The contribution of Xp22.31 gene dosage to Turner and Klinefelter syndromes and sex-biased phenotypes

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Abstract

Turner syndrome (TS) is a rare developmental condition in females caused by complete, or partial, loss of the second sex chromosome; it is associated with a number of phenotypes including short stature, ovarian failure and infertility, as well as neurobehavioural and cognitive manifestations. In contrast, Klinefelter syndrome (KS) arises from an excess of X chromosome material in males (typical karyotype is 47,XXY); like TS, KS is associated with infertility and hormonal imbalance, and behavioural/neurocognitive differences from gonadal sex-matched counterparts. Lower dosage of genes that escape X-inactivation may partially explain TS phenotypes, whilst overdosage of these genes may contribute towards KS-related symptoms. Here, I discuss new findings from individuals with deletions or duplications limited to Xp22.31 (a region escaping X-inactivation), and consider the extent to which altered gene dosage within this small interval (and of the steroid sulfatase (*STS*) gene in particular) may influence the phenotypic profiles of TS and KS. The expression of X-escapees can be higher in female than male tissues; I conclude by considering how lower Xp22.31 gene dosage in males may increase their likelihood of exhibiting particular phenotypes relative to females. Understanding the genetic contribution to specific phenotypes in rare disorders such as TS and KS, and to more common sex-biased phenotypes, will be important for developing more effective, and more personalised, therapeutic approaches.

Keywords

Turner syndrome

Turner syndrome (TS) is a rare developmental disorder thought to affect between 15-60 of every 100 000 live female births (Berglund et al., 2020). The condition is attributable to loss of sex chromosome material: the most common genetic signature associated with TS is X-monosomy (45,X) where the second sex chromosome is completely absent (40-60% of cases). In 10-20% of cases TS results from 45,X/46,XX mosaicism (i.e. where individuals possess a mixture of cells with a single X chromosome, and cells with the usual complement of two X chromosomes), and the remainder of cases are caused by karyotypes containing an isochromosome, ring X chromosome, and other rare sex chromosome variants (Berglund et al., 2020). TS is a fascinating condition, in that a high proportion (>95%) of foetuses with the abnormal karyotypes above die *in utero* or in the neonatal period (Dotters-Katz et al., 2016; Trolle et al., 2016; Vigna Goulart et al., 2016), but many of those who do survive the perinatal period have good clinical outcomes (Bondy 2009). Mortality, morbidity and symptom severity in TS appear related to karyotype, with a higher contribution of XX cells being associated with reduced adverse effects (Bondy 2009).

TS is associated with a wide range of physical phenotypes and diverse effects on multiple physiological systems (Gravholt et al., 2019). Skeletal maldevelopment as a consequence of reduced longitudinal bone growth can result in short stature, delayed skeletal maturation, angular deformity of the limbs, spinal deformity and early-onset osteoporosis (Acosta et al., 2019). Ovarian dysfunction, and consequent depletion of circulating sex hormones commonly results in primary amenorrhea and infertility (Grynberg et al., 2016; Morgan, 2007). Elevated mortality and morbidity rates in TS compared to 46,XX females are predominantly due to increased rates of cardiovascular disease and diabetes (Davis and

Geffner, 2019). Individuals with TS can display structural cardiac abnormalities including aortic and valvular anomalies (resulting in aortic dilation and dissection in some cases)(Allybocus et al., 2018); an elevated frequency of supraventricular arrhythmia and atrial fibrillation has also been in individuals with TS (Cho et al., 2020; Sozen et al., 2008). Cardiac disease and diabetes risk in TS may be exacerbated by hypertension, abdominal obesity, dyslipidemia, and elevated fasting glucose (Davis and Geffner, 2019). Other features reported in TS cases include congenital lymphodema, renal defects, sensorineural hearing loss, craniofacial dysmorphic signs, urinary system abnormalities, dermatological and autoimmune conditions, webbed neck, misshapen ears, and a broad chest with widely-spaced nipples (Kilinc et al., 2020; Morgan, 2007).

Most published studies report a poorer quality of life in individuals with TS compared to 46,XX females (Liedmeier et al., 2020), although this is not always the case (Reis et al., 2019). Poorer quality of life in women with TS may stem from a combination of physical challenges (Van den Hoven et al., 2020) and difficulties with social communication from adolescence onwards (Wolstencroft and Skuse, 2019). Unpartnered women with TS report very low-level sexual functioning and delayed sexual activity, but in partnered women with TS, sexual function appears similar to that in women without the condition (Cardona Attard et al., 2020; Pavlidis et al., 1995; Sheaffer et al., 2008). Consistent with the quality of life findings, TS is associated with higher rates of mood and anxiety disorders which tend to onset after adolescence (Anam et al., 2007; Cardoso et al., 2004; de Vries et al., 2019; Hutaff-Lee et al., 2019; Kilic et al., 2005; Liedmeier et al., 2020; Moonga et al., 2017; Morris et al., 2020), and related traits such as irritability (Li et al., 2017); severe postpartum depression with psychotic features has been described in one patient with TS who gave birth following egg donation (Shea and Wolfman, 2017). There is some evidence that individuals with Turner

syndrome, particularly mosaic subjects, are at increased risk of schizophrenia, a psychotic disorder with neurodevelopmental antecedents (Jung et al., 2014; Lee et al., 2018; Mavrogiorgou et al., 2019; Prior et al., 2000; Roser and Kawohl, 2010). TS is also associated with elevated rates of other developmental psychological disorders i.e. conditions arising predominantly from perturbed pre- or perinatal development, with symptoms present from early life onwards. Rates of Attention Deficit Hyperactivity Disorder (ADHD), a condition characterised by severe inattention, pathological impulsivity and hyperactivity, may be up to 18-fold higher in subjects with TS than in 46,XX females (Green et al., 2015; Green et al., 2017; Liedmeier et al., 2020; Lo-Castro et al., 2011; Russell et al., 2006). Rates of autism and associated traits e.g. communication and language problems and repetitive or inflexible behaviours, have also been reported to be higher in TS than in 46,XX individuals (Knickmeyer and Davenport, 2011; Liedmeier et al., 2020; Marco and Skuse, 2006), although the magnitude of the effect appears lower than for ADHD, and some studies have reported no clear between-group difference (Lepage et al., 2014). Other neurodevelopmental phenotypes including dyscalculia (Karipidis and Hong, 2020), dyslexia (Simpson et al., 2014) and motor/co-ordination problems (Nijhuis-van der Sanden et al., 2003), are more common in females with TS than in unaffected individuals.

Neuropsychological studies have defined a neurocognitive profile characteristic of TS (Hong and Reiss, 2012). Affected individuals typically demonstrate a verbal IQ (VIQ) similar or marginally lower than that of individuals without TS; subjects with TS have a performance IQ (PIQ) around 20 points lower than this (Green et al., 2017) with the VIQ-PIQ discrepancy being largely due to visuospatial perceptual and processing deficits (Murphy et al., 1994; Pennington et al., 1985; Temple and Carney, 1995). The visuospatial deficits, and the elevated risk of developmental conditions such as ADHD in TS, appear related to underlying impaired

executive function (Lepage et al., 2011); executive function deficits in TS appear to be largest with respect to attentional control and working memory, and also encompass problems with cognitive flexibility and behavioural inhibition (Green et al., 2015; Mauger C et al., 2018; Romans et al., 1998; Ross et al., 1995; Ross et al., 2002; Rovet and Ireland, 1994). Neuropsychological analyses have revealed impaired perception of emotional state in others in subjects with TS, particularly with respect to fear recognition (Hong et al., 2014; Lawrence et al., 2003).

An important research question with implications for clinical treatment is whether the physical, psychiatric, behavioural and cognitive phenotypes associated with TS are due to direct effects of the genetic abnormality, to secondary effects arising from hormonal perturbation, or from a combination of the two. Early supplementation with growth hormone appears to partially rescue the short stature phenotype in TS (Ahn et al., 2019; Gravholt et al., 2019), whilst female sex hormone replacement therapy (HRT) has been shown to alleviate multiple physical and metabolic measures (Gravholt et al., 2019). HRT also appears to enhance self-esteem, and boosts some aspects of social-emotional function and cognition (notably verbal and non-verbal memory, processing speed and motor function)(Gravholt et al., 2019). However, there remain multiple cognitive deficits in TS patients that are insensitive to either growth or sex hormone administration (Freriks et al., 2015; Ross et al., 2002; Ross et al., 2003; Ross, 2005; Ross et al., 2006), and the TS cognitive profile appears distinct from that seen in individuals with similar ovarian hormonal insufficiency (Ross et al., 2004). Hence, it is likely that genetic factors contribute directly to the behavioural and cognitive profile associated with TS, independently of hormonal factors.

The psychiatric, behavioural and cognitive phenotypes described above are presumably underpinned by neuroanatomical and functional changes within the brains of individuals with TS. Neuroanatomical studies have described: a) lower grey and white matter volumes in the premotor, somatosensory and parietal-occipital cortex, b) enlarged orbitofrontal cortex and amygdala volumes, and c) relatively 46,XX-like basal ganglia and cerebellar development in adolescents and adults with TS (Knickmeyer and Hooper, 2019; O'Donoghue et al., 2020). Importantly, decreased grey matter volume in cortical areas is seen in infants with TS who have not experienced persistent hormonal perturbation and restorative treatment, and who have been subject to limited socialisation (Davenport et al., 2020). These data suggest that some key TS neuroanatomical phenotypes result largely from prenatal, or early postnatal, processes rather than later hormonal exposure; again, this is consistent with a contributory direct genetic effect on phenotype.

The genetic basis of Turner syndrome

In the majority of cases, TS is caused by the absence of part, or all, of a sex chromosome. There are several genetic mechanisms that can explain how this chromosomal loss gives rise to the features associated with TS.

First, there is the possibility that the absence of second sex chromosome material allows the expression of phenotypes associated with X-linked genetic variants on the intact chromosome; preferential inactivation of an X chromosome with deleted material may also elicit this effect (Skuse et al., 1997). However, the same variants will not be present in all subjects with TS, and hence they are unlikely to explain phenotypic commonalities across all this group. A second possibility is the presence of cryptic Y-linked sequences in the cells of some individuals; the limited gene content of these sequences, their restricted expression

pattern, and their comparative rarity (<10% of TS cases) indicates that their contribution to most TS phenotypes is limited (although there may be a possible association with increased gonadal cancer risk (Dabrowski et al., 2020; Kwon et al., 2017). The parental origin of the intact X chromosome in TS cases may also influence phenotype, although results from studies comparing physical and brain/behavioural phenotypes in subjects with maternally- or paternally-inherited intact X chromosomes are inconsistent and to date, no candidate genomically-imprinted X-linked genes have been identified in humans (Bondy et al., 2012; Davies, 2010; Hamelin et al., 2006; Ko et al., 2010; Lee et al., 2014; Lepage et al., 2013; O'Donoghue et al., 2020; Sagi et al., 2007; Skuse et al., 1997).

The most straightforward explanation for the majority of TS features is that they are a consequence of reduced dosage for X-linked genes which typically escape X-inactivation (i.e. genes which, in 46,XX females, are expressed from both X chromosomes). This reduced gene dosage may impact the phenotype directly, or indirectly e.g. through perturbed hormonal pathways. In humans, it is thought that up to one third of X-linked genes escape X-inactivation at some developmental timepoint and in at least one tissue/cell type (Carrel et al., 2005; Tukiainen et al., 2017); these so-called 'X-escapees' are present in the pseudoautosomal regions at the telomeric ends of the short and long arms of the X chromosome (PAR1 and PAR2 respectively), and tend to cluster disproportionately on the short arm of the X chromosome (Xp), perhaps reflecting their recent evolutionary addition (Carrel et al., 2005). The fact that X-monosomic (39,XO) mice recapitulate several TS phenotypes (Arnold, 2019; Hinton et al., 2015; Lynn and Davies, 2007) provides further evidence that dosage of X-linked genes (some of which escape X-inactivation across species) rather than the alternative genetic mechanisms described above largely link TS genotype with phenotype. However, the relationship between genotype and phenotype in TS is complex, does not directly map from

one to the other, and is dependent upon transcriptional and epigenetic factors affecting gene expression across the genome (Viuff et al., 2019).

Nevertheless, there are strong candidate X-inactivation-escaping regions/genes for some TS physical phenotypes. For example, haploinsufficiency for the SHOX protein encoded by a PAR1 gene may explain skeletal abnormalities (Binder, 2011), and haploinsufficiency for KDM6A, PRKX and TIMP1 may explain ovarian dysfunction, urinary malformations and aortic abnormalities respectively (Trolle et al., 2016). Expression screens such as that recently performed in lymphoblastoid cell lines from sex chromosome ploidies could feasibly highlight additional candidates for TS-relevant physical symptoms e.g. haploinsufficiency for the transcription factor ZFX, a mediator of wider genome expression, may feasibly underpin multiple relevant phenotypes (Raznahan et al., 2018).

In terms of the neurobehavioural features of TS, haploinsufficiency for one or more proteins encoded by the Xp11.3 region (possibly EFHC2) has been suggested to explain fear recognition deficits and related changes in amygdala and orbitofrontal cortex morphology (Good et al., 2003; Weiss et al., 2007). Using a composite neuropsychological measure assaying multiple cognitive constructs, in parallel with a deletion mapping strategy, Zinn and colleagues (2007) suggested that haploinsufficiency for one or more genes within a small interval (31 genes) on Xp22.3 might explain some of the cognitive deficits reported in TS independently of effects on hormonal levels, short stature, age and X-inactivation status. On the basis of known functions, the authors proposed the *STS* and *NLGN4X* genes at Xp22.31 (**Figure 1**) as promising candidates.

Of the genes implicated by Zinn et al., only *STS* and the adjacent *HDHD1(A)/PUDP* gene have consistently been shown to escape X-inactivation; the *PNPLA4* gene probably also

escapes to some extent (Johnston et al., 2008; Raznahan et al., 2018; Tukiainen et al., 2017; Zhang et al., 2013). Escape from inactivation does not appear to be complete, with expression/activity of *STS* on the inactivated X chromosome being just under half that of the gene on the active X (Lykkesfeldt et al., 1984). The X-inactivation status of the *VCX* and *NLGN4X* genes, and of the nearby *MIR651*, *MIR4770* and *MIR4767* microRNAs, is less clear; *NLGN4X* appears to show some variability in its degree of escape (Tukiainen et al., 2017). The location of the aforementioned genes is shown in **Figure 1**, with details of the their functional annotation provided in **Table 1**. Consistent with its gene's escape from X-inactivation, individuals with TS have reduced STS enzyme activity (approximately 1.5 times) relative to unaffected females (Lykkesfeldt et al., 1984).

Genetic deletions of Xp22.31 are relatively common within the general population, present in around 1 in 1500 males and 1 in 750 females (Brcic et al., 2020; Craig et al., 2010; Langlois et al., 2009). Assessing a wide range of phenotypes in these individuals should provide insights into the extent to which haploinsufficiency for this region might explain TS features. It should be pointed out that, although haploinsufficiency for gene products from within the deleted interval is the most parsimonious explanation for any phenotypic effects, these may also arise as a consequence of mis-expression of genes adjacent to the deleted interval, or of more widespread chromosomal structure changes.

Reduced dosage of Xp22.31: contribution to TS phenotypes

The most commonly-observed genetic deletion at Xp22.31 is approximately 1.6Mb in size, and spans the *STS*, *PUDP*, *PNPLA4* and *VCX* genes, and the *MIR4767* microRNA (Brcic et al., 2020). Deletion of X chromosome-specific material at Xp22.31 in hemizygous males (or in females with TS (Solomon and Schoen, 1971)) has been associated with a number of physical

and neurobehavioural phenotypes. The most noticeable association, arising from deficiency for the steroid sulfatase enzyme, is with the dermatological condition X-linked ichthyosis (XLI), characterised by scaly skin; other associations include corneal opacities, cryptorchidism, and cardiac arrhythmia (atrial fibrillation/flutter)(Brcic et al., 2020; Fernandes et al., 2010). Neurobehavioural associations include an increased risk of developmental and mood disorders (notably autistic spectrum conditions, Attention Deficit Hyperactivity Disorder (ADHD, especially inattentive ADHD), and depression), as well as higher levels of traits linked to these diagnoses i.e. inattention, impulsivity, hyperactivity, motor problems, behavioural inflexibility, depressive-anxiety traits, irritability, and difficulties with social interaction (Brcic et al., 2020; Chatterjee et al., 2016; Diociaiuti et al., 2019; Rodrigo-Nicolas et al., 2018). A recent case report has described early-onset psychotic disorder in a boy with a typical XLI-associated deletion (Malik et al., 2017), although psychosis in patients with XLI appears to be rare. In contrast, epilepsy is commonly-observed in patients with XLI, and larger, atypical deletions encompassing the *NLGN4X* and multiple *VCX* genes are associated with other neurological manifestations including learning disability, epilepsy, developmental delay and autism (Diociaiuti et al., 2019; Kent et al., 2008; Rodrigo-Nicolas et al., 2018).

Although levels of STS activity in females heterozygous for Xp22.31 deletion are 2-2.5 times lower than in non-carrier females (Lykkesfeldt et al., 1984), until recently, the effects of haploinsufficiency for this region were assumed to be limited to mild dermatological problems (e.g. dry skin) and to delayed/prolonged labour during childbirth as a consequence of reduced *STS* expression (and consequently oestrogen secretion) in the placenta (Fernandes et al., 2010). New studies have shown that female carriers may present with a constellation of phenotypes which resemble those seen in male deletion carriers; profiling heterozygous

individuals will enable us to ascertain the specific effects of reduced Xp22.31 gene dosage against a female hormonal background.

Female heterozygotes for typical Xp22.31 deletions apparently show no, or negligible, differences from female non-carrier controls in terms of general health and wellbeing, stature, or reproductive health (Brcic et al., 2020). These data strongly suggest that reduced dosage of genes within this genomic interval does not contribute meaningfully to the key TS features of impaired growth and ovarian dysfunction; they also mean that any phenotypes in deletion carriers are unlikely to be attributable to gross hormonal abnormalities. In terms of psychiatric and behavioural measures, female carriers of XLI-associated genetic deletions, like male carriers, show evidence for higher rates of developmental/mood disorder diagnoses, and associated traits (notably irritability and mania-excitability), compared to non-carrier female controls; female carriers may also be at increased risk of postpartum mood conditions (Brcic et al., 2020; Cavenagh et al., 2019) and psychosis (Milunsky et al., 1999). Whilst female deletion carriers exhibit equivalent academic attainment to non-carrier controls, they show mildly-impaired performance on a 'Fluid Intelligence Test' taxing multiple aspects of cognition with a focus upon mathematical reasoning (Brcic et al., 2020). Neuroanatomical analysis in a small group of adult Xp22.31 female deletion carriers has revealed small-moderate reductions in the volume of some subcortical brain structures (right/left putamen, right pallidum and left nucleus accumbens) (Brcic et al., 2020), and these structural changes could plausibly underlie some of the aforementioned behavioural features. Female deletion carriers have been reported to present with corneal opacities (Fernandes et al., 2010), and whilst these individuals do not appear to be diagnosed more frequently with cardiac arrhythmias (Brcic et al., 2020), anecdotal reports suggest the possibility of subtle abnormalities.

Based upon the evidence presented above, to what extent might haploinsufficiency for genes within the Xp22.31 interval contribute towards TS phenotypes? Whilst this genetic explanation may partially explain heart rhythm anomalies, it does not appear to explain the multiple morphological and systemic features of the syndrome (short stature, ovarian dysfunction, metabolic abnormalities etc.). However, it offers further experimental support for the idea proposed by Zinn and colleagues (2007) that this small interval may be an important contributor towards mental health-related (autism, ADHD, (postpartum) depression, bipolar disorder, psychosis), fine motor, and executive function (inattention, cognitive flexibility/inhibition, dyscalculia) phenotypes in these individuals. Whether this genomic region influences TS neuroanatomy, and if so, how, is currently more difficult to determine. TS is not typically associated with reduced basal ganglia structure volumes, and actually appears to be associated with greater putamen and nucleus accumbens grey matter volumes (O'Donoghue et al., 2020; Molko et al., 2004; Zhao and Gong, 2017); unlike in individuals with TS, Xp22.31 deletion in females is not associated with enlarged amygdala volume (Brcic et al., 2020; Zhao and Gong, 2017). However, it should be appreciated that: a) the TS data is complicated by karyotype/mosaicism, and treatment and possible parent-of-origin effects, b) 39,XO mice, in which these confounds are not relevant, show evidence for reduced supracollicular nucleus accumbens volume (but increased infra-collicular nucleus accumbens volume)(Raznahan et al., 2013), and c) consistent effects on neuroanatomy may be observed in TS and Xp22.31 deletion carriers for cortical regions which have yet to be investigated in the latter group.

Candidate gene(s) for TS-associated phenotypes

Which gene, or genes, within the Xp22.31 deletion interval are most likely to contribute to the effects on mental health and cognition outlined above? In terms of adult brain gene expression, *STS* shows the highest region-specific expression (14 transcripts per million (TPM) in BA9 region of frontal cortex)(GTex Portal, 2020); developmentally, *STS* shows high levels of expression in the basal ganglia, cortex, thalamus, and cerebellar neuroepithelium (Stergiakouli et al., 2011). Together, these brain regions mediate a variety of TS-relevant functions, including numerous aspects of executive and motor function (Leisman et al., 2014). *PNPLA4* is also highly-expressed in the adult brain, including in the nucleus accumbens and caudate (10-11 TPM). *PUDP* is expressed at lower levels in adult brain, most prominently in the hypothalamus (6 TPM), whilst *VCX* appears to exhibit testis-limited expression and *MIR4767* is apparently not expressed in brain tissue (GeneCards, 2020). *PNPLA4* and *PUDP* (*HDHD1*) have recently been implicated as candidate genes for X-linked intellectual disability (Labonne et al., 2020; Prasad et al., 2018). *NLGN4X* is reasonably highly expressed in the adult brain, with highest expression in the cerebellum (13 TPM); rare variants within this gene are seen in cases of autism (Nguyen et al., 2020), whilst common variants are associated with schizophrenia, a neurodevelopmental psychotic disorder (Schizophrenia Working Group of Psychiatric Genomics Consortium et al., 2020). As *STS* is a robust X-escapee in humans, with high expression in relevant brain regions, it represents perhaps the strongest candidate *a priori* for effects on the TS mental health and neurocognitive profile, though additional contributions from *PNPLA4*, *PUDP* and *NLGN4X* are also possible.

Human molecular genetic studies indicate a role for STS in attentional processes: individuals with presumed inactivating point mutations within *STS* present with inattentive

ADHD (Kent et al., 2008), and common variants within the gene are associated with inattention in children with ADHD (Brookes et al., 2008; Brookes et al., 2010; Stergiakouli et al., 2011) and with attention in healthy adults (Humby et al., 2017). Moreover, attentional deficits in 39,XO mice are rescued by a small additional chromosome containing *Sts* (Davies et al., 2007), and mice with genetic deletion of *Sts*, or with inhibition of the STS enzyme, exhibit impaired attention (Davies et al., 2009). *Sts*-deficient mice display a range of other phenotypes relevant to TS including hyperactivity, and elevated levels of anxiety-related and perseverative behaviour (Trent et al., 2012a; Trent et al., 2013) and striatal neurochemical abnormalities (Trent et al., 2012b). Acute inhibition of STS in the postpartum period in mice lends support for a role in postpartum mood symptoms and psychosis (Davies, 2012; Humby et al., 2016).

STS catalyses the conversion of sulfated to free steroids (e.g. estrone sulfate to estrone, and dehydroepiandrosterone sulfate (DHEAS) to DHEA). Sulfated and free steroid molecules have differential solubilities, stabilities, and activities at receptors within the central nervous system (Davies, 2012; Mueller et al., 2015), and free steroids can act as precursors for synthesis of numerous androgens and oestrogens (Reed et al., 2005). Consistent with reduced STS activity in TS subjects, these individuals exhibit higher DHEAS levels, and higher oestrone sulfate:oestrone ratios, than 46,XX subjects (Dorr et al., 2019; Gravholt et al., 1999). Experimental evidence has implicated DHEA(S) levels in sexual function/drive, mood, cognition and neurodevelopmental processes (Greaves et al., 2019; Pluchino et al., 2015; Starka et al., 2015), and systemic DHEA(S) levels are associated with cardiac arrhythmia risk (Brcic et al., 2020). Circulating levels of other sex hormones, including oestrone, could be linked to numerous aspects of cognition including verbal memory and spatial abilities (Hamson et al., 2016). Together, the findings described above, strongly

implicate decreased STS activity, and the endocrine and physiological consequences of this, as underlying aspects of the TS symptom profile.

Klinefelter syndrome

TS is caused by reduced dosage of X-linked genes; there are numerous other sex chromosome conditions caused by increased X chromosome dosage, with the most common, and best described, of these being Klinefelter syndrome (KS). KS affects around 1 in 750 live male births and is most frequently associated with a 47,XXY karyotype (Skuse et al., 2018). Individuals with KS may escape clinical attention, but commonly-reported physical symptoms in individuals who are diagnosed include infertility, gonadal dysfunction, muscle weakness, a feminised appearance with reduced hair and breast growth, and reduced libido; this constellation of symptoms is likely to be related to androgen deficiency as testosterone levels are often low in KS patients (Bearelly and Oates, 2019). In addition, KS is associated with a range of brain-related phenotypes, which show considerable variability across cases. The psychiatric, neurological, behavioural, cognitive and neuroanatomical abnormalities associated with KS have been comprehensively summarised by Skuse et al. (2018). Phenotypes linked to KS include infantile hypotonia and later muscle weakness/coordination difficulties, an increased risk of affective-psychotic disorder, challenges with social interaction, impulsivity, and anxiety. In contrast to TS, individuals with KS often present with a preserved non-verbal IQ, but difficulties with verbal function such as reading and language comprehension. Again, in contrast to TS, KS is associated with increased grey matter volume in the parietal-occipital and sensorimotor cortical regions but decreased temporal region volume (with a corresponding increase in lateral ventricle size)(Itti E et al., 2006; Giedd et al., 2007; Skuse et al., 2018). In terms of subcortical neuroanatomy, individuals with KS exhibit

reduced volume of the caudate and putamen compared to 46,XY controls (Skakkebaek et al., 2014).

As in TS, phenotypes in KS may be modulated by tissue mosaicism, skewed X-inactivation, the parental origin of the supernumerary X chromosome and complex interactions with sex-linked and autosomal (epi)genetic and transcriptional processes (Skakkebaek et al., 2020). A main contributor to the KS phenotype is likely to be elevated dosage of multiple X-escapees. For some KS phenotypes e.g. tall stature there are strong candidate genes (i.e. *SHOX*)(Tuttelmann and Gromoll, 2010), but for most the underlying genetic mechanism(s) is unclear. Investigation of the phenotypes associated with Xp22.31 duplication, a relatively common genetic variant within the general population (0.3-0.4% of individuals)(Gubb et al., 2020; Liu et al., 2011), should reveal the extent to which over-dosage of this region contributes to clinical features associated with KS.

Elevated dosage of Xp22.31: contribution to KS phenotypes

Until recently, only relatively young, predominantly male, clinically-ascertained subjects with Xp22.31 microduplications had been described in case reports/series. These individuals often presented with severe developmental abnormalities, including intellectual disability/cognitive impairment, autism/autistic behaviours, global developmental delay, delayed speech and language, epilepsy/seizures, micro- or macrocephaly, muscular hypotonia and clinodactyly or shortness of the fifth finger (Gubb et al., 2020). A new study examining large samples of adult male and female Xp22.31 duplication carriers drawn from the general population has suggested that the Xp22.31 duplication variant is generally benign; whilst this finding could be partially explained by a healthy response/retention bias in the sample, it is more likely to be due to the Xp22.31 duplication acting as an 'innocent bystander'

or risk factor for the expression of other causal genetic, environmental or stochastic factors (Gubb et al., 2020).

In this large general population sample, Xp22.31 microduplications spanning *STS*, *PUDP*, *PNPLA4*, *VCX* and *MIR4767* were not associated with many of the physical features commonly-reported in KS (e.g. infertility/gonadal problems and muscle weakness) and thus duplication of these genes is unlikely to explain them. Microduplications of this region were associated with small increases in rates of inguinal hernia, mania/bipolar disorder, proton pump inhibitor prescription and happiness in males, as well as larger lateral ventricle size, whilst in females the variant was associated with elevated rates of gastro-oesophageal reflux disease (GORD) and blistering/desquamating skin disease, and with enlarged putamen volume; no association with academic achievement or cognitive function was observed for either sex (Gubb et al., 2020). To what extent do these findings tally with KS symptoms? They appear discrepant with regard to cognitive function, depressive traits alone and putamen volume, but are somewhat consistent with increased rates of mood-psychotic spectrum disorders in KS, with rare case reports of 47,XXY individuals with inguinal hernia, GORD or skin conditions (Dadheech et al., 2016; Doubi et al., 2015; Isguven et al., 2005; Kanaka-Gantenbein et al., 2007; Konheim et al., 2017; Krause, 2017; Lee et al., 2007), and with effects on ventricle size.

STS, the activity of which is elevated by 1.3-1.4fold in KS subjects (Lykkesfeldt et al., 1984), is a candidate for some of the effects common to individuals with KS and Xp22.31 duplication. Specifically, through its effects on steroid hormone pathways, the STS enzyme may influence mania susceptibility (e.g. via reduced systemic DHEAS levels (Lee et al., 2017)) and inguinal hernia/cryptorchidism risk (Traupe and Happle, 1986). Behavioural and cognitive

features of KS are unlikely to be explained by overexpression of genes within the small Xp22.31 interval investigated in Gubb et al. (2020), but could be affected by overexpression of proximate potential X-escapees, notably *NLGN4X* (Skuse et al., 2018).

Sex-biased expression of X-escapees: does reduced dosage of Xp22.31 influence sex-biased neurodevelopmental phenotypes?

Theoretically, X-escapees should be expressed more highly in female than male tissues, given the presence of two expressed alleles in the former sex, and just one in the latter. Experimental data supports this idea, although expression levels are typically only 1.2-1.5 times higher in female tissues due to reduced allelic expression from the inactivated X chromosome (Johnston et al., 2008; Tukiainen et al., 2017; Oliva et al., 2020). PAR genes have alleles on both the X and Y chromosomes and are similarly expressed across the sexes (Tukiainen et al., 2017). Many X-escapees on the X-specific portion of the X chromosome have Y-linked homologues, which may be expressed at similar levels to the X-linked allele, and whose associated protein may compensate functionally for the reduced levels of X-linked protein; in some cases, such as that of NLGN4, the X and Y-linked proteins have distinct roles despite almost identical sequences (Nguyen et al., 2020) whilst in other cases (e.g. *DDX3Y*) the Y homologue may not be translated (Berletch et al., 2011).

Overall, the X chromosome is enriched for genes highly expressed in the brain (Nguyen and Disteche, 2006), and the subset of X-linked genes which escape X-inactivation seem to be particularly important as mediators of neurodevelopmental and cognitive processes (Zhang et al., 2013). Most common neurodevelopmental disorders (e.g. autism spectrum conditions, ADHD, and dyslexia) are diagnosed considerably more often in males than females, or the course of the disorder is more severe in males than in females (e.g. schizophrenia); this male

bias is likely to be due to a combination of complex interacting biological, environmental and social factors (e.g. ascertainment and diagnostic practices)(May et al., 2019). Females affected by developmental disorders have been reported to exhibit higher rates of deleterious genetic variants compared to males affected by such conditions, even after matching for symptom severity, suggesting the possibility that females are somehow protected, or buffered, against the effects of such variants (Jacquemont et al., 2014; Werling, 2016; Zhang et al., 2020); however, some studies have questioned this model (Bai et al., 2020; Martin et al., 2018). As yet, no convincing biological mechanism has been shown to account for the general protective effect in females (should it exist). Higher expression of one or more X-linked neurodevelopmentally-important genes in females relative to males, is a plausible candidate mechanism which may act by increasing the risk threshold, or by mitigating the effects of genetic mutations and/or environmental insults.

To date, studies have largely focussed on comparing gene expression in adult male and female brain regions, with little information on developmental sex differences. Across multiple adult brain regions, *PUDP*, *PNPLA4*, *STS* and *NLGN4X* are consistently reported as being within the top 50 most highly differentially-expressed genes by sex (Oliva et al., 2020). One new study which did compare male and female fetal whole brain gene expression in large samples identified just 8 genes demonstrating moderate-high expression (>300 normalised counts) that were substantially (log2<-0.40) and significantly (adjusted $p<4.0x10^{-8}$) more highly expressed in developing female than male brains (O'Brien et al., 2019). Of these robustly differentially-expressed genes, three (*STS*, *PUDP* and *NLGN4X*) are located within Xp22.31; a fourth gene within Xp22.31 (*PNPLA4*) exhibits moderate brain expression and is significantly differentially-expressed between males and females (adjusted $p=8.6x10^{-11}$), but exhibits a smaller sex difference in expression (log2 fold difference=-0.22). Together, these

results reinforce the idea that genes within the Xp22.31 region are important in sexually-differentiated developmental brain processes.

Of the genes meeting the criteria above, *STS* shows the highest degree of differential gene expression (O'Brien et al., 2019); it has a non-expressed pseudogenic Y homologue (Yen et al., 1988). Although gene expression does not necessarily correlate with protein expression or activity, STS is more highly expressed, and demonstrates greater activity, in female than male human tissues, and non-human primate brain (Cuevas-Covarrubias et al., 1993; Hirato et al., 1991; Kriz et al., 2005; Lykkesfeldt et al., 1984; Miranda-Duarte et al., 1999; Miyakawa et al., 1994; Muller et al., 1980). In the developing and adult brain, STS is most highly expressed in brain regions whose structure is altered in idiopathic cases of neurodevelopmental disorders (Hoogman et al., 2017; van Rooij et al., 2018). Genes displaying female-biased expression during neurodevelopment are enriched for expression in Cajal-Retzius (CR) neurons (O'Brien et al., 2019); these cells affect corticogenesis via secretion of reelin (Barber and Pierani, 2016), and disruption to this process is associated with aberrant neurodevelopment (Armstrong et al., 2019). *STS* is expressed in both fetal and adult CR neurons (Steckelbroeck et al., 2004) and thus the associated enzyme could feasibly affect neurodevelopment via effects on their function. These molecular and cellular observations, in combination with convergent observations from human and animal model studies showing effects of reduced STS levels/activity on behavioural/cognitive processes disrupted in many neurodevelopmental disorders (e.g. attention, activity, cognitive flexibility, and anxiety), suggest that higher levels/activity of this enzyme developmentally in females relative to males could feasibly contribute to the 'protective effect' postulated above. This effect might be mediated locally (i.e. via direct effects on brain development/function) or systemically via effects on hormone availability and action. Given the role of this enzyme in generating steroid

hormones with significant organisational potential, its effects on anatomy and function may be widespread. Steroid sulfatase deficiency, via its effects on the balance of sulfated to free steroids, could explain the substantially elevated rates of atrial fibrillation/flutter in individuals with XLI (Brcic et al., 2020); lower expression/activity of STS in males relative to females may also contribute towards the 1.5-2 times higher risk of atrial fibrillation in the former sex (Gerdts and Regitz-Zagrosek, 2019).

Of the three genes exhibiting significant differential expression between males and females mentioned above, *NLGN4X* is the most highly-expressed in the developing human brain. Given that rare and common variants within this gene have been associated with vulnerability to autism and schizophrenia (Nguyen et al., 2020; Schizophrenia Working Group of Psychiatric Genomics Consortium, 2020), and the Y-linked homologue of the gene *NLGN4Y* appears to be functionally-distinct, higher expression of *NLGN4X* in female relative to male brain may somehow protect against developmental disorders; together, the combined higher expression of both *NLGN4X* and *STS* in female brain may buffer against developmental anomalies across a variety of neural circuits and associated cognitive functions. It is possible that *PUDP* and *PNPLA4* also play a buffering role, but as these genes demonstrate lower (differential) expression in the developing brain than *STS* and *NLGN4X*, and as these genes have not yet been robustly-linked with developmental disorders, their role is probably comparatively minor.

Conclusions and future work

There is strong reason to believe, from converging evidence provided by older deletion mapping studies and from newer and more powerful Copy Number Variant studies, that haploinsufficiency for one or more genes within the Xp22.31 underpins at least some of the

increased risk of developmental/mood disorder and neurocognitive traits in females with TS. As a robust X-escapee, STS is expected to be haploinsufficient in most TS cases, and is a very strong candidate for explaining some of the core attentional deficits in TS and for effects on general cognition and social function. The observation that rodents lacking STS (or with the enzyme inhibited) recapitulate many of the features associated with deletions encompassing *STS* in humans (despite the associated gene residing within very different genomic contexts in the two species) strongly indicates that 'deletion effects' in man are likely to result from low STS levels rather than simply being due to the mis-expression of extraneous genes.   As the subcortical neuroanatomical phenotypes of XLI-variant carrier females and females with TS are apparently discordant, reduced STS expression/activity is unlikely to affect attention via perturbation of these regions across both of these groups. Examination of cortical morphology in XLI-variant carriers may reveal commonalities with TS (e.g. in the frontal cortex) which better explain overlapping behavioural and cognitive phenotypes. If STS expression/activity is a determinant of mental health risk and cognitive function in TS, we might expect peripheral expression/activity levels of the enzyme to be inversely correlated with mental health-related symptoms, and positively correlated with cognitive performance (e.g. measures of attention), within this clinical population; we might also expect the ratio of sulfated to free steroids (e.g. DHEAS:DHEA) to be positively correlated with mental health symptoms and inversely correlated with cognitive performance. Work in animal models or cell cultures in which *Sts* expression is specifically disrupted may help to clarify which specific behavioural and brain phenotypes may be sensitive to its loss of function. Haploinsufficiency for NLGN4X is a candidate for larger effects on cognition and autistic traits, although the extent to which the expression of NLGN4X is reduced in TS may be variable. Haploinsufficiency for either STS or NLGN4X appears unlikely to contribute to the major physical and metabolic

abnormalities seen in TS. The effects of haploinsufficiency for *PUDP* and *PNPLA4* genes, and their contribution to TS phenotypes, may be clarified through comprehensive screening of heterozygous female animal models and knockout cell cultures.

Lower levels of STS and/or NLGN4X in developing male relative to female tissues may help to explain the more general phenomenon of a male bias in vulnerability to developmental disorders. To date, analyses from blood have not identified significantly lower expression of these genes in male and female subjects with developmental disorders (autism, ADHD, schizophrenia); however, this does not necessarily preclude their reduced expression as a risk mechanism in that they are expressed at very low levels in whole blood (*STS* <2 TPM, *NLGN4X* <0.01 TPM)(GTex Portal) and may not exert their effects through this tissue, and that gene expression in this tissue is not necessarily related to protein levels or enzyme activity. Studies in brain tissue from individuals with developmental disorders have also not yet implicated altered expression of these genes (e.g. Chang et al., 2015; Huang et al., 2020); however, such studies are limited by small sample sizes, by sex-biased samples, by considerable heterogeneity in donors symptoms and genetics, by *post mortem* considerations and by treatment effects. I hypothesise that after controlling for relevant variables (e.g. age, medication history etc.) individuals affected by developmental disorders will exhibit reduced central and peripheral expression/activity of these genes and their related proteins, and a higher ratio of sulfated to free steroids, relative to unaffected controls; whilst altered peripheral sulfated or free steroid levels have been noted in various developmental conditions (Weizman, 2008), as yet, levels of both have not been measured within the same patient in large samples.

Overdosage of *STS*, *PUDP*, *PNPLA4*, *VCX* and *MIR4767* genes is unlikely to play a role in the major physical, mental health and cognitive phenotypes associated with KS, but may subtly increase risk of specific conditions such as mania/psychosis and inguinal hernia; within these patients, we may expect individuals with KS and psychotic symptoms to exhibit higher peripheral STS activity and a reduced sulfated:free steroid ratio relative to KS subjects without psychosis (and healthy control subjects). Potentially, duplication of the *NLGN4X* gene may influence KS-related brain phenotypes (Wolstencroft and Skuse, 2019). Analysis of animal models transgenic for Xp22.31-associated genes (e.g. *Sts* Feng et al., 2019), or cell cultures in which these genes are overexpressed, may help to clarify their contribution (or lack thereof) to the KS symptom profile.

Understanding the genetic basis of rare conditions and sex-biased disorders will be important for identifying 'at risk' individuals at an early stage, for clarifying biological mechanism(s) and for subsequently developing better, and more tailored (e.g. sex-adapted) treatment strategies.
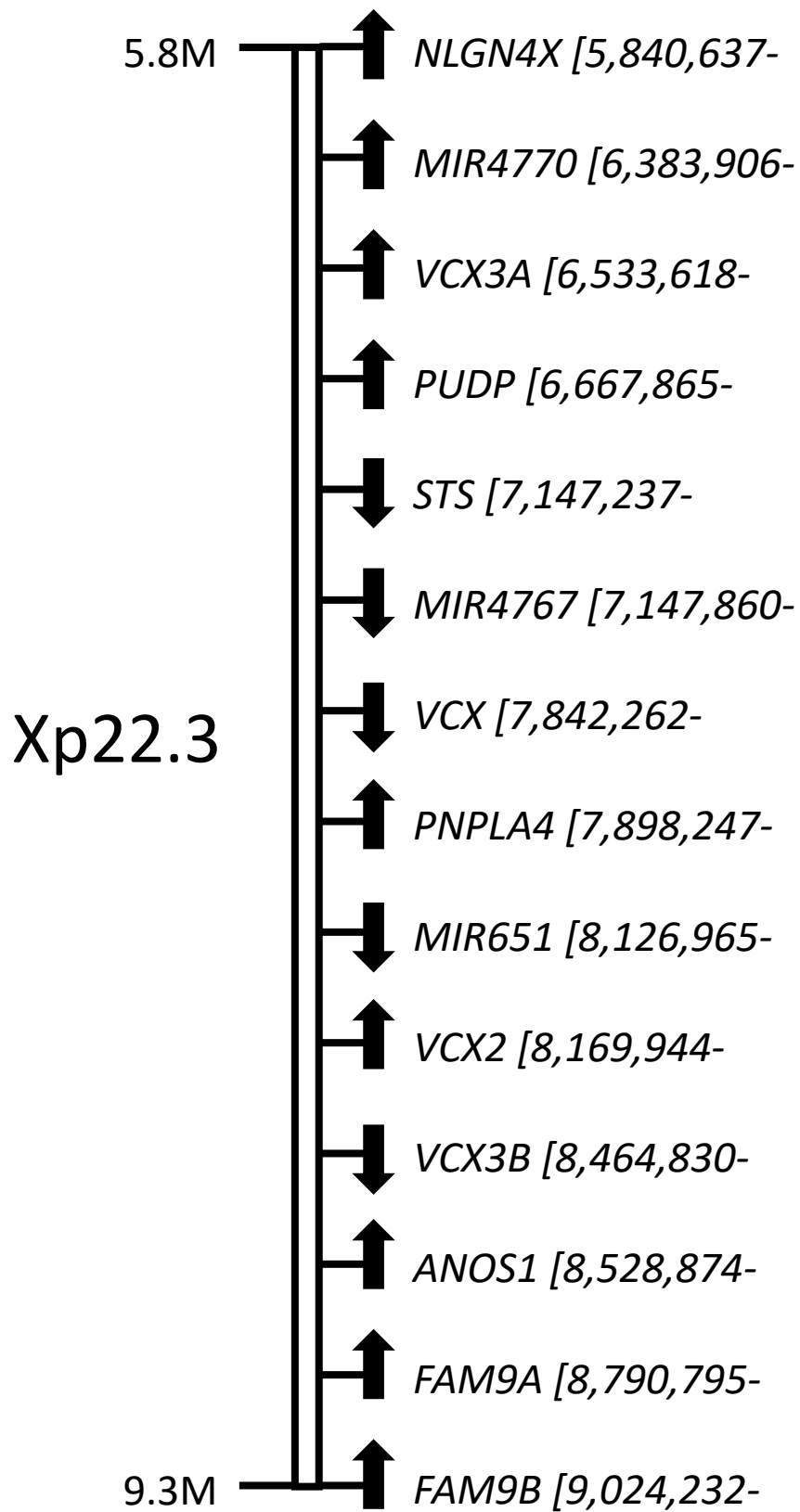
Figure titles and legends

Figure 1. Gene sequence and orientation in human Xp22.31 (based upon GRCh38.p13 and taken from Ensembl (https://www.ensembl.org/index.html, accessed 12th January 2021).

Table 1. Functional annotation of Xp22.31 genes discussed in main text.

Gene name	Gene product and function	X-inactivation status	Effect of Copy Number Variation/gene mutation
NLGN4X	Neuroligin 4 (X-linked): neuronal cell surface protein involved in cell-cell interactions at synapse	Variable escape	Deletions encompassing gene associated with increased risk of autism and developmental delay (Kent et al., 2008). Point mutations associated with increased risk of autism (Nguyen et al. 2020)
MIR4770	microRNA: function unknown	Unknown: likely partial escape	-
VCX3A	Variable Charge X-linked 3A: small, highly-charged protein of unknown function (possible role in spermatogenesis)	Expression male-specific (testis); status indeterminate	Deletions encompassing gene unlikely to be sufficient to cause intellectual disability (Cuevas-Covarrubias and Gonzalez-Huerta, 2008)
PUDP	Pseudouridine 5'-phosphatase: dephosphorylates a potential intermediate in rRNA degradation	Consistent escape	Deletion of *PUDP*, *STS*, *MIR4767*, *VCX* and *PNPLA4* is associated with increased risk of atrial fibrillation, Attention Deficit Hyperactivity Disorder (ADHD) and autistic traits, and abnormal mood (Brcic et al., 2020; Cavenagh et al., 2019; Diociaiuti et al., 2019; Rodrigo-Nicolas et al., 2018; Chatterjee et al., 2016)

Duplication of this region is associated with increased risk of inguinal hernia and mania/bipolar disorder in males, and gastro-oesophageal reflux disease and blistering/desquamating skin disorder in females; possible association with developmental disorders (Gubb et al., 2020)

Point mutations or variation in *STS* associated with increased inattentive ADHD risk and effects on attention (Humby et al., 2017; Brookes et al., 2008; Kent et al., 2008). *PUDP* and *PNPLA4* implicated as risk genes for intellectual disability (Labonne et al., 2020). |
STS	Steroid sulfatase: converts sulfated to free steroids	Consistent escape	
MIR4767	microRNA: function unknown	Unknown: likely (partial) escape	
VCX	Variable Charge X-linked: small, highly-charged protein of unknown function (possible role in spermatogenesis)	Expression male-specific (testis); status indeterminate	
PNPLA4	Patatin-like phospholipase domain-containing protein 4: role in adipocyte triglyceride homeostasis	Partial escape	
MIR651	microRNA: function unknown	Unknown: likely (partial) escape	-

Figure 1.

Xp22.3

5.8M

NLGN4X [5,840,637-

MIR4770 [6,383,906-

VCX3A [6,533,618-

PUDP [6,667,865-

STS [7,147,237-

MIR4767 [7,147,860-

VCX [7,842,262-

PNPLA4 [7,898,247-

MIR651 [8,126,965-

VCX2 [8,169,944-

VCX3B [8,464,830-

ANOS1 [8,528,874-

FAM9A [8,790,795-

9.3M

FAM9B [9,024,232-

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