



Cognitive and neurological aspects of sex chromosome aneuploidies

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Sex chromosome aneuploidies are a common group of disorders that are characterised by an abnormal number of X or Y chromosomes. However, many individuals with these disorders are not diagnosed, despite established groups of core features that include aberrant brain development and function. Clinical presentations often include characteristic profiles of intellectual ability, motor impairments, and rates of neurological and psychiatric disorders that are higher than those of the general population. Advances in genetics and neuroimaging have substantially expanded knowledge of potential mechanisms that underlie these phenotypes, including a putative dose effect of sex chromosome genes on neuroanatomical structures and cognitive abilities. Continuing attention to emerging trends in research of sex chromosome aneuploidies is important for clinicians because it informs appropriate management of these common genetic disorders. Furthermore, improved understanding of underlying neurobiological processes has much potential to elucidate sex-related factors associated with neurological and psychiatric disease in general.

Introduction

Sex chromosome aneuploidies are characterised by an atypical variation in the number or function of sex chromosomes. They are some of the most common genetic disorders in human beings, and include Klinefelter's syndrome (47,XXY; one in 600 male livebirths), Turner's syndrome (45,X; one in 2000 female livebirths) and XYY syndrome (47,XYY; one in 1000 male livebirths). However, by comparison with other chromosomal abnormalities, such as trisomy 21 (one in 600 livebirths), clinicians have relatively little awareness about diagnosis or management of associated cognitive, psychiatric, and neurological symptoms. These circumstances create a potential gap in clinical practice, with risk of missed diagnoses and high disease burden for patients who might otherwise receive treatments that would improve outcomes. As an example, about 50–85% of individuals with Klinefelter's syndrome and XYY syndrome are not identified.^{1–3} Taken together with evidence that earlier detection could positively affect psychosocial, cognitive, physiological, and reproductive outcomes,^{4,7} it is imperative for health professionals to increase their familiarity with this group of disorders.

In addition to improvements in clinical practice, increased understanding of sex chromosome aneuploidies provides an important opportunity to advance knowledge of sex-related differences in clinical disease in general. Advances in genomics and neuroimaging research have made it increasingly possible that genotype–phenotype links will be established in the foreseeable future. Sex chromosome aneuploidies are ideal models for investigation of genotype–phenotype correlations because of their well defined genetic basis and relatively well described phenotypic characteristics. Targeted research can elucidate how disrupted expression of sex chromosome genes and aberrant sex hormone production specifically affects cognitive and neurological function, and how this disruption can affect sex differences in clinical pathophysiology in general. Many immunological, cognitive, and motor features associated with sex chromosome

aneuploidies are also commonly associated with disease states that have highly skewed sex differences in prevalence and symptomatology. As such, improved knowledge of the inter-relation between genetics and nervous system function in sex chromosome aneuploidies can provide clinicians with an expanded understanding of mechanisms underlying sex differences in the nervous system.

In this Review, we summarise the major clinical features of sex chromosome aneuploidies, focusing mainly on Turner's syndrome, Klinefelter's syndrome, and XYY syndrome, although we also briefly review other supernumerary sex chromosome disorders. We present cognitive, motor, and other neurological outcomes associated with these disorders, and mechanistic models and treatment frameworks that are used. Additionally, we delineate clinical features for each of these disorders, and discuss how continuing research in this area has broad implications for future understanding of sex differences in cognitive and neurological functioning in human beings.

Turner's syndrome (45,X)

Pathophysiology

X-chromosome monosomy (ie, Turner's syndrome) is a common disorder that occurs in one in 2000 female livebirths⁸ and is characterised by the partial or complete absence of an X chromosome. Roughly 50% of individuals with Turner's syndrome have complete monosomy (ie, 45,X karyotype), rather than the full complement of 46 chromosomes.⁹ The other 50% have a range of different disorders, including deletions along the short or long arm of the X chromosome, ring X-chromosome formations, and mosaic cell lines comprised of 45,X cells and various combinations of 46,XX, 47,XXX, or other karyotypes. In addition, some individuals carry cell lines with Y chromosome material. The genetic mechanism for these chromosomal abnormalities has been attributed to nondisjunction of sex chromosomes during meiosis or in early post-zygotic stages¹⁰ (figure 1), resulting in monosomic or mosaic karyotypes, respectively. Turner's syndrome is the only complete monosomy that is viable in

human beings. One possible reason for this unique trait is that, even in typically developing girls, one X chromosome in each cell is inactivated to maintain overall gene–dose equivalence between male and female individuals (since the genetic contribution from the Y chromosome is relatively small). However, there are two notable exceptions to this rule: first, gene expression from short regions of homology between the X and Y chromosomes, known as homologous pseudoautosomal regions (PAR), give the most compelling genetic basis for the phenotype of Turner's syndrome since individuals with Turner's syndrome will be haploinsufficient for genes expressed from these regions; and second, escapee genes on the X chromosome outside PAR that bypass inactivation are relatively underexpressed in girls and women with Turner's syndrome (figure 2). Additionally, epigenetic effects such as imprinting might also have a role in the Turner's syndrome phenotype because individuals with X-chromosome monosomy inevitably carry an X chromosome inherited from one parent: most monosomal karyotypes are derived from a maternally inherited X chromosome (70–80%).¹⁰ Lastly, girls with Turner's syndrome typically undergo extensive ovarian failure from as early as 15 weeks of gestation,¹¹ resulting in decreased production of sex hormones, which undoubtedly has a direct effect on neurodevelopment, particularly in regions highly enriched with sex-steroid receptors.

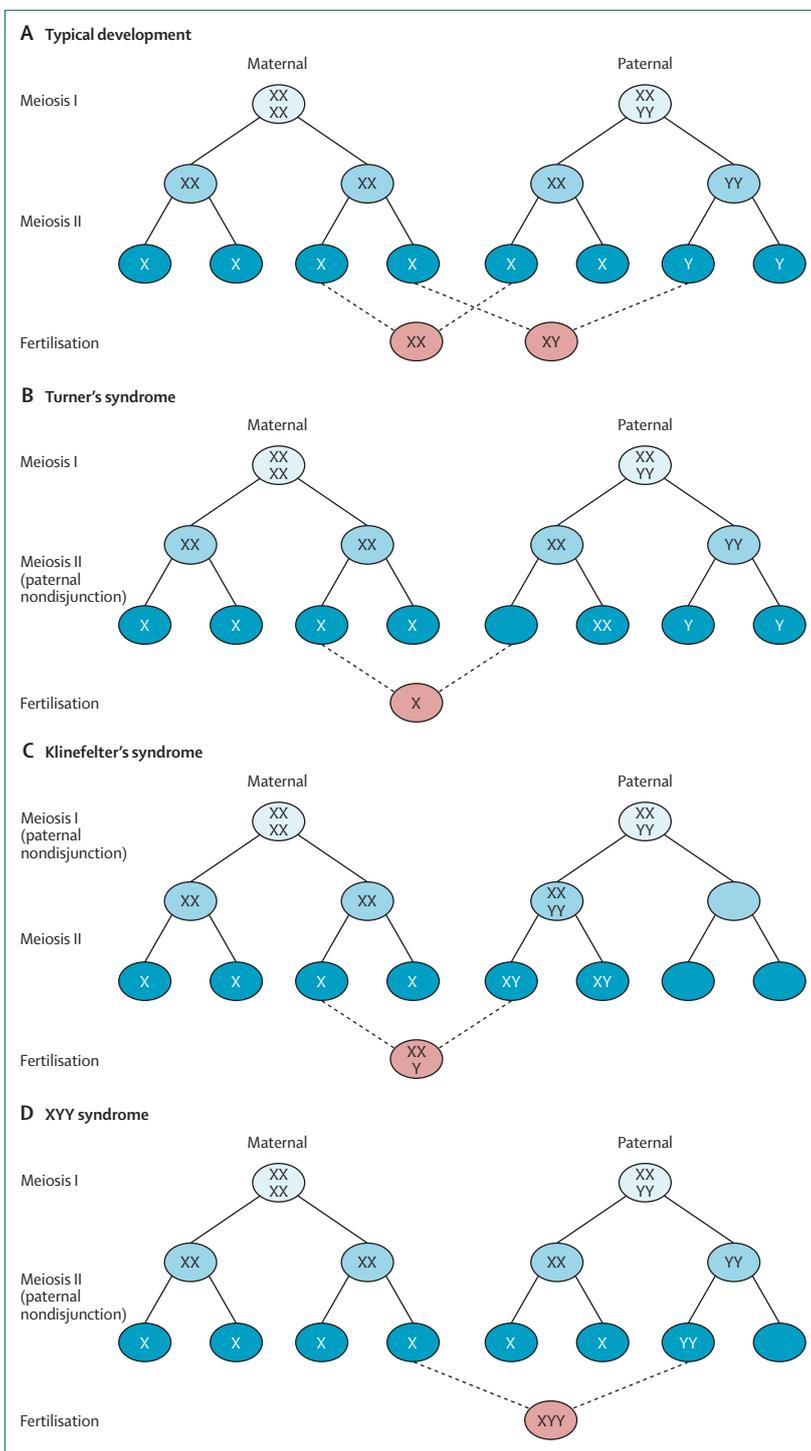
The phenotype associated with Turner's syndrome can be variable, and the degree to which an individual shows physical characteristics is related to their exact karyotype; symptom penetrance is mediated by the degree of mosaicism. However, physical characteristics associated with Turner's syndrome can be more prominent than are those for other sex chromosome aneuploidies, typically resulting in early diagnoses of young girls with this disorder. The most commonly observed features include short stature, structural cardiac abnormalities (including aortic coarctation and bicuspid aortic valve), and premature ovarian failure with associated sex hormone deficiencies and absent secondary sexual characteristics during puberty. Other common physical characteristics can include hypothyroidism, renal abnormalities, webbed neck, lymphoedema, gastrointestinal issues, hearing loss, diabetes, and orthopaedic disorders (table).

Figure 1: Nondisjunction events can occur during several stages of cell division, including meiosis I, meiosis II, or early post-zygotic stages

Cell division during meiosis I and II, in which duplicated sex chromosomes in tetraploid cells (4n, light blue) divide into diploid cells (2n, medium blue), then further separate into haploid gametes (1n, dark blue). Fertilisation between an egg carrying an X chromosome and a spermatid carrying either an X or Y chromosome, results in a typical 46,XX female or 46,XY male karyotype (A). In Turner's syndrome (B), nondisjunction events resulting in a loss of a paternal sex chromosome are the most common genetic mechanism that leads to monosomy (about 70–80%). Studies are not able to show at which meiotic stage errors are more frequent; for illustration purposes we have shown paternal nondisjunction at meiosis II. More than half of 47,XXY karyotypes (Klinefelter's syndrome) result from paternal errors at meiosis I (C), with the rest from maternal meiosis I or II, or post-zygotic mitotic errors. By contrast, 47,XYY (D) can arise only from paternal errors, either at meiosis II (about 85%) or from post-zygotic events.

Cognitive features

In addition to the observed phenotype, Turner's syndrome has characteristic neurocognitive features. General intelligence in people with Turner's syndrome is in the average to low-average range,^{12–14} with the possible exception of individuals with ring X chromosome or other



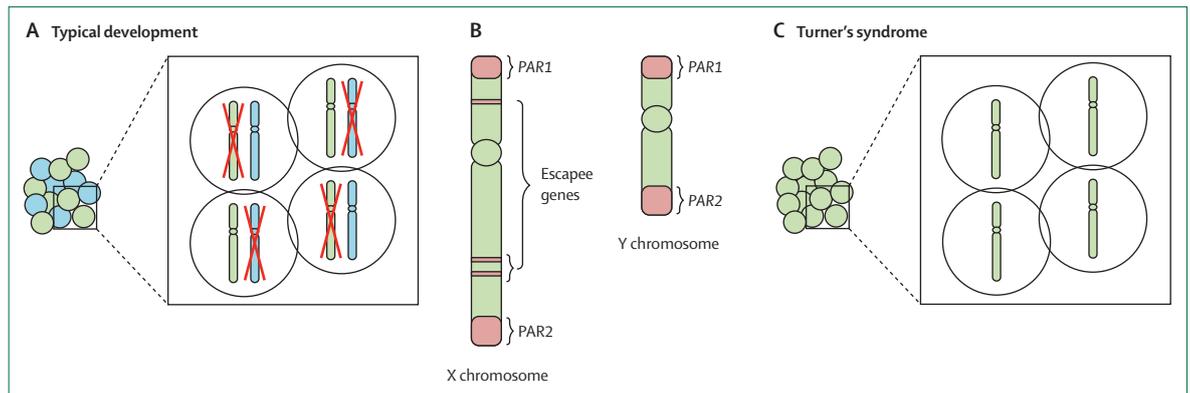


Figure 2: X inactivation

The X chromosome contains roughly 900 genes, whereas the Y chromosome has as few as 60 genes. To maintain relative gene dose equivalence between 46,XY men and 46,XX women, one X chromosome is typically inactivated in women (A). This inactivation results in a random mosaic pattern in which roughly 50% of cells have an active X chromosome of maternal origin (green) and 50% contain an active paternally inherited X chromosome (blue). (B) Exceptions to the inactivation process are: homologous pseudoautosomal regions (PAR) at the distal ends of both the X and Y chromosomes, and escapee genes that reside exclusively on the X chromosome. (C) In X-chromosome monosomy, nondisjunction results in the exclusive inheritance of one X chromosome from a single parent, resulting in all cells containing an X chromosome with the same parental origin. In this example, chromosomes are maternally inherited (green circles).

rare karyotypes who are more likely to have intellectual disability.¹⁵ However, in subdomains of cognitive ability, there is a prominent gap between verbal and performance domains of intelligence.¹⁶ Findings suggest that verbal skills, including phonological processing, receptive vocabulary, and reading comprehension, in children with Turner's syndrome are usually preserved or enhanced relative to their typically developing peers.¹⁷ By contrast, findings across studies show a relatively consistent pattern of impaired performance in higher-order non-verbal abilities, including visuomotor and mental rotation tasks, and processing speed.^{18–21} Ability in arithmetic processing is also strongly impaired. Although this ability can be affected by lower-order number skills that rely on visuospatial ability,²¹ it seems to be a distinct neuropsychological deficit.²²

Executive functioning is affected in people with Turner's syndrome, with commonly reported impairments in attention, working memory, cognitive flexibility, and abstract reasoning.^{19,23,24} Although visuospatial ability and executive function are closely inter-related, Lepage and colleagues²⁵ reported that deficits in these domains are independent in young girls with Turner's syndrome. There are also data on moderate social impairments in people with Turner's syndrome, although this finding has been more clearly defined in girls than in adult women. Impairments include core deficits in recognition of emotional affect, particularly fear,^{26,27} and impaired detection of non-verbal cues such as eye gaze.²⁸ In 2011, we showed that parents of young girls with Turner's syndrome rated their children as having more difficulty with various aspects of social functioning than their typically developing peers,¹³ although, importantly, aspects of social motivation or appetitive behaviour were similar between girls with Turner's syndrome and their unaffected peers.

Findings of imprinting effects on cognition and social functioning in Turner's syndrome have been conflicting. Data from an early study of adults with Turner's syndrome suggested that individuals with a maternally derived X chromosome were more likely to have impairments in verbal and executive function skills than were those with an X chromosome that was paternally derived.²⁹ By contrast, investigators of more recent studies of girls and adolescents with Turner's syndrome noted that a paternally derived X chromosome was associated with relatively impaired performance on verbal and non-verbal cognitive functions compared with one that was maternally derived.^{23,30} This divergence might be the result of methodological differences, but given the inclusion of distinct age cohorts in each of the studies, it might also indicate that modulating factors during puberty are particularly sensitive to epigenetic effects.

Neurological features

Apart from brain findings that correlate to cognitive aspects, the neurological features of Turner's syndrome are not well defined. Some anatomical variations are associated with Turner's syndrome, such as differences in craniofacial morphology,³¹ although the clinical significance of these findings is not clear. The most consistently reported neurological finding is early-onset sensorineural hearing loss, particularly in the high-frequency range, occurring in adults.^{32,33} Investigators have also reported impaired motor function in Turner's syndrome, with results of general surveys showing delays in gross motor milestones,³⁴ and non-specific descriptions of decreased gross-motor and fine-motor proficiency, general muscle tone, and strength, compared with those of peers.^{34–36} Although data for the motor domain are scarce and difficult to discriminate from those for cognitive control

	Turner's syndrome	Klinefelter's syndrome	XYY syndrome
Reproductive	Gonadal dysgenesis, delayed or absent pubertal development, infertility	Micro-orchidism, gynaecomastia, hypogonadism, infertility	Possible macro-orchidism
Other endocrine	Hypothyroidism	Insulin resistance or diabetes, metabolic syndrome, hypothyroidism	..
Cardiovascular	Aortic coarctation, bicuspid aortic valve, increased risk of aortic dissection, hypertension	Deep vein thrombosis, mitral valve prolapse	..
Renal	Collecting system malformations, horseshoe kidney
Neurological	Conductive hearing loss (childhood), sensorineural hearing loss (adulthood)	Seizures; tremor; non-specific motor impairments, including hypotonia	Seizures, tremor, hypotonia
Orthopaedic	Short stature, characteristic craniofacial features, scoliosis, osteoporosis (related to hypogonadism)	Tall stature, osteoporosis (related to hypogonadism)	Tall stature, macrocephaly
Pulmonary	..	Risk of pulmonary embolism	Risk of asthma
Immunological	Autoimmune thyroiditis, coeliac disease	Systemic lupus erythematosus	..
Oncological	..	Breast cancer, mediastinal germ-cell tumours	..
Lymphatic	Lymphoedema in infancy and early childhood
Intelligence	Normal FSIQ* (5–10 points below siblings), VIQ higher than PIQ	Normal FSIQ* (5–10 points below siblings), PIQ higher than VIQ	Similar to findings for Klinefelter's syndrome
Language	Reports of hyperlexia	Deficits in oral fluency, written language, reading comprehension, verbal memory	Similar to findings for Klinefelter's syndrome, although deficits can be more severe
Visuospatial	Deficits in visuomotor skills, mental rotation, spatial orientation
Arithmetic	Difficulties with calculation and subitising	Mixed evidence: some reports of arithmetic problem-solving deficits by contrast with normal mathematic-achievement scores compared with controls	Similar to findings for Klinefelter's syndrome
Executive function	Impairments in attention, processing speed, working memory, cognitive flexibility, and sequencing or planning	Similar to findings for Turner's syndrome, particularly response-inhibition impairments	Similar to findings for Klinefelter's syndrome
Speech	Possible speech issues related to hearing loss	Delay in early childhood	Similar to findings for Klinefelter's syndrome
Social	Impairments in face recognition and classification of negative emotions, parent-rated difficulties with social reciprocity and communication (for children)	Impairments in assessment of trustworthiness of faces, and classification of emotions; difficulties with social withdrawal, communication, and emotion regulation	Similar to findings for Klinefelter's syndrome
Psychiatric	Risk for ADHD and dyscalculia; equivocal evidence of autism-spectrum disorders	Increased risk for ADHD, reading disability or dyslexia, autism-spectrum disorders, depression, schizophrenia	Risk of ADHD, reading disability or dyslexia, and autism-spectrum disorders; case reports of schizophrenia

FSIQ=full-scale intelligence quotient. VIQ=verbal intelligence quotient. PIQ=performance intelligence quotient. ADHD=attention-deficit hyperactivity disorder. *Normal FSIQ is defined as around 100.

Table: Reported physiological and cognitive-behavioural features of Turner's syndrome, Klinefelter's syndrome, and XYY syndrome

and planning of motor movement, evidence suggests that motor control and speed might be affected independently of visuospatial and executive functioning, including findings of abnormal motor cortex excitability and reduced prefrontal cortical thickness in adult women with Turner's syndrome.³⁷

Imaging findings

Behavioural findings have been paralleled by several neuroimaging studies, with investigators aiming to correlate neurocognitive aspects of Turner's syndrome with brain structure and function. Generally, there is a large amount of similarity in the structural brain differences for people with X-chromosome monosomy at each of the developmental stages. The most consistent findings are decreased grey matter in the parieto-occipital regions and prefrontal cortices,^{38–40} and increased volume in temporal lobe regions, including the insula, amygdala, hippocampus, and superior temporal gyri, compared with

typically developing controls.^{41–43} The consistency of findings across studies suggests that neuroanatomical differences occur during time-sensitive developmental windows, with specific structural changes occurring by early childhood and persisting across the lifespan. However, there are also regional differences between findings in cohorts of prepubertal patients and adults with Turner's syndrome, suggesting that other areas of brain development are modifiable and putatively affected by hormonal changes during childhood or puberty.⁴⁴

Functional MRI studies have provided data for function and connectivity of neural networks associated with cognitive domains affected in Turner's syndrome. Results from studies using several different visuospatial, arithmetic, executive functioning, and social cognitive tasks converge on aberrant activation patterns in frontoparietal networks, suggesting that there might be a core neurofunctional basis that underlies many of the noted cognitive differences in Turner's syndrome.^{19,27,45,46}

The importance of frontoparietal networks is further supported by findings that microanatomical characteristics of white-matter tracts for these networks are aberrant in Turner's syndrome compared with controls.^{42,47} Investigators have also reported neuroanatomical differences linked to X-chromosome-imprinting effects, noting differences in cortical thickness and brain volume in temporal and superior frontal regions between individuals with a maternally derived X chromosome and those with a paternally derived X chromosome.⁴⁸

Clinical aspects

The neurocognitive aspects of Turner's syndrome place affected individuals at increased risk for clinical diagnoses, particularly attention and learning disorders and difficulties in social adaptation. Although the underlying mechanisms are thought to be specific to Turner's syndrome and relate to sex chromosome or hormone abnormalities or both, signs associated with the neurocognitive phenotype of Turner's syndrome correspond with clinical diagnoses, particularly in children. These risks include an 18-times increase in incidence of ADHD in girls with Turner's syndrome⁴⁹ and increased incidence of mathematical-learning disorder.⁵⁰ Clinical diagnoses of social aspects of Turner's syndrome are less sophisticated, with some evidence for increased autism-spectrum diagnoses,⁵¹ although defining social deficits in Turner's syndrome as representative of autism phenomenology is problematic.¹³ Other psychiatric diagnoses are less established and evidence for increased rates of psychiatric disorders in women with Turner's syndrome relative to other women has been mixed,^{52–54} particularly when controlling for possible confounding factors such as short stature and infertility.^{55,56} Most studies showing clinical disorders in Turner's syndrome have mainly been of children. By comparison, studies of socioeconomic and educational outcomes in adult women with Turner's syndrome show that although rates of partnerships and parenting are lower, and individual retirement age earlier, than those of their peers, many women with Turner's syndrome achieve similar years of total education, average income, and self-reported satisfaction in various domains of life.^{57–59} Naess and colleagues⁵⁸ reported that retroactive ratings of psychological stress during childhood and adolescence were increased in adult women with Turner's syndrome compared with control peers, suggesting that clinical and social features associated with Turner's syndrome follow specific developmental trajectories. Future studies of transitions from childhood to adulthood are needed to find out whether increased rates of attentional and learning disorders in girls with Turner's syndrome are identified only because of the increased prominence of these features in academic settings, or if maturational effects during adolescence result in individuals with Turner's syndrome catching up with peers in both brain and behavioural outcomes.

Reports of the few clinical interventions for cognitive and neurological symptoms in Turner's syndrome show slight effects. Ross and colleagues^{60,61} suggested that low-dose oestrogen (ethinyl estradiol 12.5–50.0 ng/kg per day) during preadolescence might have a positive effect on processing speed, memory tasks, and motor function, and that low doses of androgen might improve working memory and reduce rates of arithmetic learning disability.^{6,62} However, the small effect of these treatments might also indicate that interventions need to be targeted towards crucial developmental periods of increased neural plasticity. Interventions such as cognitive rehabilitation using mathematical learning strategies also show promise to improve neurofunctional and behavioural performance for individuals with Turner's syndrome,⁶³ suggesting that non-pharmacological treatments might also be important. Furthermore, positive findings for hormone replacement and cognitive-behavioural studies provide evidence that, rather than being deterministic, genetic differences in Turner's syndrome are tractable, and increased research of effective interventions might lead to improved clinical outcomes.

Klinefelter's syndrome (47,XXY)

Pathophysiology

Sex chromosome aneuploidies also include disorders characterised by supernumerary sex chromosomes, the most common of which is Klinefelter's syndrome. The disorder occurs as frequently as one in 600 male livebirths.⁶⁴ Individuals with Klinefelter's syndrome typically have an additional X chromosome resulting in a 47,XXY karyotype. As with Turner's syndrome, variations on this karyotype are noted, including mosaicism with 46,XY, or other karyotypes, including additional X chromosomes (eg, 48,XXXXY). Similar to Turner's syndrome, nondisjunction of sex chromosomes during gamete formation ultimately results in trisomy (figure 1), with events equally divided between paternal and maternal meiotic origins.⁶⁵ The additional X chromosome in boys with Klinefelter's syndrome undergoes X-inactivation as it does in typically developing girls. This inactivation maintains some amount of gene equivalence compared with typically developing boys and girls, although the presence of PAR and escapee genes on the X chromosome results in putative overexpression of specific genes, which probably underlies the observed phenotype. Boys with Klinefelter's syndrome are thought to have similar sex hormone concentrations to control boys until the onset of puberty, although this notion has been recently challenged.^{66,67} However, for most boys with Klinefelter's syndrome, testosterone production stops midpuberty, with varying degrees of resulting hypogonadotropic hypogonadism,⁶⁸ which might also contribute to observed Klinefelter's syndrome characteristics.

By contrast with Turner's syndrome, the physical phenotype for Klinefelter's syndrome more closely resembles typical development. Characteristics

associated with Klinefelter's syndrome are also fairly heterogeneous, although typically they include tall stature, small testes, azoospermia, and symptoms related to hypogonadism, including gynaecomastia and female habitus and body-hair distribution.

Cognitive features

By contrast with its subtle physical features, Klinefelter's syndrome is associated with a relatively consistent pattern of neurocognitive characteristics. Similar to Turner's syndrome, overall intellectual ability for individuals with Klinefelter's syndrome is in the average to low-average range and has been well characterised.⁶⁹⁻⁷¹ Detailed analyses of cognitive subdomains produce a profile that contrasts with the verbal and non-verbal intellectual

quotient in Turner's syndrome (figure 3), in which individuals with Klinefelter's syndrome generally do worse on verbal subscales than do control peers, although this finding is not always consistently reported.^{69,70,81} Evidence for more general impairments in language has been consistent, with the most widely observed deficits reported in encoding of verbal information, auditory processing, comprehension, and processing speed.^{70,82-84} Expressive speech and verbal fluency are also affected.⁸⁵ To a certain extent, verbal ability interacts with executive function processes, such as verbal working memory; therefore, executive functioning deficits, including difficulties with attention, inhibition, working memory, and cognitive flexibility,^{70,73,83,86,87} are also relatively common, although there might be some variability in these characteristics at different developmental stages.

Neurological features

Neurological and motor problems have been reported in people with Klinefelter's syndrome, although this is generally limited to observational reports of delayed motor milestones and non-specific impairments in coordination, balance, and strength.⁸⁸⁻⁹⁰ Some investigators used the standardised Bruininks-Oseretsky Test of Motor Proficiency to systematically compare coordination and gross motor function in boys with Klinefelter's syndrome and noted decreased performance on several subscales relative to normative sample means.^{70,78,79} Mechanisms underlying these differences have not been delineated, although the finding that motor impairments seem to be attenuated in boys receiving testosterone treatment suggest that some aspects of motor function might be directly related to androgen effects. There is also evidence for substantially increased rates and early onset of essential tremor in Klinefelter's syndrome based on self-report

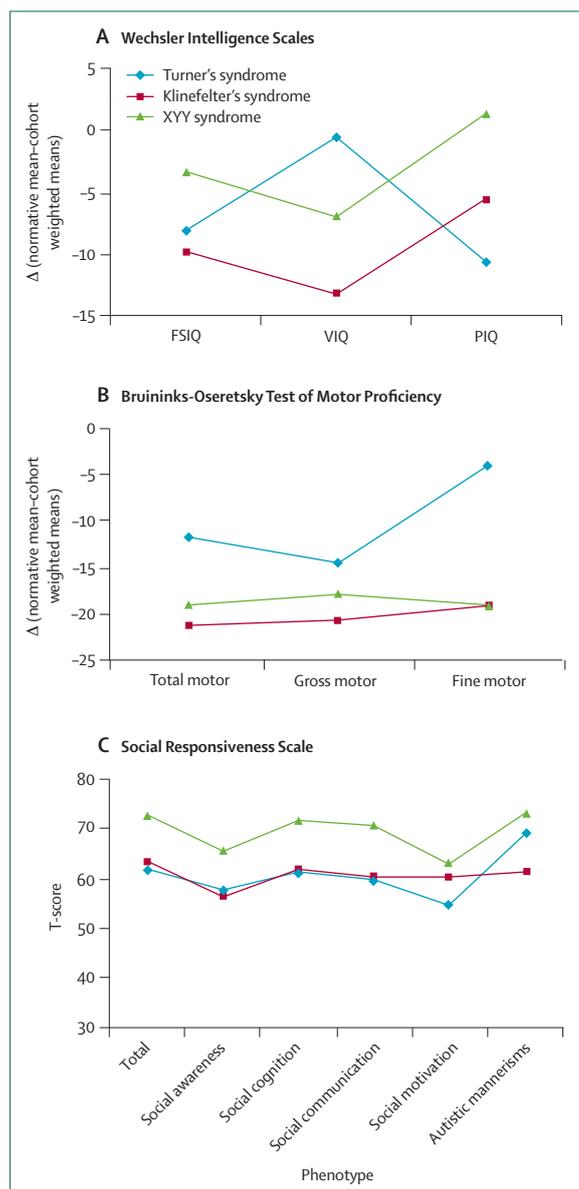


Figure 3: Behavioural phenotypes in sex chromosome aneuploidies

(A) Intelligence quotient (IQ) scores were summarised from studies using Wechsler Intelligence Scales in paediatric cohorts with Turner's syndrome,^{6,13,21,23,49,77} Klinefelter's syndrome,^{58,68,73-77} and XYY syndromes.^{58,75,77} We determined the difference between each study's reported group mean and the normative mean for Wechsler scales (100 ± 15), then we calculated a weighted mean score across all studies for each group, showing overall full-scale IQ in the average to low-average range and preserved verbal IQ in Turner's syndrome compared with relatively intact performance IQ in Klinefelter's syndrome and XYY trisomies. (B) By contrast, relative differences between reported group and normative means on the Bruininks-Oseretsky Test of Motor Proficiency suggest that motor impairments are more generalised across Turner's syndrome,^{34,35} Klinefelter's syndrome,^{70,78,79} and XYY⁷⁸ cohorts, as measured by total motor, gross motor, and fine motor composite scores. (C) Weighted mean scores from studies using the Social Responsiveness Scale show T-scores in the mild-to-moderate clinically significant range (60-75; higher scores indicate increased severity of social impairment) for individuals with Turner's syndrome¹³ and Klinefelter's syndrome,^{75,80} and particularly for individuals with XYY syndrome.⁷⁵ Given the range of ages included in the various studies, differences in specific assessments (Wechsler Intelligence Scales), and the small number of studies available for motor and social functioning, data included in this figure are used mainly for purposes of illustration only. FSIQ=full-scale intelligence quotient. VIQ=verbal intelligence quotient. PIQ=performance intelligence quotient.

questionnaires, although data are scarce.⁹¹ Lastly, several case reports and retrospective studies have associated Klinefelter's syndrome with increased rates of epilepsy.^{92–95} Given the high prevalence of Klinefelter's syndrome, it is difficult to assess whether rates of epilepsy exceed what would be expected in the general population, but results of retrospective morbidity studies of large British and Danish registries suggest a true increase in risk.^{96,97}

Imaging findings

Neuroimaging findings show consistent neuro-anatomical and functional differences relative to control peers in brain regions associated with cognitive domains affected in Klinefelter's syndrome. Most notably, several anatomical imaging studies have shown higher grey-matter volume in the parieto-occipital and sensorimotor cortices, and lower volume in insula and temporal regions, including subcortical structures such as the amygdala and hippocampus;^{98–101} the inverse of the anatomical pattern observed in Turner's syndrome (figure 4). Investigators have also reported aberrant brain structure in the prefrontal cortex, cerebellum, and lateral ventricles.^{101,102} Only two functional MRI studies have been done in people with Klinefelter's syndrome; one showed decreased recruitment of limbic structures during social judgment of faces,¹⁰³ and the other showed increased bilateral activation in temporal regions during language tasks.¹⁰⁴

Lateralisation effects in structural and functional neuroimaging findings have been much discussed by investigators, especially because of the functional lateralisation of language-related ability to the left hemisphere in typical development. There have been mixed results in studies: some showed more pronounced grey-matter decreases in the left temporal region than in the right;^{99,105} and others showed symmetrical bilateral reductions in this region.^{106,107}

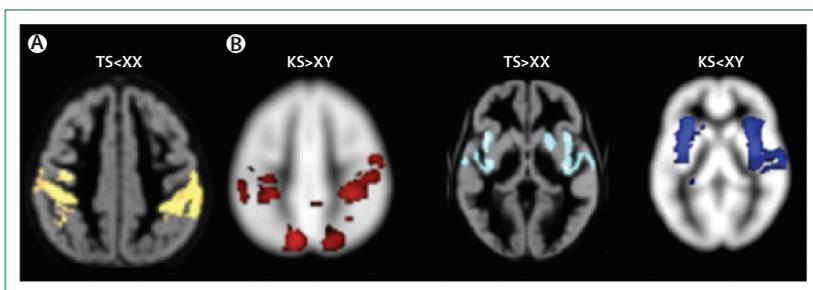


Figure 4: Voxel-based morphometry findings

Independent studies of individuals with Turner's syndrome compared with typically developing girls³⁸ (clusters significant at $p < 0.05$ family-wise error corrected), and of boys with Klinefelter's syndrome compared with typically developing boys³⁸ (clusters significant at $p < 0.01$ family-wise error corrected), using whole-brain voxel-based morphometry show complementary patterns of grey-matter volume aberration. (A) Although grey-matter volume in parietal regions is lower in Turner's syndrome than in control girls, grey-matter volume in the same area is higher in boys with Klinefelter's syndrome than in control boys in a parallel study. (B) Similarly, higher temporal and insular grey-matter volume is noted in girls with Turner's syndrome relative to control girls, and lower volume is noted in these areas for boys with Klinefelter's syndrome than for control boys. TS=Turner's syndrome. KS=Klinefelter's syndrome. XX=typically developing girls. XY=typically developing boys.

Results from functional imaging studies favour the hypothesis that the expected asymmetries are absent in individuals with Klinefelter's syndrome, as measured by activation patterns¹⁰⁴ and cerebral perfusion¹⁰⁸ during verbal tasks.

Clinical aspects

The clinical aspects of Klinefelter's syndrome tend to be language-related disorders. Global delays in speech might be evident in early development,¹⁰⁹ and longitudinal studies show that language-related learning disabilities often become prominent by early school age (age roughly 5–13 years), including difficulties with reading and writing.^{69,82,110} Up to 80% of individuals with Klinefelter's syndrome meet criteria for a learning disorder (mainly related to language),¹¹¹ with high use of special-needs education and speech therapy services for school-age children,^{112,113} and persistent difficulties through adulthood.⁸¹ Difficulties in these cognitive domains might contribute to findings that overall adaptive functioning is affected in Klinefelter's syndrome, with evidence for lower levels of education, income, and rates of employment; earlier retirement; fewer children; and decreased likelihood of partnership as adults than have men without Klinefelter's syndrome.^{4,96} Given the evidence for impaired executive functioning in Klinefelter's syndrome, it is not surprising that rates of attention-deficit hyperactivity disorder are nearly 50% in this population, with symptoms being particularly prominent in the inattention domain.^{58,114} However, the four-times higher incidence of schizophrenia^{73,115} and the high rate of schizotypal traits in individuals with Klinefelter's syndrome are surprising.⁷⁴ These findings are based on small clinical samples, which might show some ascertainment bias. However, investigators should consider the possibility that brain anomalies in Klinefelter's syndrome might provide a genuine link to psychotic disorders.⁵⁹ In addition, by contrast with Turner's syndrome, individuals with Klinefelter's syndrome have higher rates of general psychiatric diagnoses relative to the general population, including depression,¹¹⁶ autism,⁸⁰ and bipolar disorder.^{86,117} Neurobiological mechanisms for these findings have not been established and it is possible that rates are affected by environmental and genetic factors unrelated to the additional X chromosome.¹¹⁸

Results of interventions for neurocognitive and psychiatric symptoms are mixed and findings are mainly from cross-sectional analyses that subgroup individuals with Klinefelter's syndrome by testosterone-replacement status. However, some evidence suggests that treatment with testosterone might positively affect general wellbeing, concentration, verbal fluency, and motor function,^{70,105,119} including tremor.¹²⁰ However, placebo-controlled prospective studies are needed to systematically address this question.

XYX syndrome (47,XYX)

Pathophysiology

XYX syndrome is another common supernumerary sex chromosome aneuploidy with an incidence of one in 1000 male livebirths.³ The genetic mechanism for XYX syndrome also stems from nondisjunction; however, given that the karyotype is two Y chromosomes, errors exclusively result from the paternal gamete, typically during the second stage of meiosis.¹⁰ Other than early and controversial reports of behavioural features of XYX syndrome, there is a notable paucity of research on the disorder, despite its relative frequency, especially in relation to Turner's syndrome and Klinefelter's syndrome. This might be partly because physical characteristics of XYX syndrome are difficult to distinguish from typical development. Features can include tall stature in adulthood, increased testicular volume, orbital hypertelorism, and macrocephaly;¹²¹ however, there is no clear association of XYX syndrome with abnormal gonadotropic function.

Cognitive features

There has been much debate about the association of XYX syndrome with a particular cognitive-behavioural phenotype. Early reports were confounded by findings that men of tall stature in criminal institutions had an increased incidence of the 47,XYX karyotype compared with the general population.^{122,123} These data resulted in an unfortunate correlation of the karyotype with increased aggression and criminality; however, this theory has mostly been discounted given the substantial methodological flaws in sample selection for those studies. In a study in 2012,¹²⁴ researchers noted that although the absolute rate of criminal convictions in sex chromosome trisomies was increased, there were no significant differences relative to controls after accounting for socioeconomic variables, suggesting that this observation is unrelated to karyotype in itself. However, consistent evidence does suggest that a characteristic neurocognitive phenotype is present. Findings suggest that overall intelligence is within the normal or slightly low-average range,^{78,121,125} and verbal subdomains are particularly affected, similar to Klinefelter's syndrome (figure 3), although there is broad individual variability.¹¹³ Verbal impairments include difficulty in naming, receptive vocabulary, and oral fluency.^{78,114,115,121,125} Large overlap seems to exist in the cognitive profiles between individuals with Klinefelter's syndrome and those with XYX syndrome, mainly characterised by deficits in executive function and language-related skills.¹²⁶ Results of studies that have directly compared both cohorts suggest that deficits might be greater in the XYX syndrome group than in the group with Klinefelter's syndrome.⁷⁸

Neurological features

Neurological features of XYX syndrome also closely resemble those reported in Klinefelter's syndrome,

including generalised findings of delayed motor development, intention tremor, decreased fine-motor coordination, balance, and strength.^{101,112,126} These findings relied on parental reporting and should be interpreted with some caution; however, studies using standardised motor function assessments provide further confirmation of motor-planning dysfunction, hypotonia, impaired coordination, and decreased speed and strength.^{78,79} Similar to Klinefelter's syndrome, some reports suggest higher rates of epilepsy in individuals with XYX syndrome, although evidence for this is limited to case reports and evidence of higher mortality because of epilepsy in British and Danish cohort analyses.¹²⁷⁻¹²⁹ Lastly, case reports of posterior fossa malformations have been published, although this feature is of unclear clinical significance.¹³⁰

Imaging findings

Neuroimaging data for XYX syndrome are sparse. There have been only two published studies assessing structural brain differences. Although one study showed no significant difference in total or regional brain volumes between a group of men with XYX karyotype and typically developing males,¹³¹ a 2012 study by Bryant and colleagues¹³² noted increased total grey-matter and white-matter volumes compared with typically developing controls and boys with Klinefelter's syndrome. Bryant and colleagues used pattern-classification algorithms to distinguish XYX neuroanatomy from that of typically developing controls with a high degree of accuracy. They reported that pattern classifiers for boys with XYX syndrome compared with controls closely resembled those for boys with Klinefelter's syndrome compared with controls, implying a high amount of overlap in abnormalities in brain structures. Anatomical variation in regions relating to language and motor ability, including the insula and frontotemporal lobes, were shown to be particularly relevant for discrimination of both groups from controls, suggesting a shared neuroanatomical basis for these disorders.

Clinical aspects

Behavioural studies of XYX syndrome have shown variable results with some stratification on the basis of whether research cohorts were prenatally diagnosed or clinically referred postnatally diagnosed patients. However, data are fairly consistent about increased impulsivity and externalising behaviours,^{112,113,133} which also translates to rates of attention-deficit hyperactivity disorder of up to 62% for individuals with XYX syndrome.¹¹⁴ Delayed language development and difficulties with verbal fluency and reading are also frequently present,^{78,110,114} resulting in increased use of special-needs education resources.¹²⁶ Social skills are frequently reported as being impaired in boys with XYX syndrome, with a higher likelihood of clinically significant scores on standardised social screening assessments^{58,75,114} and higher incidence of autism-spectrum disorders compared with typically developing boys. As a corollary, men with XYX syndrome

also seem to be affected on global socioeconomic measures, with lower levels of education, earlier retirement, reduced chance of finding a partner or becoming a father, and lower life expectancy compared with matched controls without XYY syndrome. Men with XYY syndrome had fewer partnerships and a lower income than had men with Klinefelter's syndrome, but were more likely to become fathers, which is not surprising given that infertility is not a core feature of XYY syndrome.¹²⁷ Evidence across lifestages suggest that clinical issues are more likely to persist into adulthood for men with Klinefelter's syndrome and XYY syndromes than for women with Turner's syndrome, perhaps indicating increased penetrance of underlying neurocognitive deficits, or possibly showing interactive effects with age-related factors, sex-related factors, or both, that ultimately result in different developmental trajectories. This observation warrants further investigation. Not many studies of interventions have been undertaken, mainly because men with XYY syndrome do not have sex hormone deficiencies. One of the few pharmacological studies indicated that stimulant treatment with methylphenidate might have a positive effect on motor and cognitive function and social adaptation, as might also be expected in children with attention-deficit hyperactivity disorder who do not have sex chromosome abnormalities.¹³⁴

Other sex chromosome aneuploidies

Published work on other sex chromosome aneuploidies is scarce. Some early studies have been done of triple X or 47,XXX syndrome, which occurs in roughly one in 1000 female livebirths; however, the paucity of recent investigations is probably due to the lack of knowledge of phenotypic traits associated with this disorder, other than increased stature.^{109,135} Interestingly, neuropsychological studies of women with 47,XXX indicate a cognitive profile similar to other sex chromosome trisomies (Klinefelter's syndrome and XYY syndrome), including average overall intellectual quotient, and a gap between verbal and performance intelligence, with deficits skewed towards poorer performance on verbal domains compared with non-verbal domains.^{136,137} Similar to other sex chromosome trisomies, performance on a wide range of executive function tests is also impaired,¹¹⁰ as is academic achievement in reading and language.^{109,112,137} Impaired social adaptation, increased rates of psychopathology,^{76,113} and global delays in motor milestones and gross-motor and fine-motor coordination have also been noted.³⁴

Aneuploidies with more than three sex chromosomes, such as 48,XXXX, 48,XXYY, 48,XXXYY, 49,XXXXYY, and 49,XXXYY, are rare—about one in 18 000–100 000 livebirths.^{138,139} Only a few studies have been done of the cognitive and neurological features of these aneuploidies, and many findings rely on case reports of patients postnatally identified after clinical referral, probably skewing the generalisability of findings. However, data

suggest that phenotypes resemble commonly identified traits in other sex chromosome trisomies, including impaired verbal and language-related abilities, relative preservation of spatial processing skills, impaired executive function, and general behavioural issues related to impulsivity and decreased social adaptation.^{140,141} Compared with sex chromosome trisomies, it seems that the presence of additional X and Y chromosomes increases the severity of these core phenotypic features, with most identified individuals having substantial psychomotor delay in developmental milestones, some degree of general intellectual disability, and pronounced gaps between verbal and performance subdomains.¹⁴² Furthermore, cognitive symptoms worsen in direct relation to the number of supernumerary chromosomes: individuals with pentasomies seem more affected than those with tetrasomies.^{143,144} To a certain extent, this relation also seems to be consistent with neurological features such as motor symptoms, including hypotonia in early development and significant delays in the acquisition of motor milestones.^{141,144,145} With regard to sex hormone deficiencies, polysomies of X and Y chromosomes are commonly associated with hypergonadotropic hypogonadism and associated sexual characteristics such as micro-orchidism, similar to Klinefelter's syndrome.¹⁴⁰

Similarities across disorders

Sex chromosome aneuploidies create a broad range of observed phenotypes, with substantial variability in associated cognitive and neurological features. This variability might be partly due to ascertainment biases associated with these disorders, including the fact that girls with Turner's syndrome are more likely to present with a prominent physical phenotype, resulting in earlier detection and enrolment in services, whereas boys with sex chromosome trisomies frequently are not detected until adolescence or adulthood. Similarly, given the wide prevalence of sex chromosome aneuploidies, an additional challenge for investigators is appropriate randomisation of inclusion for study participants, such that extrapolation of findings are relevant to most individuals affected with these disorders. However, within the subset of individuals included in the published work, findings associated with the disorders are largely consistent and replicable. Furthermore, after assessment of the totality of these features across groups, overarching physiological and cognitive-behavioural symptom patterns emerge. For example, some specific cognitive and neurological domains seem to be affected across all disorders. These shared features include gross impairments in executive functioning—which is not entirely surprising because this complex higher cognitive function is affected in several neurodevelopmental syndromes—but also include impairments in motor skills and higher-order social cognitive ability. An apparent dose effect exists between number of sex chromosomes and performance in

cognitive subdomains of language and visuospatial ability, with monosomy putatively linked with non-verbal deficits, and polysomy correlated with language-based impairments. This continuum seems linear in the progression from one to three chromosomes, and then shows marked acceleration of effects as the number of sex chromosomes increases beyond three, albeit in the context of a global reduction in cognitive abilities. Findings in neurocognitive domains are paralleled by physical findings such as height, which also shows a non-linear trajectory as the number of sex chromosomes increases.¹⁴⁶ Similarly, qualitative comparisons of neuroimaging findings from studies of Turner's syndrome and Klinefelter's syndrome also suggest dose effects in grey-matter volume in regions correlated with affected cognitive domains. Taken together, these findings increasingly elucidate a framework for sex chromosome effects that occur independently of hormonal influences on neurodevelopment, a crucially important concept that has been difficult to investigate in human populations.

With regard to clinical management, consensus guidelines specifically addressing neurocognitive symptoms in sex chromosome aneuploidies are still absent, despite a broad evidence base indicating that these substantially affect adaptive functioning, particularly in childhood. As such, clinicians should thoroughly assess for neurocognitive, motor, and social functioning in individuals with sex chromosome aneuploidies, and maintain a low threshold for neuropsychological testing to establish cognitive profiles for individual patients. Partnership with schools is also useful to provide specific psychoeducational services when learning issues are present. Furthermore, difficulties with executive functions are a prominent theme across all sex chromosome aneuploidies and deficits in this domain might result in substantial difficulties for affected individuals, including impairments in processes of sequencing, working memory, inhibition, and cognitive flexibility. Although cognitive and behavioural treatments specific to sex chromosome aneuploidies have not been widely studied, interventions targeted towards ameliorating executive function deficits might provide large benefit for individuals with sex chromosome aneuploidies.

Future directions

Future research in this area has profound implications for clinical and research domains in its potential to clarify the effect of sex chromosome genes on neurocognitive functions. Genomic technologies provide powerful methods to elucidate the genetic mechanisms associated with sex chromosome function. Mammalian studies have already shown that processes moderating X-chromosome inactivation and dose compensation between the X chromosome and autosomes are more complicated than was previously thought.¹²⁰ Specific focus on dysfunction of these mechanisms in sex chromosome aneuploidies is

Search strategy and selection criteria

We searched PubMed using a search string of the names of sex chromosome aneuploidies ("Turner syndrome", "Klinefelter syndrome", etc). We restricted results to only reports of human clinical studies published from Jan 1, 2003, to Jan 1, 2014, and relevant studies from earlier years. We considered only original studies published in peer-reviewed journals in English. We generated the final reference list on the basis of relevance to the topics in this Review.

needed to better understand their contribution to resulting syndromic phenotypes, with particular attention on the identification of which genes in PAR and regions escaping inactivation are ultimately implicated in aberrant neuronal development. Furthermore, improved understanding of the genotype–phenotype relation in sex chromosome aneuploidies might lead to new insights for sex differences in neurodevelopment, and, ultimately, link genetic biomarkers to neuroendophenotypes and cognitive–behavioural phenotypes. Further work on clinical interventions and genetic and molecular therapeutic targets is needed, given the relatively few clinical options that are available. Although clinicians could have a substantial effect on patients' quality of life by increasing their awareness of these disorders and referring affected individuals for neuropsychological evaluations or hormone replacement when indicated, more effective interventions are crucial to address the neurological features we describe. Future studies focusing on these issues have great potential to improve treatment for sex chromosome aneuploidies and also to increase understanding of genetic influences on sex differences in general.

Contributors

Both authors did the literature search, created the figures, and wrote and revised the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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