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Clinical Significance of the Parental Origin of the X Chromosome in Turner Syndrome

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Context: The phenotype in Turner syndrome (TS) is variable, even in patients with a supposedly nonmosaic karyotype. Previous work suggested that there were X-linked parent-of-origin effects on the phenotype.

Hypothesis: The TS phenotype is influenced by the parental origin of the missed X chromosome.

Design: This was a multicenter prospective study of TS patients and both their parents, determining parental origin of the X-chromosome, and characterizing the clinical phenotype.

Patients and Methods: Eighty-three TS patients and their parents were studied. Inclusion criteria were TS with karyotype 45,X or 46Xi(Xq). Four highly polymorphic microsatellite markers on the X-chromosome DMD49, DYSII, DXS1283, and the androgen receptor gene and three Y chromosome markers, SRY, DYZ1, and DYZ3.

Outcome Measures: The study determined the correlation between the parental origin of the X chromosome and the unique phenotypic traits of TS including congenital malformations, anthropometry and growth pattern, skeletal defects, endocrine traits, education, and vocation.

Results: Eighty-three percent of 45,X retained their maternal X (X^m), whereas 64% 46Xi(Xq) retained their paternal X (X^p, $P < 0.001$). Kidney malformations were exclusively found in X^m patients ($P = 0.030$). The X^m group had lower total and low-density lipoprotein cholesterol ($P < 0.003$), and higher body mass index SD score ($P = 0.030$) that was not maintained after GH treatment. Response to GH therapy was comparable. Ocular abnormalities were more common in the paternal X group ($P = 0.017$), who also had higher academic achievement.

Conclusions: The parental origin of the missing short arm of the X chromosome has an impact on overweight, kidney, eye, and lipids, which suggests a potential effect of an as-yet-undetermined X chromosome gene imprinting. **(*J Clin Endocrinol Metab* 92: 846–852, 2007)**

NORMAL FEMALES (46,XX) possess both a maternally (X^m) and a paternally derived X chromosome (X^p). About 50% of Turner syndrome (TS) patients have a 45,X monosomy, whereas the rest are mosaics or have a structural X or Y chromosome abnormalities (1, 2), but all have a deletion of the short arm of chromosome X (Xp).

The phenotype in TS is variable even in patients with a supposedly nonmosaic karyotype; the reasons for this variability are not clear, and it led to a speculation that the TS phenotype may be influenced by the parental origin of the retained X chromosome. Differences in physical or behavioral phenotype between subjects with 45, X^p and 45, X^m TS might therefore indicate the existence of imprinted genetic loci leading to expression of genes from only one of the parents who transmits them.

The parental origin of the X chromosome in TS has been the subject of several studies (3–8). Results of most, but not all, of these small and retrospective studies show that in the majority of patients the X^p chromosome is lost; thus, 60–80% of TS patients retain a X^m. Interestingly, aborted fetuses have higher incidence of X^p, suggesting that genetic imprinting may play an important role in the loss of TS fetuses (9).

Three studies correlated birth weight and height as well as other physical, anatomical, and physiological parameters in 33, 25, and 40 TS patients and found no significant differences in patients who retained the maternal or the paternal X chromosome (8, 10, 11). Tsezou *et al.* (8) also reported no difference between the groups regarding growth during the first and second year of GH therapy. On the other hand, Chu *et al.* (12) found that imprinting may play a role in cardiovascular anomalies and neck webbing but not renal anomalies. Skuse *et al.* (13) investigated 80 girls with TS, of whom 25 had an X chromosome of paternal origin, and found evidence for

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Abbreviations: ANCOVA, Analysis of covariance; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; hGH, human GH; LDL, low-density lipoprotein; NS, not significant; SDS, SD score; TS, Turner syndrome; X^m, maternally derived X chromosome; X^p, paternally derived X chromosome; Xp, short arm of chromosome X.

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a difference in sociocognitive function between X^m and X^P. The latter showed satisfactory social adjustment and had higher verbal and executive functional skills, whereas X^m patients had better visual-spatial memory tests.

Different phenotypes according to the parental origin of the X chromosome may indicate X imprinting, which has not been documented in humans so far. On the other hand, mice show X-linked imprinting effects on cognitive processes (14), the imprinted gene candidate being Xlr3b, which may be of importance in mediating behavioral effects.

The present study attempted to identify the phenotypic effects of possible X-linked imprinted genes in a large group of 83 TS patients who definitely miss the Xp arm (66 monosomic 45,X females and 14 with iso-Xq). We determined the parental origin of the retained X chromosome, subdivided the patients by the karyotype and compared in these groups the frequency of the unique phenotypic traits of TS, including congenital malformations, anthropometry and growth pattern, skeletal defects, endocrine traits, education, and vocation, thus testing the hypothesis that 45, X^P would be distinguished from 45, X^m. This may direct future research to the putative X-linked imprinted gene/genes on the Xp arm that may contribute to an eventual phenotypic variability according to parental origin.

Patients and Methods

This was a prospective study of TS patients and both their parents, determining parental origin of the X chromosome, and prospectively characterizing the clinical phenotype. The study was approved by the ethical committees of all participating centers. Subjects received verbal and written information concerning the study, and parents and patients signed informed consents.

Patients and clinical assessment

The study group included 83 patients with TS and their parents in a multicenter study, involving patients from Israel (28), Poland (39), Italy (10), and Turkey (6). The mean (±SD) patient's age was 15.1 ± 7.0 yr (range 0.4–39 yr). The patients were recruited during the year 2003 from the participating centers. Inclusion criteria were the following: karyotype 45,X or 46Xi(Xq); patients with mosaics, ring, or Y chromosomes were excluded; availability of samples of both parents and their consent to participate in the study. Each patient was reexamined by the coordinating physician in each center. Physical stigmata diagnosed on the basis of radiologic examinations such as echocardiogram, renal ultrasonography, and dual-energy x-ray absorptiometry (DXA) studies were collected retrospectively. Biochemical studies were done either prospectively or within the last year. Complete clinical, anatomical, and biochemical information was recorded in a table including more than 100 criteria and then evaluated by a single coordinator for the purpose of a unified evaluation in different centers.

X chromosome origin

Genomic DNA from TS patients and both their parents was extracted from peripheral leukocytes of all 83 families. Four highly polymorphic microsatellite markers were selected for their high percentage of heterozygosity (80.4–93.3%), their allele number (8, 10–13, 15–20), and their location on both Xp and Xq, and were amplified by PCR: DMD49 (Xp21.2), DYSII (Xp21.2), and DXS1283 (Xp22.3) and androgen receptor (Xq11.2). To detect possible hidden Y chromosome mosaics, three Y markers were selected for their location on Yp, centromer, and Yq; SRY, DYZ1, and DYZ3 markers were amplified by PCR. Internal controls (DYSII with SRY, IR5 with DYZ1 and DYZ3) were simultaneously amplified in a multiplex PCR. Female personnel carried out all experiments to prevent false-positive results. Primers and amplification conditions were as previously reported (7).

Statistical analysis

All statistical calculations were performed with SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL). χ^2 (Fisher exact, when appropriate) test was performed to examine relationship between categorical variables; results are not adjusted for multiple testing. The Mann-Whitney test was used to examine the possible relation between birth weight/gestational age/insulin/homeostasis model assessment and the parental origin of chromosome X. A *t* test was used to compare growth parameters and biochemical data between X^P and X^m patients. Analysis of covariance (ANCOVA) was used to adjust for age and body mass index (BMI), and results were compared with unadjusted analysis. Relation between patients' pretreatment and on GH treatment used Wilcoxon signed ranks test. Correlation coefficients were calculated between continuous variables.

Results

X chromosome origin

The study group consisted of 83 females with TS and missing Xp, 66 of whom had 45,X karyotype, missing both Xp and Xq, and 14 of whom had 46Xi (Xq), missing Xp, but triploid for Xq genes. The parental origin of the single X chromosome was determined in 80 of 83 patients using the markers mentioned above (one sample was inadequate and in another two the results were inconclusive). No unexpected X mosaicism was found in any patient by the four X chromosome markers.

The most informative marker as to the parental origin was DXS1283 on Xp22.3 that was examined in 82 patients and was informative in 69 (84%); DYSII was informative in 82%, DMD49 in 73%, and androgen receptor of Xq locus in only 65% of the patients. Amplification of the Y chromosome revealed a single case with previously unknown positive SRY, but no other Y markers, in a 45,X patient, who retained her X^m.

Overall, the retained X chromosome was maternal (X^m) in 60 (75%) of the patients and paternal (X^P) in 20 (25%) patients; these data are consistent with previous reports (10, 11, 13). A significant difference was found between 45,X and 46Xi(Xq) subjects. A clear majority (83%) of the former retained their X^m, whereas 64% of the latter retained their X^P ($P < 0.001$). Yet none of the clinical data reported in the following paragraphs was found different between 45,X and 46Xi(Xq) subjects.

Clinical data

The mean age for the all group was 15.1 ± 7.0 yr (range 0.4–39 yr). The mean age for the X^m group was 13.9 ± 7.0 yr (range 0.4–39.5 yr) and 19.3 ± 5.5 yr in the X^P group (range 7.9–29.3 yr).

The difference in the paternal or maternal origin of the X chromosome did not influence the birth weight (2.87 ± 0.56 kg in X^P and 2.76 ± 0.55 kg in X^m) or gestational age (38.9 ± 1.6 and 39.1 ± 1.6 wk, respectively). The incidence of spontaneous puberty at the appropriate age was also similar in the two groups [X^P, two of 17 (11.7%), and X^m, five of 30 (16.6%); not significant (NS)]. Only one patient (X^m) gave spontaneous birth.

Hypertension and major anomalies of the heart did not differ according to parental origin of the X chromosome (Table 1). Twenty percent of retained X^m and 35% of X^P had cardiac anomalies (NS); 8 and 15%, respectively, had hyper-

TABLE 1. Major physical anomalies according to parental origin of retained Xp

	X^m affected/total (%)	X^p affected/total (%)	Total affected (%)	Literature (%)
Cardiovascular				
Aortic coarctation	6/60 (10)	3/20 (15)	9/80 (11)	
Bicuspid aortic valve	6/60 (10)	4/20 (20)	10/80 (13)	
Aortic stenosis	4/60 (7)	2/20 (10)	6/80 (8)	
Aortic regurgitation	1/60 (2)	1/20 (5)	2/80 (3)	
Other anomaly	1/54 (2)	1/14 (7)	2/68 (3)	
Total	12/60 (20)	7/20 (35)	19/80 (24)	20–40
Hypertension				
Systolic > 90th centile	4/60 (7)	2/20 (10)	6/80 (8)	
Diastolic > 90th centile	4/60 (7)	3/20 (15)	7/80 (9)	
Total	5/60 (8)	3/20 (15)	8/80 (10)	7–17
Renal anomalies by ultrasonography				
Horseshoe kidney	2/60 (3)	0/20 (0)	2/80 (3)	
Ectopic kidney	0/60	0/20 (0)		
Renal agenesis	1/60 (2)	0/20 (0)	1/80 (1)	
Double-collecting system	7/60 (12)	0/20 (0)	7/80 (9)	
Ureteropelvic stenosis	2/60 (3)	0/20 (0)	2/80 (3)	
Total	12/60 (20)	0/20 (0)[a]	12/80 (15)	25–43

[a] Fisher's exact test, $P = 0.031$.

tension in the absence of primary renal or cardiovascular cause. On the other hand, kidney malformations were an exclusive manifestation of X^m patients; 20% of the X^m patients and none of the X^p had renal anomalies ($P = 0.030$, Table 1). When analyzed according to their karyotype, no significant differences were observed for any of the major physical anomalies.

Minor physical stigmata of the face, chest, bones, or limbs were similar among X^m and X^p patients (Table 2). The same was true for disorders of the thyroid, ear, skin, and gastrointestinal tract but not for the eye abnormalities that were significantly more prevalent in the X^p group ($P = 0.017$, Table 3).

Biochemical data

Three of the TS patient with a 45,X karyotype had type 1 diabetes mellitus; two of them retained X^m and one retained X^p. One X^m patient had type 2 diabetes. Serum glucose, insulin, and homeostasis model assessment as a measure of insulin resistance were similar in the two groups and normal. The X^m group had lower total cholesterol ($P < 0.004$) and low-density lipoprotein (LDL) cholesterol ($P < 0.05$) than the X^p group (Table 4). ANCOVA to age and BMI gave $P = 0.003$ for the total cholesterol and $P = 0.045$ for the LDL cholesterol.

Bone

The prevalence of fractures was identical in the two groups, and so was bone density by DXA, measured in 43 subjects above the age of available reference (Table 5).

Growth

Sixty-two of the TS patients had been treated with recombinant human GH (hGH); 17 of them retained X^p (starting at age 10.8 ± 2.8 yr), and 45 retained X^m (starting at age 9.9 ± 3.1 yr; NS). None received anabolic steroids or additional drugs. GH dosage did not differ significantly between the groups (ranging from 0.04 to 0.34 mg/kg·d in the X^m and 0.03

TABLE 2. Minor physical anomalies according to parental origin of retained Xp

	X^m affected/total (%)	X^p affected/total (%)	Total affected (%)	Literature (%)
Facials				
Epicanthal fold	22/60 (37)	9/20 (45)	31/80 (39)	
High arched palate	50/60 (83)	19/20 (95)	69/80 (86)	
Micrognathia	24/60 (40)	6/20 (30)	30/80 (38)	
Short neck	52/60 (87)	16/20 (80)	68/80 (85)	
Webbed neck	24/60 (40)	9/20 (45)	33/80 (41)	50
Low-set ears	25/60 (42)	9/20 (45)	34/80 (43)	
Low hairline	37/60 (62)	16/20 (80)	53/80 (66)	66
Thorax				
Shield chest	40/60 (67)	9/20 (45)	49/80 (61)	44–70
Widely spaced nipples	42/59 (71)	10/18 (56)	52/77 (68)	
Bone abnormalities				
Scoliosis	12/59 (20)	7/20 (35)	19/79 (24)	10
Kyphosis	4/46 (9)	2/17 (12)	6/63 (10)	
Cubitus valgus	46/59 (78)	13/20 (65)	59/79 (75)	55–66
Short fourth metatarsus	13/60 (22)	4/19 (21)	17/79 (22)	24
Short fourth metacarpus	27/60 (45)	11/20 (55)	38/80 (48)	
Madelung deformity	6/43 (14)	2/13 (15)	8/56 (14)	
Limbs				
Peripheral edema	25/60 (42)	6/20 (30)	31/80 (39)	
Nails deformity	29/60 (48)	11/20 (55)	40/80 (50)	

TABLE 3. Thyroid, ear, eye, skin, and gastrointestinal disorders according to parental origin of retained Xp

	X^m affected/total (%)	X^p affected/total (%)	Total affected (%)	Literature (%)
Thyroid disorder				
Hypothyroidism	14/60 (23)	4/20 (20)	18/80 (22.5)	22
Ear disorders				
Recurrent otitis	23/59 (39)	9/20 (45)	32/79 (41)	68
Conductive loss	12/58 (21)	6/20 (30)	18/78 (23)	
Sensorineural loss	1/56 (2)	0/20 (0)	1/76 (1)	
Total (any anomaly)	28/60 (47)	11/20(55)	37/80 (46)	
Eye disorders				
Nystagmus	1/56 (2)	0/18 (0)	1/74 (1)	
Strabismus	4/60 (7)	3/20 (15)	7/80 (9)	30
Color blindness (partial)	1/48 (2)	0/20 (0)	1/68 (2)	
Amblyopia	10/58 (17)	7/20 (35)	17/78 (22)	
Ptosis	8/60 (13)	4/20 (20)	12/80 (15)	16–29
Total (any anomaly)	18/60 (30)	12/20 (60)[a]	30/80 (38)	63
Skin disorders				
Multiple naevi	37/60 (62)	17/20 (85)	54/80 (7)	30–65
Alopecia	2/60 (3)	0/20 (0)	2/80 (3)	
Vitiligo	2/60 (3)	2/20 (10)	4/80 (5)	
Keloid	0/60 (0)	1/20 (5)	1/80 (1)	
Ichtyosis	1/57 (2)	0/18 (0)	1/77 (1)	
Psoriasis	5/60 (8.3)	1/20 (5)	6/80 (7.5)	
Gastrointestinal disorders				
Gastrointestinal bleeding	1/60 (2)	1/20 (5)	2/80 (3)	3
IBD	1/60 (2)	0/20 (0)	1/80 (1)	
Cirrhosis	0/60 (0)	0/60 (0)	0/60 (0)	
High liver enzymes	3/60 (5)	3/20 (15)	20/80 (8)	44

IBD, Inflammatory bowel disease.
[a] $P = 0.017$.

to 0.36 in the X^p). Using the TS-specific growth charts (15), the pretreatment height SD score (SDS) was -0.25 ± 0.88 for X^p patients and $+0.13 \pm 0.99$ in X^m patients (NS). Growth response was similar during the first year of GH treatment, and the current height and adult height of those who reached that point (eight patients in each group) did not differ as well. This remained true for each of the karyotype subgroups. The mean height gain (from initiating GH treatment to current height) was 1.49 ± 0.77 SDS in the X^p and 1.44 ± 1.00 SDS in the X^m group, subdividing this height gain in the years (till current age or ~20 yr, the end of growth) gave the mean height gain per year. In the X^p patients (15), it was 0.289 ± 0.21 SDS each year, and in the X^m patients (42), it was 0.4 ± 0.31 SDS/yr (NS). Again analyzing these in the TS girls with 45,X karyotype only gave similar results without preferential growth response in either groups.

The BMI SDS during childhood and before hGH treatment was 0.2 ± 1.1 for X^p and 1.1 ± 1.9 for X^m groups ($P = 0.030$, Table 6), and the most recent BMI SDS during this study was 0.9 ± 1.3 and 1.27 ± 1.8, respectively (NS). The percent of obese TS patients (BMI SDS > 2) was 33.3% in the X^p and 28.5% in the X^m group (NS).

Psychosocial aspects, education, and occupation

We addressed two parameters by self- and parental reporting. Learning difficulties were evaluated by the need for special education; thereby, 23% of the TS patients had some degree of learning difficulties, 18.7% of the X^p, and 25% of the X^m patients (NS). The analysis of a subgroup of patients over the age of 20 yr revealed that twice as many X^p patient (five of seven, 76%) had academic skills or degrees, compared with X^m patients (four of 11, 36%); with its small sample size, these data are not significant statistically, but they lend support to a previous report (16).

Parental data

The mean maternal and paternal ages were 26.6 and 29.7 yr, respectively, with no difference between the X^m and X^p groups or their karyotype. The pretreatment height SDS cor-

TABLE 4. Mean (± SD) of serum lipids and insulin resistance according to parental origin of retained Xp

	X^m (n = 58)	X^p (n = 20)	*P*
Lipids			
Total cholesterol (mmol/liter)	170 ± 35	201 ± 31	0.003
High-density lipoprotein (mg/dl)	62 ± 15	62 ± 15	0.863
LDL (mg/dl)	97 ± 27	116 ± 30	0.045
Triglycerides (mg/dl)	97 ± 44	97 ± 44	0.542
Carbohydrates			
Fasting glucose (mg/dl)	83 ± 10	77 ± 13	0.088
Fasting insulin (IU/ml)	7.6 ± 4.1	10.1 ± 10.3	0.671
Homeostasis model assessment for insulin resistance	1.5 ± 0.8	1.5 ± 1.1	0.861

ANCOVA to age and BMI for the total cholesterol, $P = 0.014$, and for the LDL cholesterol, $P = 0.035$.

TABLE 5. Bone health according to parental origin of retained Xp

	X^m	X^p	*P*
DXA Z score			
Total body	−1.16 ± 0.91 (n = 31)	−1.27 ± 1.35 (n = 12)	NS
Spine	−1.1 ± 1.1 (n = 12)	−1.3 ± 1.6 (n = 10)	NS
Femur	−1.0 ± 1.0 (n = 9)	−1.1 ± 0.9 (n = 8)	NS
Fractures	n = 60	n = 19	
Per 1000 subject-years	6.5	6.5	NS

related strongly in the X^p with the maternal and paternal height (r = 0.652 and 0.661, respectively (Table 7). In the X^m patients, the correlation with paternal height (r = 0.525) was greater than the correlation with maternal height (r = 0.369).

The overall frequency of abnormalities found in our study group (independent of their parental origin) was quite similar to the literature (Table 8).

Discussion

Parental imprinting of X chromosome genes was suggested as a possible explanation for some of the diverse phenotypic features in TS. The present study investigated in detail the possible correlation of phenotypic expression with the parental origin of the X chromosome in the largest ever cohort of TS patients. Similar to previous reports, 75% of our patients with 45,X or 46Xi(Xq) retained X^m and lost their X^p, whereas 25% retained their X^p and lost their X^m chromosome. Yet the prevalence of either the maternal or paternal X chromosome in the distinct karyotypes was very different. A majority of 45,X patients (83%) retained their X^m. The first studies of parental origin in 45,X observed that there is a higher rate of paternally derived single X chromosome in spontaneous abortions than liveborn (9), although following studies (3, 11) had shown the opposite. Paternal meiotic errors, particularly susceptibility for XY nondisjunction during meiosis, and to a lesser extant postzygotic mitotic loss, result in X^m genotype in most 45,X patients (16). Interestingly, most patients with 46Xi(Xq) (64%) in our study retained their X^p. Previous reports on larger group of 46Xi(Xq) patients had shown that formation of isochromosomes of Xq is a sporadic event, equally likely to be maternally or paternally derived and that the mechanism of formation is independent of the parental age (21); mostly they result from sister-chromatid breakage and reunion in the proximal Xp.

The multicenter design of this study was essential to assemble the largest ever number of subjects in this type of a study, but it also led to obvious difficulties in the rigor of clinical details. Even though, the small sample size made it difficult to have obtained enough power to detect mild differences, but the possibility to detect larger differences was attainable. To minimize these constraints, the clinical characterization was prospective; it was done by a single observer in each center, and they all used a unified table of more than 100 clinical features, which were later analyzed by the study coordinator. Although the age difference was significant statistically, its implication on each parameter studied is negligible in our opinion, even on the lipid profile. We admit to a possibility that some of the statistically significant results may be a spurious result of multiple testing. Physical stigmata diagnosed on the basis of imaging, such as heart defects, renal abnormalities, and bone mineralization defects were collected retrospectively or within the last year, but by different experts, with obvious possible discrepancy. We found no evidence of previously undetected mosaicism as far as four microsatellite markers can tell, but untested domain mosaicism can certainly not be fully excluded.

The overall frequency of abnormalities found in our sample group (independent of parental origin) was comparable with the prevalence reported in the literature for most of the abnormalities checked, total cardiac anomalies being on the lower range reported and renal anomalies found less frequently (Table 8).

Preferential loss of X^p in this study, and others, and higher incidence of retained X^p in aborted fetuses (9) led to the hypothesis that deletion of the X^m may have a more profound phenotypic impact (5, 10, 16, 17). The present results reject this hypothesis; in fact, the current prospective study and a summary of most of the previous studies disclose that of the major phenotypic features, the prevalence of cardiac anomalies was similar in the two groups, whereas that of renal anomalies was greater in our X^m group but not so in previous reports. Due to significant heterogeneity among the cardiac and renal variables and small numbers in previous studies, it was impossible to give a total frequency.

Eye disorders were more prevalent in the X^p group (18). Whereas intrauterine lymphedema was believed to be related to prenatal death, none of the phenotypic features that are thought to be related to intrauterine lymphedema was

TABLE 6. 45,X TS patient growth according to parental origin of retained Xp

	X^m (n = 41)	X^p (n = 9)	*P*
Age	15.0 ± 5.06	18.8 ± 6.7	
Age at GH start	10.0 ± 3.16	9.5 ± 2.3	NS
GH dosage	0.08 ± 0.8	0.08 ± 0.1	NS
Pretreatment height SDS[a]	0.2 ± 1.0	−0.2 ± 1.1	NS
Pretreatment BMI SDS	1.2 ± 0.6	0.2 ± 0.6	0.030
Growth velocity SDS first-year GH	4.9 ± 3.1	4.9 ± 2.6	NS
Final height SDS	1.6 ± 1.4	1.6 ± 1.3	NS
Current BMI SDS	1.0 ± 1.5	0.9 ± 1.3	NS

[a] SDS according to TS growth chart.

TABLE 7. Parental data according to parental origin of retained Xp

	X^m (n = 60)	X^p (n = 20)	*P*	
Father's height SDS	−0.04 ± 1.3	−0.3 ± 1.4	NS	
Mother's height SDS	−0.24 ± 1.1	−0.15 ± 1.2	NS	
Target height SDS	−0.12 ± 1.0	−0.26 ± 1.1	NS	
Pretreatment height SDS correlation with			X^m	X^p
Paternal height	r = 0.525	r = 0.661	<0.001	<0.001
Maternal height	r = 0.369	r = 0.652	<0.001	<0.001
Target height	r = 0.568	r = 0.751	<0.001	<0.001

found to stratify according to parental origin of the X chromosome, with the reservation of higher loss of X^p fetuses.

Using a mouse model for TS, a cluster of three X-linked genes was found to show transcriptional repression of paternal alleles (19). Imprinting of these three genes, Xlr3b, Xlr4b, and Xlr4c, is independent of X chromosome inactivation and has a dynamic and complex pattern of tissue and stage specificity. X^p-retaining XO mice are developmentally retarded and smaller than their XX controls, whereas X^m mice are larger than their XX controls on the 10th day of embryonic life (20). In humans, the opposite has been suggested: whereas the origin of the single X had no effect on general intelligence quotient, 45,X females with X^p chromosome had superior verbal and executive skills, compared with those with X^m chromosome (13). With a relatively small number of adult patients, the current study supports these findings: twice as many X^p patients had academic skills or degrees than X^m patients.

We also cannot support the findings in mice for a role for X chromosome imprinting in human postnatal growth or bone maturation and malformations, which are attributed partly to haploinsufficiency of the short stature homeobox SHOX gene at Xp22.3. Previous studies suggested a positive correlation between the final height of TS patients and that of their mothers (22) and a significant correlation with the maternal height and target height in X^m patients only (12, 23). A correlation of TS patients height with maternal and target height in both X^m and X^p subjects (8) was described in other reports. In the present study, X^m and X^p subjects had similar growth data. The same is true for the odds to develop spontaneous puberty. In X^m but not X^p patients, the correlation with paternal height was greater than the correlation with maternal height. On the other hand, X^m patients were significantly overweight, compared with the X^p group. Two obesity-related syndromes (Beckwith-Wiedemann and Prader-Willi syndromes) are subject to parental imprinting, but thus far no X chromosome imprinting has been implicated in obesity. The current results suggest that such a mechanism may yet to be discovered.

The fact that most of the patients in this study had been treated with hGH allowed us to compare relatively large groups of X^m and X^p TS patients' response to treatment (24). To minimize possible influences of the differences in treatment regimes among the centers, we compared the mean of several variables and found no significant difference in pretreatment height, response to GH therapy, growth velocity in the first year of treatment, or final adult height. GH dosage did not differ significantly, and neither did the age at GH initiation. In the absence of a uniform GH treatment protocol, this is obviously incomplete, and further analysis of hGH treatment response is required. We did not find the suggested evidence of an X-linked imprinting effect on GH response as shown in a recent study (23).

Hypercholesterolemia has been demonstrated in TS girls as young as 11 yr and does not seem to be influenced by the karyotype or degree of obesity (25, 26). In this study 28% of the patients exhibited high total and LDL cholesterol levels; the levels were significantly higher in X^p subjects and did not correlate with BMI. The mean age difference of 4.2 yr between the groups exceeds the expected age-related rise in total and LDL cholesterol.

Insulin resistance did not stratify according to the origin of the retained X chromosome. These findings may suggest that the sexual dimorphic pattern of serum lipids is influenced by not only sex steroids but also an as-yet-undetermined X chromosome imprinting. A recent study on 89 elder TS patients had shown that monosomy for X^m chromosome was associated with greater visceral fat accumulation as measured by computed tomography and a more atherogenic lipid profile (higher triglycerides, total cholesterol, and LDL cholesterol) than monosomy for X^p (27). The wide age difference between the two study groups makes it difficult to compare, but this again supports the role of imprinted X linked genes in metabolic regulation.

With the data available on 208 TS patients studied so far (3–8) including those of the present report, it may be a time for some conclusion on the impact of parental origin of the X chromosome on phenotypic findings. The parental origin of the X chromosome seems to have some impact on several phenotypic traits of TS, including overweight, kidney, eye,

TABLE 8. Data from current and previous studies of heart and kidney anomalies according to parental origin of retained Xp

Study	Cardiac anomalies		Renal anomalies	
	Affected/total X^m	Affected/total X^p (*P*)	Affected/total X^m	Affected/total X^p (*P*)
Ross *et al.* (25)	11/17	0/7 (<0.006)	3/17	1/7 (>0.9)
Mathur *et al.* (10)	7/18	3/7 (>0.90)	3/18	0/7 (0.54)
Lorda-Sanchez *et al.* (11)	7/12	0/4 (0.09)	10/19	2/2 (0.49)
Chu *et al.* (12)	9/43	1/20 (0.15)	6/38	2/15 (>0.90)
Present study	12/60	7/20 (0.23)	12/60	0/20 (0.032)
Total	46/150	11/58	34/152	5/51

and lipids, which suggest a potential effect of as-yet-undetermined Xp arm gene/genes imprinting.

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