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Effects of X-Monosomy and X-Linked Imprinting on Superior Temporal Gyrus Morphology in Turner Syndrome

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Abstract

Background—Turner syndrome (TS) results from complete or partial monosomy X. The cognitive phenotype of TS involves preservation of verbal skills with visuospatial functioning deficits. The superior temporal gyrus (STG), which is involved in language capacities, has not been investigated in TS.

Methods—The STG was measured in 30 female subjects (mean age = 14.73 ± 6.41; range = 7.56 –33.30) with TS and 30 age-matched control subjects (mean age = 14.63 ± 5.90; range = 6.35–32.65) using volumetric magnetic resonance imaging analyses.

Results—Right STG, including both gray and white matter volumes, was significantly larger in TS compared with control subjects. Overall left STG volume was not significantly different between groups, although left white matter volume was increased in the TS subjects. The TS subgroup with a maternally derived X chromosome (Xm) demonstrated more aberrant STG volumes compared with subjects with a paternally (Xp) derived X and control subjects. The difference in STG volumes between Xm and control subjects involved both white and gray matter. The Xm subjects differed from Xp subjects only in terms of gray matter.

Conclusions—These findings suggest that X-monosomy and X-linked imprinting negatively affect STG development, possibly by disrupting neural pruning mechanisms.

Keywords

Turner syndrome; X-monosomy; superior temporal gyrus; genomic imprinting; MRI; neural pruning

Introduction

Turner syndrome (TS) is a complex phenotype associated with gender chromosome aneuploidy with complete or partial monosomy X. Although most TS conceptuses die early in pregnancy, TS is one of the most common gender chromosome abnormalities, affecting approximately 1 in 2000 live-born female infants (Jacobs 1992; Jones 1997). The physical phenotype includes short stature, ovarian failure, webbed neck, aortic coarctation, impaired

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glucose tolerance, autoimmune thyroid disease, and hypertension (Jones 1997; Zinn et al 1998). There is considerable heterogeneity of phenotypic features, with short stature and gonadal dysgenesis being the most consistent characteristics (Jones 1997).

Cognitively, girls and women with TS typically demonstrate normal global intellectual functioning; however, nonverbal abilities are often significantly impaired (Ross et al 2002; Zinn et al 1998). Subjects with TS show deficits in visuospatial, visuoperceptual and visuoconstructional abilities, arithmetic skills, executive functioning, motor function, attention, and memory functioning (Bender et al 1993; Haberecht et al 2001; Nijhuis-van der Sanden et al 2000; Pennington et al 1985; Romans et al 1997; Ross et al 1996; Rovet et al 1994; Temple and Carney 1995; Williams et al 1991). Recent studies suggest that some neurocognitive deficits associated with TS tend to improve with estrogen treatment, whereas others do not (Ross et al 2002).

Psychosocial difficulties also are characteristic of TS (Ross et al 2002; Skuse et al 1997). Adolescent girls with TS seem to be less socially active than their peers, demonstrate more immature behaviors, attention deficits, and hyperactivity and tend to cope with difficulties in a less adaptive manner, using denial and repression (McCauley et al 2001). Girls with TS tend to have more difficulties getting along with peers, are more isolated, and have fewer friends compared with control subjects (Siegel et al 1998).

There is much heterogeneity in type and severity of physical and cognitive presentation among TS subjects, based partly on differences in karyotype. Individuals with only some cells being monosomy X (e.g., XX/X mosaics or XY/X mosaics), or who have only a part of one X chromosome missing, typically have fewer severe deficits compared with individuals who demonstrate complete X monosomy (Jones 1997). Variability may also result from genomic imprinting, a mechanism of gene regulation that causes differential gene expression. Specifically, whether an imprinted gene is expressed depends on its parental origin (Constancia et al 1998; Nicholls 2000). Imprinted genes seem to have specific effects on brain development, depending on their parental origin (Keverne 1997, 2001; Keverne et al 1996). Although the issue remains controversial, some studies of this phenomenon in TS demonstrate a possible imprinting effect on behavioral phenotype (Bishop et al 2000; Donnelly et al 2000; Skuse et al 1997). Additionally, a study by our laboratory on parietal lobe morphology in 26 female subjects with TS demonstrated reduced occipital white matter and increased cerebellar gray matter in subjects with Xm compared with control subjects; however, the Xm and Xp subjects did not differ significantly from each other in terms of brain morphology (Brown et al 2002).

Neuroimaging studies indicate parietal lobe abnormalities as the most consistent finding in subjects with TS. Decreased volume in this area is often correlated with visuospatial deficits (Murphy et al 1993; Reiss et al 1993, 1995). One area that has not been examined in TS is the superior temporal gyrus (STG). Numerous studies using various techniques, such as functional magnetic resonance imaging (MRI), positron emission tomography (PET), and evoked potentials, have demonstrated the importance of the STG in processing complex auditory stimuli including speech and music. The STG appears to be involved in several aspects of language processing including speech perception, analysis, and production and verbal self-monitoring (Benson et al 2001; Binder et al 2000; Burton et al 2001; Dhankhar et al 1997; Hickok et al 2000; Howard et al 2000; McGuire et al 1996). Aphasic disorders are common among individuals with lesions to this area with the type of aphasia being relative to specific regions of the STG (Kreisler et al 2000). The STG appears to consist of several separate areas including Heschl's gyrus, the planum temporale, and temporal polar cortex (Pearlson 1997). Additionally, it has been shown that speech processing may involve

multiple, and possibly hierarchically organized, functional areas of the STG (Binder et al 2000; Howard et al 2000).

As indicated earlier, the cognitive profile seen in TS patients involves relative preservation of verbal language skills. Many studies have indicated that individuals with TS actually show superior skills compared with control subjects in certain verbal areas. Girls with TS demonstrate higher reading levels, accuracy, and comprehension compared with controls (Temple and Carney 1996). Subjects with TS have also been shown to have better receptive vocabulary skills and understand significantly more low-frequency words than control subjects (Temple 2002). Additionally, girls with TS appear to excel at tasks involving verbal abstract reasoning and verbal comprehension (LaHood and Bacon 1985).

Several studies have investigated the association of STG volumes with cognitive phenotype in specific neurodevelopmental disorders. For example, STG volumes are disproportionately increased in individuals with Williams syndrome (Reiss et al 2000), who, like girls with Turner syndrome, demonstrate cognitive strengths in the verbal domain and weaknesses in visuospatial processing (Bellugi et al 2000). Conversely, STG volumes are significantly decreased in Down (Frangou et al 1997; Pinter et al 2001; Wisniewski 1990) and Klinefelter syndromes (Patwardhan et al 2000), disorders in which verbal skills are relatively weaker compared with overall cognitive level. Accordingly, we tested the hypothesis that STG morphology would serve as a biological marker of relatively preserved verbal function in girls with TS.

Additionally, a preliminary investigation of genetic imprinting effects on STG development has been reported. Based on our previous findings of genetic imprinting effects on brain morphology in TS (Brown et al 2002), we hypothesized that subjects with TS having a maternally derived X chromosome would show more aberrant neuro-anatomy compared with normal control subjects.

Methods and Materials

Subjects

Subjects consisted of 30 individuals with Turner syndrome (mean age = 14.73 ± 6.41; range = 7.56–33.30) and 30 age-matched typically developing female subjects (mean age = 14.63 ± 5.90; range = 6.35–32.65). Among those with TS, 20 had the maternally derived X chromosome (mean age = 15.2 ± 6.9; range = 7.6–33.3), and 10 had the paternally derived X chromosome (mean age = 13.6 ± 5.5; range = 7.6–24.4). This ratio of subjects with Xm to Xp is consistent with what is typically found in the TS population (Jacobs et al 1990, 1997). Age was not significantly different between the Xp and Xm groups ($F = .498$, $p = .49$). Subjects with TS were recruited through the National Turner Syndrome Foundation, the Denver Gender Chromosome Abnormality Study, the Human Growth Foundation, local physicians, and the Stanford Psychiatry Neuroimaging Laboratory Web site. Only subjects with a monosomic 45, X genotype (nonmosaic) were included in this study given that mosaicism tends to confound the effects of the monosomic X state (Jones 1997; Zinn et al 1998).

Control subjects were recruited through local newspapers and parent group newsletters. A control subject was included if her age was within 2 years of a TS subject. Control subjects were excluded for having any history of neurologic, psychiatric, or substance use disorders and also for current illicit substance or psychotropic medication use. Any TS or control subjects with orthodontic braces was excluded. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield 1970). The two groups were frequency matched for handedness (chi-squared p value = .67) with the TS group having 28 right-handed and 2

left-handed subjects and the control group having 26 right-handed and 4 left-handed subjects. After providing a complete description of the study to all participating subjects and their caretakers, written informed consent was obtained under protocols approved by the Institutional Review Board of Stanford University.

Genetic Analysis

Genetic testing was done on blood samples from the subjects and both parents if available. Patients, their parent(s), and, when available, their sibling(s) had testing at the androgen receptor (Xq11.2-Xq12), HPRT (Xq26.1-Xq26.1), DXS6809 (pter-Xqter), and DXS9895 (X chromosome). When both parents were available, the parental origin of the patient's X was shown by clear differences in alleles. When only one parent was available, parental origin of the patient's X was determined by presence of an allele in the patient that was not present in the available parent at one or more loci. In the three families in which parental origin of the patient's X chromosome was not clear, the following additional markers were used to determine parental origin: DXS6799 (Xpter-Xqter), DXS8378 (Xpter-Xqter), DXS9898 (X chromosome), DXS101 (Xq22-Xq22), DXS733 (Xq24-Xq26), DXS1120 (Xq22.2-Xq22.3), DXS731 (Xq27-Xq28), DXS1125 (Xq11.2-Xq13), DXS1190 (Xpter-Xqter), and DXS1123 (Xq27-Xq27/Xq28-Xq28).

Image Acquisition

Given the increased incidence of anxiety and hyperactivity among individuals with TS, most subjects were prepared for the scanning session using a mock scanner that included a behavioral training program focused on desensitization of scanner-related fears and shaping of compliant behavior. Magnetic resonance brain images were then obtained with whole body GE Signa Horizon scanners (GE Medical Systems, Milwaukee, WI) at Stanford University School of Medicine, Johns Hopkins University School of Medicine, and National Jewish Medical and Research Center in Denver. A recently published paper from our lab at Stanford University has addressed the question of compatibility of data collected from multiple sites and included data from the sites used in our study (Patwardhan et al 2001). Coronal three-dimensional volumetric spoiled gradient echo (SPGR) series were acquired using the following parameters: repetition time = 35 or 45, echo time = 6, flip angle = 45, number of excitations = 1, field of view = 20 or 24 cm and matrix size = 256 × 256 for 124 contiguous slices of 1.5 mm width.

Image Processing

All image processing was completed at Stanford University. Scans from other sites were delivered digitally via FTP (file transfer protocol) transfer. Raters blinded to diagnosis visually inspected the SPGR images to exclude those that could not be processed because of excessive motion artifact; no images met exclusion criteria, however. The MRI scans were imported into BrainImage (Stanford University, Stanford, CA) for semiautomated whole-brain segmentation and quantification in the coronal plane using previously described and validated methods (Kates et al 1999; Reiss et al 1998). Interrater reliability obtained by interclass correlation exceeded .90.

The STG was manually delineated for each subject, also in the coronal plane, using data sets derived from the whole-brain analysis. These data sets were standardized in their orientation parallel to the plane defined by the anterior and posterior commissures. The STG was defined laterally by the cortical surface and medially by a line connecting the deepest extension of the superior temporal sulcus to the furthest extent of the inferior ramus of the sylvian fissure. The STG was defined anteriorally by the median between the head of the putamen and the anterior commissure. The most posterior slice of the STG was drawn at the

level where the crus of the fornix was clearly identified laterally from the pulvinar. Interrater reliability for the STG measurement indicated by interclass correlation was .97.

The intellectual functioning of TS and normal control subjects was assessed using the Wechsler Adult Intellectual Scale, Third Edition (WAIS-III; Wechsler 1997) for subjects 17 years of age and older and the Wechsler Intellectual Scale for Children, Third Edition (WISC-III) for subjects under the age of 17 (Wechsler 1991). Full Scale IQ (FSIQ) data were not available for one TS subject. Additionally, Verbal IQ (VIQ) and Performance IQ (PIQ) scores were not available for four TS and seven control subjects.

Statistical Analyses

Univariate analysis of covariance (ANCOVA) was used to examine group differences in total cerebral tissue with age as a covariate. A multiple analysis of covariance (MANCOVA) was used to determine if the groups differed in their profiles of right and left STG total tissue volumes. A separate MANCOVA was then calculated to determine if there was a significant group tissue type (gray and white matter) effect. Age and total cerebral tissue were included as covariates in both MANCOVA analyses. Group differences in STG volumes between parental origin groups (Xm, Xp, and control groups) also were examined using MANCOVA with Bonferroni post hoc analyses. A repeated-measures ANOVA was calculated to determine any right–left STG asymmetry within and between the groups. Differences in IQ scores between groups were compared using univariate analyses of variance (ANOVA). Exploratory analyses of IQ and age correlates with STG volumes were conducted. For the STG and IQ correlations, variance in STG volumes due to total cerebral tissue and age were residualized by regression analysis and then correlated with IQ scores. For all statistical tests, an alpha of .05 was chosen as the threshold for statistical significance.

Results

Sample Characteristics

Age and IQ data for the two groups are presented in Table 1. Subjects with TS had significantly lower FSIQ ($F = 11.6$; $df = 1,59$; $p = .001$), VIQ ($F = 5.21$; $df = 1,49$; $p = .03$), and PIQ scores ($F = 28.6$; $df = 1,49$; $p = .000$) compared with control subjects. Additionally, the difference between VIQ and PIQ (VIQ > PIQ) was significantly greater in TS compared with control subjects ($F = 6.23$; $df = 1,49$; $p = .02$). Bonferroni post hoc analyses of IQ scores across the three origin groups indicated that Xm and Xp subjects were significantly lower than control subjects in terms of FSIQ, VIQ, and PIQ but did not differ from each other. Because of unequal variances in the IQ scores between groups, follow-up nonparametric tests also were calculated and these revealed similar results.

STG Volumes: TS versus Control Subjects

Visual inspection of total cerebral tissue volumes between groups indicated that the data were not normally distributed (TS mean = 1036 ± 96 cm^3; Control mean = 1079 ± 82 cm^3). Therefore, nonparametric tests were used that showed no difference in total cerebral tissue between the two groups (Mann–Whitney $U = 352$, $p = .15$). As shown in Table 2, a Wilks lambda value of .743 ($F = 9.50$; $df = 2,55$; $p = .000$, $Eta^2 = .26$) indicated a significant group effect in the profile of left and right STG volumes, irrespective of age or total cerebral tissue. In this model, total cerebral tissue was a significant covariate ($p = .002$), but age was not ($p = .287$). Follow-up ANOVAs indicated that TS subjects' right STG volumes were significantly larger ($F = 18.3$; $df = 1,60$; $p = .000$; $Eta^2 = .25$) than control subjects, whereas the left STG was not significantly different ($F = 3.9$; $df = 1,60$; $p = .06$; $Eta^2 = .06$).

A significant group effect for tissue type (gray vs. white) effect was indicated by a Wilks lambda value of .717 (F = 5.23; df = 4,53; p = .001; Eta^2 = .28). Specifically, ANOVAs showed significantly greater right STG gray, right STG white and left STG white matter volumes in TS subjects (Table 2). Left STG gray was not significantly different between the groups. Total tissue was a significant covariate in this analysis (p = .002), but age was not. There was no significant difference between the two groups in terms of the number of slices used to measure the STG (t = −1.04; p = .30). The main effects of STG volume remained after covarying for IQ.

Repeated-measures analysis indicated that the right STG tended to be significantly larger than left STG in the TS group (F = 4.7; df = 1, 56; p = .03, Eta^2 = .07), whereas control subjects had more symmetrical STG volumes. The right > left by diagnosis interaction was significant at p = .003 (F = 18.6; df = 1,56 Eta^2 = .15).

Parental origin effects on STG volumes (see Table 3) between the two TS parental origin groups (Xm and Xp) and control subjects also were significantly different with a Wilks lambda of .621 (F = 7.23; df = 4108; p = .000 Eta^2 = .21). ANOVAs indicated a significant main effect for parental origin group in both left (F = 6.59; df = 2,60; p = .003; Eta^2 = .19) and right (F = 14.58; df = 2,60; p = .000; Eta^2 = .35) STG volumes. Total tissue was a significant covariate in the analysis (p = .001), but age was not (p = .184). Bonferroni post hoc pairwise comparisons among the Xm, Xp, and control groups revealed that right and left STG volumes in Xm subjects were significantly greater than those of control (left: p = .01, Eta^2 = .14; right: p = .000, Eta^2 = .37) and the Xp subjects (left: p = .01, Eta^2 = .20; right: p = .01, Eta^2 = .17). The STG volumes did not differ between the control and the Xp groups.

A main effect for parental origin group also was found in terms of tissue-specific differences with a Wilks lambda of .585 (F = 4.00; df = 8104; p = .000, Eta^2 = .24) with both age (p = .02) and total tissue (p = .01) being significant covariates. Subsequent ANOVAs indicated that left (F = 6.04; df = 2,60; p = .004; Eta^2 = .18) and right (F = 10.4; df = 2,60; p = .000; Eta^2 = .28) gray as well as left (F = 3.08; df = 2,60; p = .05; Eta^2 = .10) and right (F = 9.04; df = 2,60; p = .000; Eta^2 = .25) white matter STG volumes were significantly different between the parental origin groups. Bonferroni post hoc pairwise comparisons between the parental origin groups indicated significantly greater gray matter STG volume in the Xm subjects compared with both control (left: p = .04, Eta^2 = .09; right: p = .000, Eta^2 = .28) and Xp subjects (left: p = .01, Eta^2 = .28; right: p = .03, Eta^2 = .14), again with no difference between the control and Xp groups. Xm subjects also demonstrated significantly larger white matter STG volumes compared with control subjects (left: p = .05, Eta^2 = .16; right: p = .000, Eta^2 = .26) but were not different from Xp subjects in terms of this variable. White matter volumes in the STG also were not different between control and Xp subjects.

STG and IQ Correlations

Because of unequal variance in the IQ scores, nonparametric correlation analyses (Spearman) were used and, as shown in Table 4, these indicated that left STG total tissue volumes were significantly negatively correlated with FSIQ (r = −.32; p = .05) and VIQ (r = −.38; p = .03) in the TS but not the control group (FSIQ: r=−.07; p = .36; VIQ: r = .3; p = .44); however, the Fisher r to z transformation indicated that the correlations between the two groups were not significantly different (FSIQ: z = −.95; p = .17; VIQ: z = −1.4; p = .08). The same pattern, with even stronger correlations, was shown for right STG (FSIQ: r = −.42; p = .01; VIQ: r = −.51; p = .004). Only the correlation for VIQ was significantly different between groups (z=−1.66; p = .05). Additionally, parametric correlations (Pearson) indicated that age was significantly related to both left (r = −.39; p = .03) and right (r=−.40; p = .03) STG volumes in control but not TS subjects (left: r=−.20; p = .28; right: r=−.09; p

= .63). Again, however, these correlations were not significantly different between groups (left STG: $z = -.76$; $p = .22$; right STG: $z = -1.22$; $p = .11$).

Discussion

In this study, high-resolution volumetric MRI analysis revealed disproportionately larger right STG volumes in subjects with TS compared with typically developing control subjects. This difference involved both gray and white matter. Although the difference in total left STG volume only approached significance between the groups, white matter in the left STG was significantly greater in the TS sample. Additionally, compared with control subjects, there was marked asymmetry in the TS subjects' STG volumes, with right being significantly greater than left.

Another important finding of our study was the main effect for the parent of origin group differences in STG volume, with regard to both overall tissue and tissue specific volumes. Specifically, the differences in STG volumes observed between TS and control subjects appear to be driven largely by the TS subjects with Xm origin. Subjects with Xm had significantly larger left and right STG volumes compared with both control and their Xp counterparts, whereas the STG volumes of subjects with Xp did not differ from control subjects. The difference in STG volumes between Xm and control subjects involved both white and gray matter; subjects with Xm differed from those with Xp only in terms of gray matter. It should be noted, however, that the analyses involving parental origin groups operated with limited statistical power because of the small number of subjects with Xp. Therefore, these findings need to be replicated using a larger sample.

The larger right STG volume and right greater than left ($R > L$) asymmetry in the TS group is likely due to disruption in or alteration of developmental neural pruning mechanisms. Studies of both animal and human subjects have demonstrated that brain development is characterized by a steady increase in synaptic density from the early fetal stage until, with some regional variation, synaptogenesis reaches a peak at approximately 3 years of age. Following a period of relative stability, synapses and dendrites are systematically eliminated, or pruned, beginning at approximately age 5 and continuing until puberty. Synapse density then remains relatively stable throughout adulthood, having been reduced by 50%–60%, varying by brain region (Chechik et al 1999; Churchill et al 2002; Huttenlocher 1984, 1990; Huttenlocher and Dabholkar 1997; Irwin et al 2001).

Synaptic and dendritic pruning is believed to be activity dependent. Specifically, connections that are more frequently used tend to be strengthened and stabilized whereas less used pathways are eliminated, resulting in more efficient systems (Churchill et al 2002). Faulty pruning has also been implicated in other neurodevelopmental disorders such as fragile X and Rett syndromes (Churchill et al 2002; Johnston 2001). Disrupted pruning specific to the STG has been most extensively studied in schizophrenia. Excess pruning in this area appears to be correlated with significant perceptual and language deficits (Hoffman and McGlashan 1997; Pearlson 1997).

Apart from the putative neurodevelopmental effects of the imprinted loci on the X chromosome, additional explanations for disrupted pruning mechanisms in the STG of subjects with TS remain unspecified. Additionally, the specific functional impact of disproportionately increased STG volumes is unknown. As indicated earlier, increased STG volumes have been associated with Williams syndrome (Reiss et al 2000). These authors suggested that the larger STG volumes may relate to the preservation of some linguistic functions in these subjects; however, STG volume in the Williams syndrome study did not

include right and left STG delineation, and specific correlations with cognitive data were not made.

The functional significance of the right > left STG asymmetry found in the TS group is also unclear. It is traditionally held that language is lateralized to the dominant hemisphere, which would likely be the left hemisphere among our sample, given that the majority was right handed. Also, studies on language lateralization have demonstrated asymmetries in STG regions (i.e., planum temporale) associated with handedness. Typically, a L > R asymmetry has been associated with dextrals and the reverse for sinistrels (Foundas et al 1994; Habib et al 1995; Shapleske et al 1999); however, recent functional MRI studies indicate that language abilities may be represented more bilaterally in the STG (Binder et al 2000; Howard et al 2000), and it has long been known that gender affects language lateralization. Specifically, researchers have reported a reversal of planum temporale asymmetry (R > L) in female subjects (Shapleske et al 1999). These studies assume that increased tissue is associated with increased functioning, however. Additionally, these studies have largely involved typically developing individuals, did not correlate function with volume, and have been criticized for inaccurately assessing handedness (Shapleske et al 1999). Further compounding the issue of asymmetry are findings that girls and women with TS may have greater right hemisphere involvement in language functioning (Rovet 1990). The functional correlates of the aberrant STG morphology demonstrated among individuals with TS in our study requires further investigation.

The negative correlation of increased tissue volume with cognitive functioning found in our study suggests that increased STG volume among female TS subjects may be related to lowered language ability; however, it should be noted that although the IQ scores for subjects with TS were significantly lower than those of control subjects, the TS subjects' IQ scores were, on average, within normal limits except for PIQ, which was often within the "below average" range. Alternatively, a morphologically abnormal right STG may underlie the emotional, social, memory, and visuospatial difficulties observed among girls and women with TS rather than relating to verbal functioning in this population. It has been shown that STG morphology relates to social intelligence in Asperger's syndrome, a pervasive developmental disorder characterized by a verbal > visual cognitive profile, similar to that of Turner syndrome (Baron-Cohen et al 1999). Additionally, girls and women with TS often have significant problems with anxiety, hyperactivity, and obsessions (Abd et al 1999). Studies of children with anxiety disorders have demonstrated greater STG volumes with R > L asymmetry compared with control subjects (De Bellis et al 2002a, 2002b).

Furthermore, the STG has efferent connections with inferior parietal lobes and prefrontal cortex. The STG also receives input from the limbic system, in particular, the amygdala, parahippocampus, and entorhinal cortex, which provides the main input to the hippocampus. These networks are involved in attention and memory functioning, two areas of notable cognitive dysfunction in girls with TS. As indicated earlier, parietal cortex has been shown to be significantly reduced in subjects with TS (Murphy et al 1993; Reiss et al 1995). It is interesting to note that the brain abnormalities found by Murphy and colleagues were greater on the right than the left side. Additionally, Murphy and colleagues demonstrated decreased hippocampal volumes in female subjects with TS compared with control subjects. Decreased volume in the parietal and mesial temporal areas found among individuals with TS may impact activity-dependent synaptic pruning down the line in the STG region of these subjects. Thus, it may be the disruption of these parietofrontal–limbic–STG networks that contribute to the neuropsychologic deficits found in girls and women with TS rather than abnormalities in a single structure.

With respect to maturation, STG volume was negatively correlated with age in the controls; however, this was not the case in the TS subjects. Decreasing tissue volume, particularly gray matter volume, is a consistent finding in typically developing individuals (Courchesne et al 2000; Giedd et al 1999; Sowell et al 1999, 2001). Furthermore, several studies on normal brain maturation have demonstrated specific volume reductions in STG with age, including reduction in total STG volume (Bigler et al 2002), dendritic degeneration (Jacobs and Scheibel 1993), and decrease in mean synaptic density (Huttenlocher and Dabholkar 1997). Additionally, studies of cerebral blood flow and metabolism indicate normal, age-related perfusion decreases in the STG of typically developing individuals (Martin et al 1991; Van Laere et al 2001). These normal, age-related changes in STG volume seem to correspond with expected decreases in certain cognitive functions. For example, changes in tissue volume and hemispheric asymmetry in the STG regions have been associated with changes in verbal functioning among healthy elderly individuals (Bellis et al 2000; Huttenlocher and Dabholkar 1997; Sowell et al 2002). It is unclear why STG morphology in TS does not exhibit the maturational trajectory seen in normal aging or how the lack of correlation between STG tissue volume and age affects cognitive ability in TS. Therefore, further investigation of maturational changes in TS subjects' STG is needed to determine the effects, if any, of disproportionately large, temporally stable STG volumes on neuropsychologic functioning.

Turner syndrome offers a unique opportunity to investigate the possibility of X-linked imprinting effects on cognitive functioning. Because girls and women with TS have only one X, either the paternally or the maternally derived, the individual contributions of each genome on brain development can be examined. One study demonstrated differential effects of imprinted genes on brain development using chimeric mouse embryos containing either duplicated maternal (Gg) or duplicated paternal (Ag) genomes (Keverne et al 1996). Gg cells were predominately located in the cortex and striatum, whereas Ag cells were largely absent in these areas. Conversely, Ag cells were abundant in the hypothalamus, whereas Gg cells were nearly nonexistent. The authors identified two XO chimeras, one with the paternal and one with the maternal X. Each of these embryos demonstrated the same distribution of Gg and Ag cells within the cortex and hypothalamus as the disomic embryos. Additionally, Gg cells appeared to increase brain tissue growth, whereas Ag cells tended to slow growth in the forebrain. The authors suggest that the imprinted genes may work in tandem within normal cells to control brain tissue growth. The genes on the maternally derived genome may direct neural reproduction while the paternally inherited genes compensate through apoptosis and other such mechanisms.

Our study presents brain morphologic data in human subjects that suggests the possibility of X-linked imprinting. With respect to the STG, girls and women with Xm showed greater discrepancy from healthy control subjects compared with those with Xp. In fact, those with Xp did not differ from typically developing control subjects in terms of STG for overall or tissue specific volumes. This observation is consistent with Keverne et al's (1996) findings. Specifically, if the Xp restraint on cell proliferation is reduced or absent, as it is in girls and women with Xm, brain growth in certain areas may occur with decreased modulation. Further investigation of regional brain volumes and morphology associated with imprinting in subjects with TS is warranted.

In terms of functional manifestations of X-linked imprinting in TS, it has been suggested that girls and women with Xp perform significantly better on measures of social cognition, verbal intelligence, and executive functioning compared with subjects with Xm (Skuse et al 1997). Additionally subjects with Xm show significantly impaired delayed verbal recall compared with control subjects whereas those with Xp demonstrated relative deficits on tasks of delayed visual recall (Bishop et al 2000). The IQ scores between origin groups in

our study were not significantly different. This may have been because of the small number of individuals with the Xp genotype or the missing IQ data (or both). Additionally, functional differences associated with imprinting may occur in more specific or subtle cognitive functions not elucidated by IQ scores.

Weaknesses of our study include the small sample size of the Xp group. The parental origin analyses lacked statistical power, especially in the comparisons between the Xp and control groups. Future studies should also include subparcellation of the STG region given the cytoarchitectonic and functional differences observed in this area (Binder et al 2000; Howard et al 2000; Pearlson 1997). The separate STG regions may be differentially affected by X-monosomy or X-linked imprinting. Also, estrogen and growth hormone information was not available for all subjects, therefore the possible effects of hormone treatments on STG morphology could not be addressed. Studies have failed to consistently demonstrate the influence of estrogen levels and growth hormone on cognitive functioning in female subjects with TS (Berch and Bender 2000; Ross et al 1997); however, hormone treatments may affect brain morphology, particularly in terms of synaptic reorganization and pruning (Wolff et al 1995).

Another weakness of this study is the large age range of the subjects. This may have caused confounds in terms of brain development. Age was included as a covariate in statistical analyses of volumetric data; however, the potential impact of estrogen insufficiency was not addressed. Younger subjects would not likely be taking estrogen, whereas older subjects would; the effects of this difference on brain development was not investigated. Additionally, the choice of comparison group has been raised as a methodologic concern when studying girls and women with TS (Berch and Bender 2000). Future studies might use typically developing control subjects that are better matched for IQ, individuals with similar brain abnormalities, or male or nonverbal learning disordered comparison groups. This study also lacked a more specific language measure that may have been more sensitive to differential verbal abilities between the Xm, Xp and control groups. Additionally, longitudinal studies of regional brain morphology in Turner syndrome are necessary to examine maturational changes associated with X-monosomy and X-linked imprinting.

In summary, this study demonstrated significantly increased right STG volumes in subjects with TS compared with control subjects. This involved both white and gray matter and was irrespective of age or IQ. Additionally, we showed preliminary evidence for an X-linked imprinting effect on STG morphology. Specifically, subjects with TS who had a maternally derived X chromosome demonstrated significantly greater STG volumes compared with both control subjects and subjects who had a paternally derived X chromosome. X-monosomy, X-linked imprinting, or both may have an impact on STG development. Also, STG volume in subjects with TS did not decrease with age as it does in typically developing individuals, suggesting that primary (genetic) or secondary (e.g., hormonal) mechanisms in TS disrupt the maturational trajectory of this brain region. Functional correlates of aberrant STG morphology and development in Turner syndrome are currently unclear and require further investigation.

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Table 1

Age and IQ Data

	TS	*n*	Xm	*n*	Xp	*n*	Con	*n*
Age	14.7 ± 6.4	30	15.2 ± 6.9	20	13.6 ± 5.5	10	14.6 ± 5.9	30
Age Range	7.6–33.3	30	7.6–33.3	20	7.6–24.4	10	6.4–32.7	30
FSIQ[b]	96.7 ± 16	29	96 ± 19	20	100 ± 10	9	111 ± 17	30
VIQ[a]	103 ± 20	26	101 ± 23	18	107 ± 12	8	114 ± 14	23
PIQ[b]	89 ± 13	26	88 ± 15	18	95 ± 10	8	111 ± 15	23
VIQ-PIQ[a]	13.5 ± 14	26					3.3 ± 13	23

Con, control; FSIQ, Full-Scale IQ score; PIQ, Performance IQ score; TS, Turner syndrome; VIQ, Verbal IQ score; Xm, Turner syndrome, maternal origin; Xp, Turner syndrome, paternal origin.

[a] Significant at $p = .05$ for TS vs. Con

[b] Significant at $p = .01$ for TS vs. Con

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Table 2

Superior Temporal Gyrus Volumes in TS and Control Subjects

	TS	Con	Wilks's Lambda	Omnibus *p* Value	ANOVA *p* Value	Eta^2
STG Group by Side			.74	.000		.26
STG Group by Tissue Type			.72	.001		.28
Left STG	18.5 ± 2.4	17.8 ± 2.2			.06	.06
Gray	13.7 ± 1.9	13.4 ± 1.8			.25	.02
White	4.9 ± 1.0	4.4 ± .7			.01	.11
Right STG	20.5 ± 3.0	18.5 ± 2.5			.00	.25
Gray	14.7 ± 2.4	13.3 ± 2.1			.00	.19
White	5.9 ± 1.1	5.2 ± .9			.00	.18

ANOVA, analysis of variance; Con, control; STG, superior temporal gyrus. TS, Turner syndrome.

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Table 3

Superior Temporal Gyrus Volumes between Origin Groups

	Xm *n* = 20	Xp *n* = 10	Con *n* = 30	Wilks's Lambda	Omnibus *p* Value	ANOVA *p* Values	Eta^2
STG by Side				.62	.000		.21
STG by Tissue Type				.59	.000		.24
Left STG	19.4 ± 2.2	17.3 ± 2.1	17.8 ± 2.3			.003[a]	.19
Gray	14.4 ± 1.8	12.6 ± 1.6	13.4 ± 1.8			.004[a]	.18
White	5.0 ± .9	4.7 ± 1.3	4.4 ± .7			.05[a]	.10
Right STG	21.4 ± 2.5	19.0 ± 3.2	18.4 ± 2.5			.000[a]	.35
Gray	15.3 ± 2.1	13.7 ± 2.5	13.3 ± 2.2			.000	.28
White	6.1 ± 1.0	5.2 ± 1.0	5.2 ± .9			.000[b]	.25

ANOVA, analysis of variance; Con, control; STG, superior temporal gyrus; Xm, Turner syndrome, maternal origin; Xp, Turner syndrome, paternal origin.

[a] Xm > Xp, Con; $p < .05$ (post hoc)

[b] Xm > Con; $p < .05$ (post hoc)

Table 4

Correlational Data

	FSIQ	VIQ	PIQ	Age
TS				
Left STG	−.32[a]	−.38[a]	−.28	−.20
Right STG	−.42[b]	−.51[b]	−.28	−.09
Con				
Left STG	−.07	.03	−.09	−.39[a]
Right STG	−.05	−.06	−.07	−.40[a]

Con, controls; FSIQ, Full Scale IQ score; PIQ, Performance IQ score; STG, superior temporal gyrus; TS, Turner syndrome; VIQ, Verbal IQ score.

[a] significant at .05 level

[b] significant at .01 level