, in light of the heterogeneity of XXYY and the recruitment bias of this study.

No objective assessments of cognition or adaptive function were performed, and the study relied on parental report. However, families recruited into the IMAGINE ID cohort were genetically tested by NHS RGCs as result of a confirmed diagnosis of ID. In addition, comparison of the DAWBA mental age questions with the ABAS functional academic subscale shows good correlation in a subset of the IMAGINE ID cohort. Our measures of behaviour were also based on caregiver reports, which may introduce bias into the study, but there are few reliable and valid assessments of mental health and behaviour for children with ID. Young children (4– 10), let alone children with ID, are not reliable informants on their own behaviour and mental health.

Future studies should consider multiple caregiver and teacher reports to triangulate information. The study design is cross-sectional; further longitudinal studies would be of benefit in order to further delineate the XXYY mental health and behavioural phenotype across the lifespan.

Implications and future research

Our results have important implications for clinical practice and intervention: whilst the prevalence of ASD, ADHD and anxiety in those with XXYY is similar to those with ID of known genetic origin; the rates of conduct problems are higher. Knowledge of these difficulties with conduct problems may reduce the stigma associated with having a child with significant conduct problems, which are often attributed to parenting practices. It is helpful to raise awareness that these conduct problems may be a feature of the XXYY phenotype, rather than simply attributing them to the 'naughty child' stereotype.

Future research in this field should focus on understanding the developmental course of conduct problems in XXYY and compare the nature of the difficulties in XXYY with ID of non-genetic causes. At present, the developmental trajectory of conduct problems in XXYY is not clear, and there is no way to determine whether children with XXYY are more likely to fall into the childhood limited or the life course persistent trajectory (Odgers *et al*. 2007). Should they fall in the childhood limited trajectory, this would be important prognostic information that would be reassuring for parents. At present, we must work based on evidence from the general literature on conduct problems. We know that the children with conduct problems at highest risk of poor long-term outcomes are those with additional family risk factors (socio-economic status, childhood adversity, etc.) (Loeber *et al*. 2000; Burke *et al*. 2002). The most intensive interventions should be targeted at children with XXYY with these risk factors until the trajectories are fully understood.

Conflict of Interest
None declared.

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