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Cognition and the Sex Chromosomes: Studies in Turner Syndrome

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Abstract
Turner syndrome (TS) is a human genetic disorder involving females who lack all or part of one X chromosome. The complex phenotype includes ovarian failure, a characteristic neurocognitive profile and typical physical features. TS features are associated not only with complete monosomy X but also with partial deletions of either the short (Xp) or long (Xq) arm (partial monosomy X). Impaired visual-spatial/perceptual abilities are characteristic of TS children and adults of varying races and socioeconomic status, but global developmental delay is uncommon. The cognitive phenotype generally includes normal verbal function with relatively impaired visual-spatial ability, attention, working memory, and spatially dependent executive function. The constellation of neurocognitive deficits observed in TS is most likely multifactorial and related to a complex interaction between genetic abnormalities and hormonal deficiencies. Furthermore, other determinants, including an additional genetic mechanism, imprinting, may also contribute to cognitive deficits associated with monosomy X. As a relatively common genetic disorder with well-defined manifestations, TS presents an opportunity to investigate genetic and hormonal factors that influence female cognitive development. TS is an excellent model for such studies because of its prevalence, the well-characterized phenotype, and the wealth of molecular resources available for the X chromosome. In the current review, we summarize the hormonal and genetic factors that may contribute to the TS neurocognitive phenotype. The hormonal determinants of cognition in TS are related to estrogen and androgen deficiency. Our genetic hypothesis is that haploinsufficiency for gene/genes on the short arm of the X chromosome (Xp) is responsible for the hallmark features of the TS cognitive phenotype. Careful clinical and molecular characterization of adult subjects missing part of Xp links the TS phenotype of impaired visual spatial/perceptual ability to specific distal Xp chromosome regions. We demonstrate that small, nonmosaic deletion of the distal short arm of the X chromosome in adult women is associated with the same hallmark cognitive profile seen in adult women with TS. Future studies will elucidate the cognitive deficits and the underlying etiology. These results should allow us to begin to design cognitive interventions that might lessen those deficits in the TS population.

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Introduction

Turner syndrome (TS) is a chromosome disorder involving the absence of all or part of one X chromosome. The incidence of TS is 1 in every 2,500 live female births. The phenotype includes short stature, ovarian failure, specific anatomic abnormalities such as webbed neck, and a characteristic neurocognitive profile. There is substantial individual variation in the presence and severity of the different TS features. Unlike other common chromosome disorders such as trisomy 21, TS does not typically cause general mental retardation [1]. Instead, the TS neurocognitive phenotype consists of selective deficits in certain domains. Verbal abilities are usually normal; however, 45,X girls and women, on average, have impaired visual-spatial and visual-perceptual abilities, motor function, nonverbal memory, executive function and attentional abilities compared to normal females matched for age, height, IQ, and socioeconomic status [2–6].

The TS Neurocognitive Phenotype

The cognitive phenotype in TS resembles Harnadek and Rourke's [7] characterization of nonverbal learning disability (NLD). This disorder is characterized by academic deficits in arithmetic, mathematics, and science. Additionally, individuals with NLD are at risk for impaired adaptation to novel situations, impaired social competence, and internalized forms of psychopathology (anxiety and depression). Harnadek and Rourke hypothesized that NLD arises from impaired nonverbal memory, attention, concept formation, and problem solving.

This pattern of NLD deficits is very similar for children, adolescents, and adults with TS [5, 8] and could be due to one or a combination of multiple environmental, genetic, or endocrine factors. The persistent cognitive phenotype includes a typical pattern of impaired performance in related areas, including visual-motor tasks that have a spatial component, tasks that involve manipulation of spatial-relational information, and attention tasks requiring control of impulsivity and self-monitoring. Impaired manipulation of spatial-relational information interferes with a broad spectrum of cognitive functions, including perception of spatial information and spatially loaded aspects of memory, i.e. stored items of information, based on their relationship to other items. Deficits in manipulation of spatial-relational information are indexed by impaired spatial-perceptual ability, spatial-re-

lational memory, and working memory, including manipulation of spatial configurational information. The impairment in working memory with slower, less efficient information processing is also associated with impaired executive function.

Environmental factors could influence the social-behavioral and cognitive development of girls with TS. Their short stature and occasionally unusual facial characteristics could affect the way they are treated and thus, the cognitive and behavioral outcomes that are measured. However, it has been demonstrated that adult women with TS differ similarly from short stature controls and from normal stature female sibling controls [9, 10].

Alternatively, the genetic abnormality in TS, determined by absence of one or more genes on the X chromosome, could affect brain development directly, giving rise to the cognitive and behavioral phenotype. Skuse [11] has suggested that a genetic locus at Xp11.3 is associated with increased amygdala size, which in turn influences emotional functioning in TS. Candidate genes whose loss may result in the TS phenotype are currently under investigation by our group. Finally, the cognitive and behavioral deficits in TS could be due to the absent ovarian production of estrogen, androgen, or both.

Although the developmental mechanisms are uncertain, the academic and social outcomes and relative functional concerns are similar for TS and NLD as characterized above. Harnadek and Rourke [7] presented a set of assessment and treatment guidelines for children with NLD that includes methods to improve visual-spatial-organizational skills as well as ways to use verbal skills to compensate for nonverbal learning deficits. The recommendations are summarized in table 1 as previously described [12].

Brain Structure and Function in TS

The hallmark TS cognitive phenotype described above most likely reflects alterations in functions preferentially mediated by the right cerebral hemisphere, especially the right frontal and parietal regions. However, the overall neurocognitive assessments of TS girls and adults have previously shown a pattern consistent with multifocal brain dysfunction [8, 13] without any pathognomonic brain localization.

Certain consistent electrophysiological and neuroimaging abnormalities have been reported across wide age ranges. In electrophysiological studies, TS girls and adults had evoked potentials differing in attention and orienta-

Table 1. Clinical implications and recommendations for NLD in TS

Early assessment to identify and characterize cognitive strengths and weaknesses. Prevention and intervention strategies for maximizing learning.

Proactive use of tutoring to assure that students are keeping up with and comprehending classroom material.

Specific instruction in organizational, study, and time management skills.

Ready access to computer learning and use of calculators.

Parents need to be knowledgeable about the specifics of TS-associated learning disabilities.

Teachers need to be educated about the need to focus on the good language skills of girls with TS and not rely heavily on visuospatial processing.

Extra test taking time or intervention so work can be done with extended time limits.

If mathematical problems are identified, remediation in numerical skills, breaking down problems into component steps, and checking work should be offered.

If the person has attentional problems, present smaller, more structured classrooms may be needed and/or further evaluation of attention with consideration of a behavioral modification program and/or medication trial to increase ability to attend to task.

Specific training in social and communication skills.

Teachers and school personnel should be encouraged to intervene if excessive teasing is noted.

Parents need to be encouraged to play an active role in helping their daughters develop and maintain friendships with involvement in both structured group or team activities and more informal activities.

To improve self-competency, TS girls should be encouraged to pursue areas where they show talent or interest, e.g. sports where size is not an issue or music.

Girls who have poor motor skills may need occupational or motor skill training, and may need to be excused from certain PE activities.

Girls need age-appropriate expectations in terms of participation in social activities and beginning to take on responsibilities such as home chores.

Preparation for the transition to adulthood.

Girls should be informed about their diagnosis and the associated learning and medical problems with a focus on the idea of coping adaptively with specific problems.

Parents and girls need to be educated about the learning disabilities. They need to be informed that even with intervention, learning problems do not disappear with age, but instead are persistent and remain significant risk factors throughout adult life. NLD can be a major impediment to emancipation from family and career achievement.

Vocational/educational planning should begin in high school with a focus toward making sure TS girls participate in the volunteer and early job experiences that will prepare them to move successfully into the work world.

Increased attention should be paid to assure that girls and young women with TS have adequate education about sexuality and the reproductive options available to them.

Participation in patient advocacy groups such as the Turner Syndrome Society of the United States (http://www.turner-syndrome-us.org/) can provide important new information as well as a supportive peer group.

tion responses [14] and EEG differences compared to control subjects [15]. Previous neuroradiologic studies demonstrated volume reduction of right parietal-occipital brain matter, right posterior regions (parietal and temporal), bilateral dorsolateral prefrontal cortex, the caudate nucleus, and the left parietal-perisylvian region [6, 16–19]. These findings may be related to cognitive differences in TS and indicate probable bilateral cerebral dysfunction. Decreased metabolism has also been found bilaterally, in the occipital and parietal cortex in studies of

regional cerebral glucose metabolism [20]. In addition, there is possible frontal-striatal dysfunction with prefrontal hypometabolism and bilateral differences in the caudate lobe distinguishing TS from controls on PET study [21].

Bilateral brain abnormalities have also been found in autopsy studies of TS females. Heterogeneous abnormalities including mild cortical dysplasia and brain atrophy with small gyri in the temporal and occipital lobes [22, 23] were described. It has been hypothesized that differ-

ences in amygdala size in TS contribute to the social/emotional impairment [11]. The interval of early adolescence may be particularly important because cortical gray matter increases in general at this age, slightly more in boys (10%) and then decreases after adolescence [24].

Disordered working memory has been attributed to dysfunction of the frontal-striatal axis [25]. The co-occurrence of spatial deficits and memory impairment also implicates right posterior cortical dysfunction. MRI, PET scan and other data have demonstrated right parietal abnormalities in TS [17, 18, 21]. Given that both acquired lesions and developmental anomalies in this region are associated with similar cognitive dysfunction, a similar relationship probably also exists in TS. Posterior involvement is reflected by processing deficiencies affecting components of attention, as well as a variety of visuospatial, visual perceptual and visual constructive functions. Frontal dysfunction is consistent with difficulties with motor-intentional behaviors, spatial working memory and limitations in aspects of executive function. According to this model, the broad neurocognitive difficulties seen in TS are not modality-specific or secondary to focal deficiencies, but rather represent complex impairment of multiple bilateral brain substrates and multiple cognitive modalities.

Sex Steroid Effects on the Brain

Alterations in TS brain development are most likely not caused by a single factor. Rather, they are probably the result of a complex interaction between genetic abnormalities, hormonal deficiencies, and other unspecified determinants of brain development. There is strong evidence implicating sex hormone influence on brain and behavior. Both animal and human studies have shown clear-cut structural effects of both estrogen and androgen on subcortical nuclear regions such as the hypothalamic/preoptic area as well as forebrain regions that are related to behavior [26–28]. Animal studies have demonstrated either prenatal or early postnatal androgen-induced changes in spatial abilities or spatial memory associated with specific brain alterations [29–31]. Sex steroids may function (1) transiently as neuromodulators by potential mechanisms such as occupying receptors and initiating an enzyme cascade, modifying uptake of neurotransmitters, or by altering neuronal electrical activity, (2) permanently by altering synapse formation and remodeling, or (3) both [32, 33]. Gonadal hormones may act genomi-cally through receptors and/or through transsynaptic and membrane effects, independent of classical receptors.

Estrogen influences cognitive function and mood in females. Adult women have improved verbal memory, articulatory processing speed and fine motor abilities in the higher estrogen phase of the menstrual cycle and in association with estrogen treatment after menopause [34, 35], suggesting positive estrogen effects on several aspects of cognitive function. Potential hormonal factors in TS brain development and behavior include the absence of estrogen very early in development during infancy or the absence of estrogen later in childhood and adolescence prior to standard estrogen replacement in adulthood. The TS neurocognitive phenotype includes estrogen-dependent and estrogen-independent components. Ross et al. [36] showed that estrogen replacement in young TS girls improved spatially-mediated motor function and verbal memory. This demonstrates that certain deficits are estrogen-responsive, while others that appear early in childhood and persist into adulthood are relatively estrogen-independent. Estrogen replacement in TS girls and adults does not appear to have any effect on the hallmark visual-spatial deficits described here.

Androgen also influences cognitive function in females. Androgen replacement seems to have dissociable effects from estrogen replacement. Several lines of evidence support an association in humans between androgen and spatial ability, mathematical reasoning, muscle strength, and to a lesser extent, working memory. The first line relates to observed gender differences, the second to androgen deficiency and replacement states, and the last to unusual human models from nature. Males generally outperform females in visual-spatial tasks involving mental rotation, spatial perception, spatial visualization, mathematics, and problem solving [37–39]. In addition, higher testosterone levels are correlated with superior spatial abilities in normal women (ages 18–99) [40]. Girls born with androgen excess in association with congenital adrenal hyperplasia have superior spatial abilities compared to siblings [41–43]. Testosterone has been used in female to male transsexuals [44] and resulted in improved visual-spatial memory. Women treated with androgen and estrogen after ovariectomy have improved memory, complex information processing, and logical reasoning [45, 46]. Neuropsychological impairment occurs in male subjects with androgen deficiency. Men with untreated congenital hypogonadotropic hypogonadism have diminished production of testosterone as well as impaired spatial ability, verbal memory and attention relative to controls [47]. Genetic males with complete androgen insen-

sitivity syndrome, who lack androgen receptors and cannot respond to testosterone, have relatively impaired performance on the WAIS Digit Span subtest, compared to controls [48]. Last, oxandrolone treatment of TS girls, who are androgen-deficient, is associated with improved working memory after 2 years of treatment [49].

Genetic Aspects of the TS Neurocognitive Phenotype

Haploinsufficiency

By definition, monosomy X implies that multiple genes on the second X chromosome are missing; therefore, half-normal dosage (haploinsufficiency) of X genes may be related to the TS cognitive deficits. Recent studies provide strong evidence that reduced expression of gene(s) can impair selective cognitive domains. Lai et al. [50] showed that haploinsufficiency of FOXP2, a chromosome 7 transcription factor gene expressed in the brain during development, causes selective speech and language deficits. Haploinsufficiency of one or a few genes in a small region of chromosome 7 may be responsible for impaired visual-spatial cognitive abilities characteristic of Williams syndrome, a contiguous gene deletion syndrome. Careful clinical and molecular analysis of subjects with partial deletions of the William syndrome critical region implicated haploinsufficiency of the LIM-kinase 1 gene in visual-spatial construction deficits [51, 52].

TS candidate genes are thought to escape X-inactivation. Previous cytogenetic and molecular studies suggest that most TS physical features map to the short arms of the X and Y chromosomes [25, 53–55]. Identifying genes or critical regions responsible for individual TS features other than short stature (e.g. cognition, renal malformations, palate abnormalities, lymphedema, etc.) has been problematic. Most studies used only cytogenetic and not molecular techniques to define X chromosome abnormalities. The variability of TS features even among 45,X patients necessitates statistical methodology for genotype/phenotype correlations. One way to deduce the underlying genotype/phenotype relationships in TS is to compare the phenotypes of individuals missing various portions of one sex chromosome in order to assign specific features to 'critical regions.' A trait maps to a region if deletion of that region accounts for the variance in that trait. In actuality, most TS traits are probably due to multiple genes, each contributing to the phenotypic variance.

It would be overly simplistic to assume that haploinsufficiency of cognitive genes affect only single domains, or that a cognitive domain like visual-spatial ability is influenced by only one or two genes. Most genes involved in cognition probably influence multi-focal aspects of brain development, and most cognitive abilities are likely influenced by multiple genes. Biochemical and experiential influences may further modify brain structure and function. Thus, deletion of a TS gene or a Williams syndrome gene may influence the development of visual-spatial ability to the greatest extent, but may also affect diverse brain regions and thus other cognitive abilities. Also, the ultimate cognitive outcome in a TS female is the result of this specific genetic deficit plus the individual's unique non-TS cognitive profile (other genetic cognitive determinants), sex hormone status, environment, and education.

The TS neurocognitive phenotype is thus a complex rather than a Mendelian trait. Differences between TS and control subjects demonstrated by neuropsychological, neurophysiologic and neuroanatomic studies are quantitative rather than qualitative, and individual results do not unequivocally distinguish TS subjects. Thus there is overlap in the distributions of neurocognitive abilities in the TS and the normal populations. In the ideal case of monozygotic twins discordant for TS, differences in cognitive ability can be attributed more clearly to genetic factors. However, twins concordant or discordant for TS are very rare. Reiss et al. [17] performed detailed neurocognitive and neuroanatomic magnetic resonance imaging (MRI) evaluations of one discordant twin pair. These studies demonstrated that the twin with monosomy X but not her sister showed the typical TS cognitive deficits as well as abnormal findings in the right posterior (parietal and temporal) and the left parietal-perisylvian brain regions.

Based on the assumption of haploinsufficiency of X chromosome genes causing at least in part the visual-spatial deficiencies in TS, other genetic variants of TS would have variable degrees of haploinsufficiency that would influence the cognitive phenotype. For example, mosaicism for the normal 46,XX cell lines may be associated with a milder cognitive phenotype, depending on the mosaicism distribution in the brain. In another example, ring X (r(X)) chromosomes can result in a more severe, atypical, phenotype. Whereas the incidence of mental retardation is approximately 10% in individuals with TS, among the subset of individuals with TS who carry an r(X), the incidence is increased to approximately 30% [56].
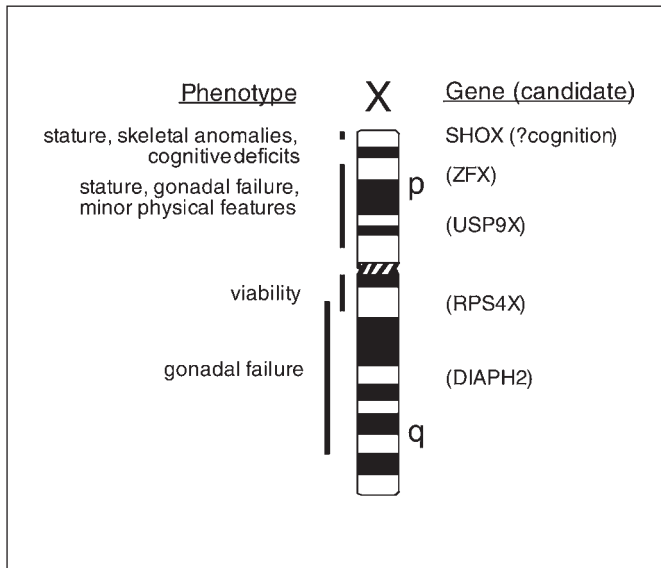
Fig. 1. Map of TS phenotype and potential candidate genes.

Imprinting

An additional genetic mechanism, imprinting, may contribute to cognitive deficits associated with monosomy X, depending on whether the single X chromosome is from the father or the mother. Imprinting has been implicated in several chromosome disorders, e.g., Prader-Willi and Angelman syndromes, involving deletions of the paternal or maternal copy of a portion of chromosome 15, respectively. In general, physical features of TS do not show imprinting effects [54]. In contrast, Skuse et al. [57] found that 45,X TS patients whose single X was maternal had significantly poorer verbal skills, higher-order executive function and socio-behavioral skills than patients whose single X was paternal in origin. Importantly, they did not observe any imprinted effects on measures of visual-spatial ability, the hallmark TS-associated neurocognitive deficit. Their findings have not been independently replicated. In our previous studies, we did not observe any parent-of-origin differences in verbal IQ, performance IQ, visual-spatial/perceptual function, or any social outcome or self-image measure. In an attempt to examine these issues more closely, mouse models are being used to identify potential imprinted genes in TS. A cluster of imprinted mouse X-linked genes and parent of origin behavioral effects were recently reported [58, 59]. The relevance of these mouse genes and phenotypes to TS remains to be determined.

Genetic Fine Mapping

In the absence of pathognomonic TS neurocognitive findings, we used a theoretical model for the estrogen-independent aspects of TS cognitive deficits in order to define the phenotype for the purpose of mapping. We utilized a quantitative statistical method, discriminant function analysis (DFA), to test relationships between phenotypes and X chromosome deletions. DFA is a mathematical tool for deriving a linear function that optimally weights parameters to permit sensitive and specific differentiation of a TS group from normal controls. The results provide a summary statistic for purposes of phenotype mapping that identifies which subjects with partial monosomy X have the defined TS-associated neurocognitive phenotype. We previously demonstrated that DFA can be used to identify both children and adults with a defined TS neurocognitive profile [60]. Many of the cognitive domains and component tasks in the resulting children and the adult DFAs were similar and tended to measure visual-spatial perception. However, optimal discrimination was achieved by including tasks from other cognitive domains as well. Although our choice of cognitive abilities to test was informed by a theoretical model for the TS-associated deficits, the DFA did not assume a priori knowledge as to which of these deficits best characterize TS, nor did DFA explain these deficits.

Our results provide a framework for identifying candidate TS neurocognitive genes, just as has been done previously for TS physical features [61] (fig. 1). Using a combination of molecular mapping and DFA, we identified a small interval of distal Xp, deletion of which showed a statistically significant association with the hormone-independent defined TS neurocognitive phenotype. We studied a population of females with nonmosaic partial deletions of Xp or Xq. No association between deletions of the Xq and TS neurocognitive deficits was observed (unpublished data). By contrast, partial deletions of Xp were associated with typical TS neurocognitive deficits. We reported our findings on 34 females with various Xp deletions [62]. Almost half manifested the defined TS-associated neurocognitive profile, including six subjects missing only portions of Xp22.3 (fig. 2). By contrast, two subjects with interstitial Xp deletions sparing distal Xp22.3 did not have the phenotype. Furthermore, there was no apparent relationship between the defined TS neurocognitive phenotype and either stature or ovarian functional status. We concluded that the defined TS neurocognitive phenotype is genetic in etiology and is due at least in part to haploinsufficiency for gene(s) in distal
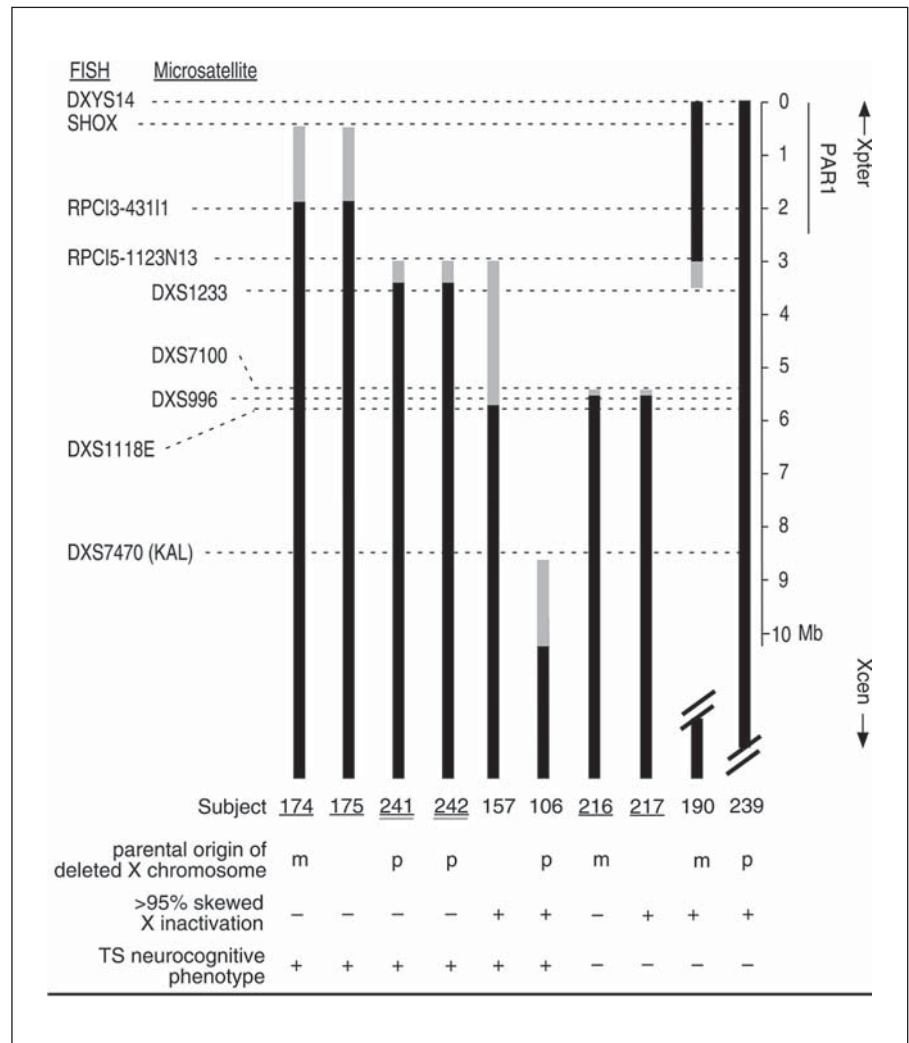
Fig. 2. Deletion mapping and phenotypes of patients with distal Xp deletions.

Xp22.3. The smallest deletion associated with the TS neurocognitive phenotype was in a mother and daughter missing less than two megabases (Mb) of terminal Xp, comprising only about 1% of the entire X chromosome (fig. 2). This deletion fell within the Xp-Yp pseudoautosomal region.

We have confirmed the localization of a TS candidate gene to this region by mapping deletions of additional adult patients with partial monosomy for Xp (fig. 3a). The discriminant function results were similar for subjects deleted for distal Xp (fig. 3b) and TS subjects, both of whom differed from normal female controls. The mean discriminant function (DF) score for the 22 deletion subjects with the smallest distal Xp deletions (bin 1, the distal 3 Mb) was similar to the DF score for adult TS women (55.5 ±

17.4 vs. 58.0 ± 17.3). The results in the group with the smallest deletions (bin 1) also differed significantly from controls (55.5 ± 17.4 vs. 67.8 ± 19.0, p < 0.0001, ANO-VA). These results set the stage for identifying specific X-linked gene(s) influencing visual-spatial cognitive ability. The 2.6-Mb Xp-Yp pseudoautosomal region would seem likely to play a role in TS: X and Y copies of the region are identical, and all genes within the region appear to escape X inactivation [63]. However, short stature related to haploinsufficiency of SHOX is the only clinical finding consistently associated with deletions of this region [64–66]. To date, 14 pseudoautosomal genes have been identified, 11 of which lie within the TS neurocognitive critical region (fig. 4). This list can be further narrowed and prioritized on the basis of gene expression pat-
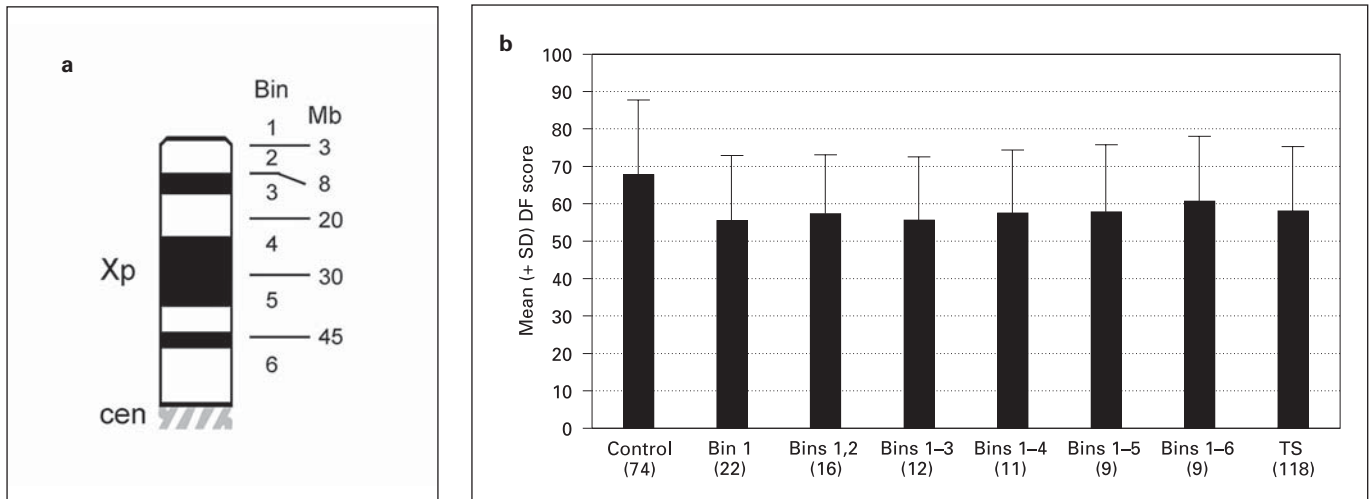
Fig. 3. **a** Map of Xp deletions clustered according to bins used in the analysis shown in figure 3b. **b** DF scores (mean ± SD) in adult patients with partial deletions of Xp, according to defined bins, versus TS adults versus controls. Number of subjects indicated in parentheses.
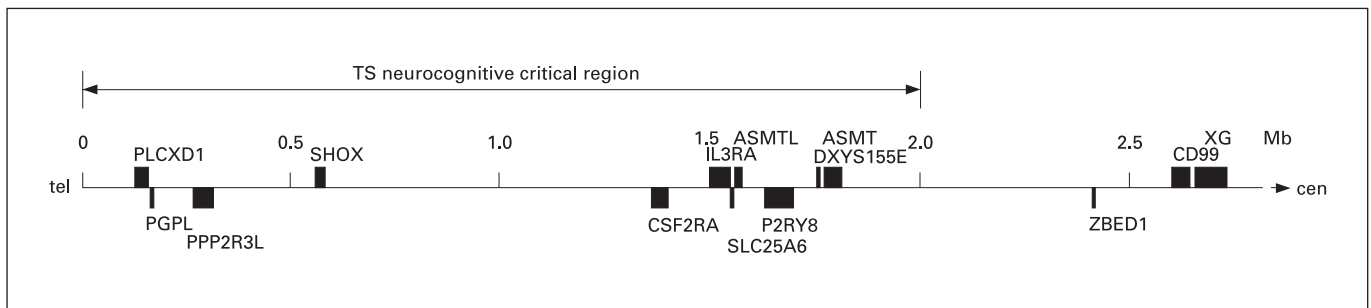

Fig. 4. Genes in the TS neurocognitive region in the pseudoautosomal region.

terns; at least three of the genes (CSF2RA, IL3RA, P2RY8) are selectively expressed in lymphocytes and are thus unlikely to influence brain development. Although it appears that this distal Xp candidate gene influences visual-spatial ability, additional genes elsewhere on the X chromosome may also contribute to the TS cognitive phenotype [67]. Some of these may be identified by studying animal models. Further studies will refine the list of candidate genes and delimit their contribution to the TS neurocognitive phenotype.

Conclusion

Characterization of specific TS causative genes would provide insight into the pathophysiology of 45,X TS as well as the process of normal neurocognitive development. Alterations in TS brain development most likely result from a complex interaction between genetic and hormonal deficiencies. Future studies will elucidate the cognitive deficits and the underlying etiology. These results should allow us to begin to design cognitive interventions that might lessen those deficits in this population.

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