X-chromosome gene dosage as a determinant of impaired pre and postnatal growth and adult height in Turner syndrome

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Abstract

Objective: Short stature is a key aspect of the phenotype of patients with Turner syndrome (TS). SHOX haploinsufficiency is responsible for about two-thirds of the height deficit. The aim was to investigate the effect of X-chromosome gene dosage on anthropometric parameters at birth, spontaneous height, and adult height (AH) after growth hormone (GH) treatment.

Design: We conducted a national observational multicenter study.

Methods: Birth parameter SDS for gestational age, height, and AH before and after GH treatment respectively, and height deficit with respect to target height (SDS) were classified by karyotype subgroup in a cohort of 1501 patients with TS: 45,X (36%), isoXq (19%), 45,X/46,XX (15%), XrX (7%), presence of Y (6%), or other karyotypes (17%).

Results: Birth weight, length ($P < 0.0001$), and head circumference ($P < 0.001$), height and height deficit with respect to target height (SDS) before GH treatment, at a median age of 8.8 (5.3–11.8) years and after adjustment for age and correction for multiple testing ($P < 0.0001$), and AH deficit with respect to target height at a median age of 19.3 (18.0–21.8) years and with additional adjustment for dose and duration of GH treatment ($P = 0.006$), were significantly associated with karyotype subgroup. Growth retardation tended to be more severe in patients with XrX, isoXq, and, to a lesser extent, 45,X karyotypes than in patients with 45,X/46,XX karyotypes or a Y chromosome.

Conclusion: These data suggest that haploinsufficiency for an unknown Xp gene increases the risk of fetal and postnatal growth deficit and short AH with respect to target height after GH therapy.

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Introduction

Turner syndrome (TS) is a condition in which all or part of one X chromosome is absent from some or all cells, affecting approximately one in every 2500 liveborn girls (1). It is characterized by growth retardation, with short adult stature and gonadal dysgenesis. It may be

associated with a large number of diseases and conditions: physical abnormalities, congenital cardiac/renal malformations, and acquired conditions that may occur at any time in the patient's life (1, 2, 3, 4, 5, 6, 7, 8). Its genetic basis is highly variable, with diverse causal gene defects.

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The most frequently observed karyotypes are 45,X (45–50%) and the mosaic karyotype of 45,X/46,XX (40%). Karyotypes with an isochromosome of X (isoXq or isoXp), Y chromosome, X ring chromosome, and deletions of the X chromosome are less frequent (9).

Short stature is the cardinal finding in girls with TS, affecting more than 95% of patients. This growth deficiency is already well established by the middle of the second trimester of gestation (10). In a French study of 160 patients, 45% of patients were found to have been small for gestational age (SGA), for length and/or weight (11). Height velocity decreases during childhood and the height deficit increases during adolescence due to the absence of a pubertal growth spurt, resulting in a spontaneous adult height (AH) approximately 20 cm shorter than mid-parental height (143 cm in France) (11, 12). Most clinical trials have shown that treatment with recombinant human growth hormone (GH) can yield a mean height gain of about 7 cm, varying with age at treatment initiation and treatment duration (13, 14).

Haploinsufficiency of the SHOX gene is responsible for about two-thirds of the height deficit observed in TS (15). This gene is located within the telomeric part of PAR 1 and escapes X chromosome inactivation (16). Thus, each individual has two functional copies of this gene, one inherited from each parent. Its main effect is to promote differentiation and to stop the proliferation of hypertrophic growth plate chondrocytes. Haploinsufficiency results in the excessive proliferation of these chondrocytes and a premature fusion of the growth plate (17, 18). SHOX gene function is dosage dependent. A heterozygous mutation can cause Léri–Weill dyschondrosteosis, resulting in a mean AH of -2.2 SDS (15). The loss of both alleles causes Langer syndrome, which is associated with a more severe height deficit (16). By contrast, the gain of additional copies is generally associated with tall stature, but the relationship is nonlinear (19, 20). Haploinsufficiency of other genes may also contribute to growth impairment in TS.

The effect of karyotype on growth in TS patients remains a matter of debate, and most studies to date have concerned small series of patients. Some authors have reported more severe spontaneous growth deficits in patients with monosomy of the short arm of the X chromosome than in those with disomy (11, 21, 22, 23, 24, 25, 26). Others found no significant difference in height between several karyotype subgroups (27, 28, 29). AH after GH treatment has been evaluated as a function of karyotype in only one study, and the results obtained were not significant (30).

In this study, we evaluated auxological data at birth, spontaneous postnatal growth, and AH after GH treatment as a function of karyotype subgroup, in a large cohort of patients with TS.

Patients and methods

Patients

This national observational multicenter study included all patients ($n=1536$) with TS diagnosed up to January 2013 and followed within the French National Rare Disease Network. TS was diagnosed prenatally in 254 patients (17%) and at birth in 220 (14%). Median age (25–75th percentile) at diagnosis for the 1038 patients diagnosed postnatally was 10.0 (6.1–13.3) years. Patients were classified into six subgroups on the basis of karyotype: 45,X ($n=549$, 36%), isoXq ($n=280$, 19%), 45,X/46,XX ($n=221$, 15%), XrX ($n=106$, 7%), presence of Y ($n=87$, 6%), and other karyotypes ($n=258$, 17%). The karyotype was unknown for 35 patients.

Protocol

Growth and karyotype data were collected from medical records, on standardized data collection forms completed retrospectively for the time of TS diagnosis and time points at 5-year intervals thereafter. Birth length (BL), birth weight (BW), and birth head circumference were assessed for patients with a known gestational age (GA) at birth ($n=1037$). Spontaneous growth during childhood was evaluated in patients treated with GH, immediately before the initiation of this treatment ($n=1075$). Patients were considered to have reached AH if they were over the age of 18 years, and GH therapy had been stopped and if they were over the age of 17 years and had been on adult combined estrogen and progesterone therapy for more than 1 year after the end of GH therapy ($n=527$). A flow chart summarizing this information is shown in Fig. 1. Patients received a daily subcutaneous injection of open-label GH at an initial median dose of 0.048 (0.040; 0.054) mg/kg per day, in accordance with current guidelines (http://www.has-sante.fr/portail/upload/docs/application/pdf/pnds_turner_web.pdf, (31)). Puberty began at a median age of 12.0 (11.2; 12.5) years in patients with spontaneous puberty. Median age at the initiation of estrogen therapy was 14.0 (12.9; 15.3) years in patients with induced puberty. The total duration of GH treatment for patients who had achieved AH was 5.8 (3.6; 8.5) years.

Figure 1

Flow chart of the study.

The study protocol was approved by the Paris Nord Ethics Review Committee for Biomedical Research Projects (CEERB) (N° 12–029).

Methods

The genetic analyses carried out included standard karyotype analyses of more than 20 cells or fluorescence *in situ* hybridization with about 100 studied cells in 829 patients, karyotype analyses of <20 cells in 243 patients, and the type of analysis carried out was unknown for 464 patients. Birth measurements and postnatal height are expressed as SDS for GA and chronological age, respectively, based on the normative data for the general population at birth (32) and, thereafter, for the general (33) and TS populations (12). SGA was defined as a BL or weight of -2 SDS or less. Target height was calculated as mid-parental height minus 6.5 cm (34). The height deficit was calculated as the difference between the child's height in SDS and the target height in SDS.

Statistical analysis

Data are expressed as medians (25th–75th percentiles) or numbers (%). The five well-defined karyotype subgroups (45,X, isoXq, 45,X/46,XX, XrX, and presence of Y) were

compared in Kruskal–Wallis tests for continuous variables with a non-Gaussian distribution, one-way ANOVA or generalized linear models for continuous variables with a Gaussian distribution, or χ^2 -tests for categorical variables. The patients with other karyotypes ($n=258$) were not included in the analyses due to the large heterogeneity of this subgroup. The 'global test' was used to determine whether there was at least one significant difference between the groups. Comparisons for height and for distance to target height before GH treatment, as a function of karyotype, were adjusted for age. Comparisons for AH and distance to target height after GH treatment, as a function of karyotype, were adjusted for known confounding factors, such as the dose and duration of GH treatment. Bonferroni correction was applied to adjust the significance threshold for multiple comparisons. All tests were two-tailed, and values of $P<0.01$ were considered statistically significant. The analysis was performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Anthropometric parameters at birth

Median GA at birth was 39 (38–40) weeks, and 10% of the patients with TS were born premature (Table 1). Premature birth appeared more likely for patients with XrX and isoXq karyotypes, but median GA did not differ significantly between karyotype subgroups. Overall, BL SDS was more strongly affected than BW SDS (-1.16 vs -0.90 SDS) ($P<0.0001$), and the frequency of SGA was 24% for BL and 19% for BW (24 vs 19%; $P<0.0001$). Each of the anthropometric parameters (BL, BW, and birth head circumference, SDS for GA) was found to differ significantly between karyotype subgroups (Table 1). Despite high levels of variability, patients with XrX and isoXq displayed more severe growth retardation at birth, for BW, BL, and head circumference, than patients with other karyotypes. Consequently, the prevalence of SGA was higher among patients with XrX and isoXq, in whom it affected one-third of patients, than among patients with other karyotypes, in whom its frequency range was 13–26%, depending on the karyotype subgroup and the parameter (BL or BW) considered (Fig. 2).

Spontaneous postnatal growth before GH treatment

At the time of evaluation, at a median age of 8.8 (5.3; 11.8) years, height and distance to target height (SDS) were

Table 1 Clinical characteristics at birth of patients with TS ($n = 1501$) and by karyotype subgroup. Data reported in bold highlight differences.

	All ($n = 1501$) ^a	XrX ($n = 106$)	IsoXq ($n = 280$)	45,X ($n = 549$)	45,X/46,XX ($n = 221$)	Presence Y ($n = 87$)	P value
Gestational age (weeks)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	0.40
N	1037	77	200	371	153	55	
Prematurity (%) ^b	108 (10%)	12 (16%)	28 (14%)	28 (8%)	15 (10%)	3 (6%)	0.04
N	1037	77	200	371	153	55	
Birth weight (g)	2770 (2460; 3120)	2560 (2215; 2790)	2690 (2340; 3005)	2790 (2500; 3100)	2970 (2580; 3300)	2800 (2505; 3173)	
(SDS)	−0.90 (−1.75; −0.20)	−1.53 (−2.24; −0.76)	−1.12 (−2.03; −0.34)	−0.88 (−1.62; −0.25)	−0.64 (−1.54; 0.20)	−0.85 (−1.55; −0.02)	<0.0001
N	1024	77	197	369	151	53	
Birth length (cm)	47.0 (45.0; 48.0)	46.0 (44.0; 47.0)	46.0 (45.0; 48.0)	47.0 (45.0; 48.0)	48.0 (46.0; 49.3)	47.0 (46.0; 48.0)	
(SDS*)	−1.16 (−1.86; −0.42)	−1.55 (−2.12; −0.91)	−1.23 (−2.21; −0.49)	−1.16 (−1.84; −0.58)	−0.71 (−1.58; −0.06)	−1.16 (−2.10; −0.34)	<0.0001
N	1003	75	190	360	147	54	
Birth head circumference (cm)	33.0 (32.0; 34.0)	32.5 (32.0; 33.3)	33.0 (31.5; 33.5)	33.0 (32.0; 34.0)	34.0 (32.0; 34.5)	33.3 (33.0; 34.5)	
(SDS*)	−0.72 (−1.27; −0.10)	−1.11 (−1.71; −0.54)	−0.85 (−1.61; −0.33)	−0.54 (−1.27; −0.10)	−0.33 (−1.23; 0.28)	−0.63 (−1.11; 0.28)	<0.001
N	706	59	130	253	110	34	

*SDS for GA, N , available data. Differences between groups were evaluated by ANOVA, Kruskal–Wallis, or χ^2 -tests, as appropriate.

^aPatients with other karyotypes ($n = 258$) were not included in the analyses due to the heterogeneity of the karyotypes observed.

^bGA < 37 weeks.

significantly associated with karyotype subgroup after adjustment for age and correction for multiple testing ($P < 0.0001$). Patients with XrX, isoXq, and, to a lesser extent, 45,X karyotypes were more strongly affected than patients with mosaicism or the presence of a Y chromosome (Table 2, Fig. 3A).

AH after GH treatment

At the time of AH evaluation, at a median age of 19.3 (18.0; 21.8) years, after adjustment for the duration and dose of GH treatment and for multiple testing, AH deficit, as evaluated by determining the distance to target height (SDS), was significantly associated with karyotype subgroup ($P = 0.006$). AH deficit with respect to target height was greater in patients with XrX, isoXq, and, to a lesser extent, 45,X karyotypes than in patients with mosaicism or a Y chromosome (Table 3, Fig. 3B).

Discussion

This study, one of the largest cohorts of TS patients ever studied, clearly demonstrated an association between karyotype subgroup and spontaneous prenatal and postnatal growth. The median rates of preterm birth and SGA were consistent with previous studies, although higher rates of SGA have been reported (11). However, there appeared to be a slight excess of premature neonates among our patients with XrX and isoXq, and these

Figure 2

Prevalence of patients born SGA by karyotype subgroup. SGA was defined as a BL or weight of -2 SDS or less for GA. P values were obtained in one-way ANOVA tests (with *post hoc* Bonferroni correction for multiple comparisons). P values 0.01 were considered statistically significant.

Table 2 Spontaneous postnatal growth of patients with TS ($n = 1075$) and by karyotype subgroup, before the initiation of GH treatment. Data reported in bold highlight differences.

	All ($n = 1075$) ^a	XrX ($n = 89$)	isoXq ($n = 210$)	45,X ($n = 418$)	45,X/46,XX ($n = 126$)	Presence Y ($n = 59$)	P value
Age at the evaluation preceding GH treatment initiation (years)	8.8 (5.3; 11.8)	7.8 (4.3; 11.8)	9.3 (6.6; 11.9)	7.8 (4.2; 11.4)	9.8 (6.5; 12.5)	9.6 (6.8; 11.5)	0.0003 ^b
N	1060	88	207	411	124	59	
Height (SDS based on the general population (34))	-2.60 (-3.29; -2.02)	-2.85 (-3.70; -2.38)	-2.98 (-3.63; -2.38)	-2.60 (-3.33; -1.88)	-2.35 (-2.95; -1.76)	-2.44 (-3.11; -1.85)	<0.0001 ^c
N	958	78	189	374	107	50	
Height (SDS based on the TS population (12))	0.47 (-0.32; 1.26)	0.07 (-0.55; 0.70)	0.17 (-0.64; 0.78)	0.36 (-0.39; 1.23)	0.88 (0.14; 1.84)	0.60 (0.12; 1.54)	<0.0001 ^c
Height deficit with respect to target height (SDS based on general population(34))	2.38 (1.75; 3.09)	2.74 (2.11; 3.57)	2.74 (2.17; 3.50)	2.46 (1.83; 3.09)	2.10 (1.44; 2.68)	2.38 (1.63; 2.98)	<0.0001 ^c
N	847	70	171	322	97	44	

^aN, available data.^bPatients with other karyotypes ($n = 258$) were not included in the analyses due to the heterogeneity of the karyotypes observed.^cDifferences between groups were evaluated in Kruskal-Wallis tests.^dP values adjusted for chronological age before GH treatment. Adjusted analyses were carried out with general linear models.

patients also displayed a significantly more severe growth deficit, affecting BL, BW, and head circumference (expressed as SDS for GA), than patients from other karyotype subgroups. Previous studies have reported different effects on birth anthropometric data in TS patients (24, 26, 27), and some of these studies found no association with karyotype subgroup (27), probably due to the limited number of subjects studied. In two studies, BW was shown to be more affected in patients monosomic for the SHOX gene than in patients disomic for this gene (24, 26). A detailed analysis of all anthropometric data as a function of GA extended our understanding of the impact of karyotype subgroup in TS on fetal growth, in terms of BW, BL, and head circumference. We found that spontaneous postnatal growth was more strongly affected in patients with XrX, isoXq, or, to a lesser extent, 45,X karyotypes than in those with mosaicism or with a Y chromosome. These findings are consistent with some (11, 21, 22, 23), but not all studies (27, 28, 29, 35, 36), and some studies have even reported conflicting findings (patients with 45,X taller than those of other karyotype subgroups) (35, 36). Interestingly, this group of French TS patients was taller, by about 0.5 SDS on average, than the reference population of TS patients, providing evidence for an upward secular drift in spontaneous height (37). Another important finding demonstrated here for the first time is that GH therapy does not decrease the association between karyotype and AH deficit. By contrast, in a study of 987 patients with TS who had reached AH after GH treatment, an analysis of karyotype subgroups did not identify karyotype as one of the determinants of AH in these individuals (30), probably because the contribution of target height was not taken into account. In our study, we showed, through a precise analysis of AH with respect to target height, that patients with XrX, isoXq, and, to a lesser extent 45,X had more severe growth deficits in terms of both spontaneous growth and growth after GH treatment than those of other karyotype subgroups, highlighting the major role of X chromosome dosage in growth not only for spontaneous pre and postnatal growth but also after height improvement due to GH therapy.

The effect of the SHOX gene on height is well documented, for both fetal and postnatal growth (15, 16, 17, 18). However, little is known about the contribution of other genes to growth. Previous studies have indicated a possible role of other height loci located on the short arm of the X chromosome (chromosome p), close to the pseudoautosomal region (38). Some non-pseudoautosomal genes have been shown to undergo incomplete inactivation, and some of these candidate genes are

Figure 3

(A) and (B) Height deficit with respect to target height (SDS) before GH treatment and after adult height had been achieved by karyotype subgroup. Median, interquartile range, and range are shown. *P* values were derived from general linear models (with *post hoc* Bonferroni correction for multiple testing). *P* values <0.01 were considered statistically significant. Comparisons for height and for distance to target height before GH treatment, as a function of karyotype, were adjusted for age. Comparisons for adult height and distance to target height after GH treatment, as a function of karyotype, were adjusted for the dose and duration of GH treatment.

involved in skeletal development and height (39). Further studies are required to determine the causal variants underlying the association between karyotype subgroup and anthropometric parameters in TS, but our observations seem to reflect, at least partly, incomplete dosage compensation for the Xp chromosome. They also suggest that haploinsufficiency for, as yet unidentified, Xp genes increases the risk of a larger AH deficit with respect to TH both before and after GH treatment in patients with TS.

The strengths of this observational cohort study with extensive national coverage include the large number of patients with TS for whom comprehensive data were

Table 3 Adult height after the cessation of GH treatment in patients with TS (*n* = 527) and according to karyotype subgroup. Data reported in bold highlight differences.

	All (<i>n</i> = 527) ^a	XrX (<i>n</i> = 48)	IsoXq (<i>n</i> = 109)	45,X (<i>n</i> = 224)	45,X/46,XX (<i>n</i> = 47)	Presence Y (<i>n</i> = 36)	<i>P</i> value
Age at the evaluation of adult height (years)	19.3 (18.0; 21.8)	18.9 (17.7; 20.9)	19.5 (18.3; 21.8)	19.3 (18.0; 21.9)	20.1 (18.3; 22.8)	20.1 (18.4; 24.1)	0.25 ^b
Adult height (SDS based on the general population (34))	152 (147; 156)	150 (146; 155)	151 (146; 156)	152 (147; 156)	152 (148; 158)	156 (151; 158)	0.04 ^c
Adult height (cm)	1.75 (1.04; 2.54)	2.23 (1.17; 2.78)	1.94 (1.41; 2.92)	1.74 (1.04; 2.47)	1.54 (0.85; 2.28)	1.07 (0.68; 1.93)	0.006 ^c
Adult height deficit with respect to target height (SDS based on the general population (34))	9.5 (5.5; 14.2)	12.5 (6.3; 15.5)	10.8 (8.0; 16.5)	9.5 (5.5; 13.6)	8.8 (4.5; 12.5)	6.0 (2.0; 10.5)	0.006 ^c
Adult height deficit with respect to target height (cm)							
<i>N</i>	414	40	90	166	34	27	

N, available data. *P* values <0.01 were considered statistically significant (Bonferroni correction).

^aPatients with other karyotypes (*n* = 258) were not included in the analyses due to the heterogeneity of the karyotypes observed.

^bDifferences between groups were evaluated in Kruskal-Wallis tests.

^cAdjusted for the dose and duration of GH treatment; adjusted analyses were carried out with general linear models.

collected, making it possible to evaluate infrequent karyotype subgroups, such as the rare XrX subgroup, and to adjust for major confounding factors, including all major birth measurements, according to GA, height deficit with respect to target height, and duration and dose of GH treatment. However, this study also had several inherent limitations, due to its observational and retrospective nature. Karyotyping was carried out on blood samples, but there remains some debate about whether exclusive monosomy X applies to all tissues, as some degree of mosaicism has been observed. However, it is widely accepted that routine karyotype analyses on 20 cells are sufficient to detect mosaicism down to levels of about 5% (9). The sensitivity of the method used to detect mosaicism in our patients should therefore have been adequate. It was also not possible to control for the effects of potential concomitant morbidities inherently associated with TS. However, we believe that such factors were correctly managed, at least postnatally, and that they were thus unlikely to have a major effect on our estimates of association. The relationships described are therefore plausible.

In conclusion, our study provides the first evidence, to our knowledge, of a link between karyotype subgroup and phenotypic variation in both spontaneous fetal and postnatal growth, and growth after GH, in individuals with TS. This association provides insight that could guide further studies to improve our understanding of the pathophysiological pathways, other than that involving the SHOX gene, underlying short stature in TS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Gravholt C, Juul S, Naeraa R & Hansen J. Morbidity in Turner syndrome. *Journal of Clinical Epidemiology* 1998 **51** 147–158. (doi:10.1016/S0895-4356(97)00237-0)
- Gravholt C. Epidemiological, endocrine and metabolic features in Turner syndrome. *European Journal of Endocrinology* 2004 **151** 657–687. (doi:10.1530/eje.0.1510657)
- Hjerrild B, Mortensen K & Gravholt C. Turner syndrome and clinical treatment. *British Medical Bulletin* 2008 **86** 77–93. (doi:10.1093/bmb/ldn015)
- Pinsker J. Clinical review: Turner syndrome: updating the paradigm of clinical care. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E994–1003. (doi:10.1210/jc.2012-1245)
- Stochholm K, Juul S, Juel K, Naeraa RW & Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3897–3902. (doi:10.1210/jc.2006-0558)
- Urbach A & Benvenisty N. Studying early lethality of 45,XO (Turner's syndrome) embryos using human embryonic stem cells. *PLoS ONE* 2009 **4** e4175. (doi:10.1371/journal.pone.0004175)
- Sagi L, Zuckerman-Levin N, Gawlick A, Ghizzoni L, Buyukgebiz A, Rakover Y, Bistrizter T, Admoni O, Vottero A, Baruch O *et al.* Clinical significance of the parental origin of the X chromosome in Turner syndrome. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 846–852. (doi:10.1210/jc.2006-0158)
- Elsheikh M, Dunger D, Conway G & Wass JA. Turner's syndrome in adulthood. *Endocrine Reviews*, 2002 23120–23140.
- Sybert VP & McCauley E. Turner's syndrome. *New England Journal of Medicine* 2004 **351** 1227–1238. (doi:10.1056/NEJMra030360)
- FitzSimmons J, Fantel A & Shepard T. Growth parameters in mid-trimester fetal Turner syndrome. *Early Human Development* 1994 **38** 121–129. (doi:10.1016/0378-3782(94)90223-2)
- Cabrol S, Saab C, Gourmelen M, Raux-Demay MC & Le Bouc Y. Turner syndrome: spontaneous growth of stature, weight increase and accelerated bone maturation. *Archives de Pédiatrie* 1996 **3** 313–318.
- Sempé M, Hansson Bondallaz C & Limoni C. Growth curves in untreated Ullrich-Turner syndrome: French Reference Standards 1–22 Years. *European Journal of Pediatrics* 1996 **155** 862–869. (doi:10.1007/BF02282835)
- Stephure DK & Canadian Growth Hormone Advisory Committee . Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadian randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 3360–3366. (doi:10.1210/jc.2004-2187)
- Soriano-Guillen L, Coste J, Ecosse E, Léger J, Tauber M, Cabrol S, Nicolino M, Brauner R, Chaussain JL & Carel JC. Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 5197–5204. (doi:10.1210/jc.2005-0470)
- Ross JL, Scott C Jr, Marttila P, Kowal K, Nass A, Papenhausen P, Abboudi J, Osterman L, Kushner H, Carter P *et al.* Phenotypes associated

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- with SHOX deficiency. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 5674–5680. (doi:10.1210/jcem.86.12.8125)
- 16 Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. *Hormone Research in Paediatrics* 2011 **75** 81–89. (doi:10.1159/000324105)
  - 17 Marchini A, Marttila T, Winter A, Caldeira S, Malanchi I, Blaschke RJ, Häcker B, Rao E, Karperien M, Wit JM *et al.* The short stature homeodomain protein SHOX induces cellular growth arrest and apoptosis and is expressed in human growth plate chondrocytes. *Journal of Biological Chemistry* 2004 **279** 37 103–37 114. (doi:10.1074/jbc.M307006200)
  - 18 Munns CF, Glass IA, LaBrom R, Hayes M, Flanagan S, Berry M, Hyland VJ, Batch JA, Philips GE & Vickers D. Histopathological analysis of Leri–Weill dyschondrosteosis: disordered growth plate. *Journal of Hand Surgery* 2001 **6** 13–23. (doi:10.1142/S0218810401000424)
  - 19 del Rey G, Jasper H, Bengolea SV, Boywitt A, De Bellis R & Heinrich JJ. Trisomy of the short stature homeobox-containing gene (SHOX) due to duplication/deletion of the X chromosome: clinical implications on the stature. *Hormone Research in Paediatrics* 2010 **74** 297–304. (doi:10.1159/000309418)
  - 20 Ottesen AM, Aksglaede L, Garn I, Tartaglia N, Tassone F, Gravholt CH, Bojesen A, Sørensen K, Jørgensen N, Rajpert-De Meyts E *et al.* Increased number of sex chromosomes affects height in a nonlinear fashion: a study of 305 patients with sex chromosome aneuploidy. *American Journal of Medical Genetics Part A* 2010 **152A** 1206–1212. (doi:10.1002/ajmg.a.33334)
  - 21 Massa G, Vanderschueren-Lodeweyckx M & Malvaux P. Linear growth in patients with Turner syndrome: influence of spontaneous puberty and parental height. *European Journal of Pediatrics* 1990 **149** 246–250. (doi:10.1007/BF02106283)
  - 22 Cohen A, Kauli R, Pertzalan A, Lavagetto A, Roitman Y, Romano C & Laron Z. Final height of girls with Turner's syndrome: correlation with karyotype and parental height. *Acta Paediatrica* 1995 **84** 550–554. (doi:10.1111/j.1651-2227.1995.tb13693.x)
  - 23 Low L, Sham C, Kwan E, Karlberg J, Tang G, Cheung PT, Pang H, Tse W, But B, Yu CM *et al.* Spontaneous growth in Chinese patients with Turner's syndrome and influence of karyotype. *Acta Paediatrica* 1997 **86** 18–21. (doi:10.1111/j.1651-2227.1997.tb08823.x)
  - 24 Yaegashi N, Uehara S, Ogawa H, Hanew K, Igarashi A, Okamura K & Yajima A. Association of intrauterine growth retardation with monosomy of the terminal segment of the short arm of the X chromosome in patients with Turner's syndrome. *Gynecologic and Obstetric Investigation* 2000 **50** 237–241. (doi:10.1159/000010323)
  - 25 Robles Valdés C, del Castillo Ruiz V, Oyoqui J, Altamirano Bustamante N, de la Luz Ruiz Reyes M & Calzada León R. Growth, growth velocity and adult height in Mexican girls with Turner's syndrome. *Journal of Pediatric Endocrinology and Metabolism* 2003 **16** 1165–1173.
  - 26 Hagman A, Wennerholm UB, Källen K, Barrenäs ML, Landin-Wilhelmsen K, Hanson C & Bryman I. Women who gave birth to girls with Turner syndrome: maternal and neonatal characteristics. *Human Reproduction* 2010 **25** 1553–1560. (doi:10.1093/humrep/deq060)
  - 27 Park E, Bailey JD & Cowell CA. Growth and maturation of patients with Turner's syndrome. *Pediatric Research* 1983 **17** 1–7. (doi:10.1203/00006450-198301000-00001)
  - 28 Ranke MB, Pflüger H, Rosendahl W, Stubbe P, Enders H, Bierich JR & Majewski F. Turner syndrome: spontaneous growth in 150 cases and review of the literature. *European Journal of Pediatrics* 1983 **141** 81–88. (doi:10.1007/BF00496795)
  - 29 Rochiccioli P, Malpuech G, Colle M, Limal JM, Battin J, Mariani R, Sultan C, Nivelon JL, Simonin G, Bost M *et al.* Study of final height in Turner's syndrome: ethnic and genetic influences. *Acta Paediatrica* 1994 **83** 305–308. (doi:10.1111/j.1651-2227.1994.tb18099.x)
  - 30 Bondy MB, Lindberg A, Ferrández Longás A, Darendeliler F, Albertsson-Wikland K, Dunger D, Cutfield WS, Tauber M, Wilton P, Wollmann HA *et al.* Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Pediatric Research* 2007 **61** 105–110. (doi:10.1203/01.pdr.0000250039.42000.c9)
  - 31 Bondy CA. Care of girls and women with Turner syndrome: A Guideline of the Turner Syndrome Study Group. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 10–25. (doi:10.1210/jc.2006-1374)
  - 32 Mamelle N, Munoz F & Grandjean H. Fetal growth from the AUDIPOG study. I. Establishment of reference curves. *Journal de Gynecologie Obstetrique et Biologie de la Reproduction* 1996 **25** 61–70.
  - 33 Sempé M, Pedron G & Roy-Pernot MP. *Auxologie, méthode et séquences*, 1979 205.
  - 34 Tanner JM, Goldstein H & Whitehouse RH. Standards for children's height at ages 2–9 years allowing for heights of parents. *Archives of Disease in Childhood* 1970 **45** 755–762. (doi:10.1136/adc.45.244.755)
  - 35 Lenko HL, Perheentupa J & Söderholm A. Growth in Turner's syndrome: spontaneous and fluoxymesterone-stimulated. *Acta Paediatrica Scandinavica. Supplement* 1979 **277** 57–63. (doi:10.1111/j.1651-2227.1979.tb06193.x)
  - 36 Mazzanti L, Nizzoli G, Tassinari D, Bergamaschi R, Magnani C, Chiumello G & Cacciari E. Spontaneous growth and pubertal development in Turner's syndrome with different karyotypes. *Acta Paediatrica* 1994 **83** 299–304. (doi:10.1111/j.1651-2227.1994.tb18098.x)
  - 37 Isojima T, Yokoya S, Ito J, Naiki Y, Horikawa R & Tanaka T. Proposal of new auxological standards for Japanese girls with Turner syndrome. *Clinical Pediatric Endocrinology* 2010 **19** 69–82. (doi:10.1297/cpe.19.69)
  - 38 Zinn AR, Tonk VS, Chen Z, Flejter WL, Gardner HA, Guerra R, Kushner H, Schwartz S, Sybert VP, Van Dyke L *et al.* Evidence for a Turner syndrome locus or loci at Xp11.2-p22.1. *American Journal of Human Genetics* 1998 **63** 1757–1766. (doi:10.1086/302152)
  - 39 Tukiainen T, Pirinen M, Sarin AP, Ladvall C, Kettunen J, Lehtimäki T, Lokki ML, Perola M, Sinisalo J, Vlachopoulou E *et al.* Chromosome X-wide association study identifies loci for fasting insulin and height and evidence for incomplete dosage compensation. *PLoS Genetics* 2014 **10** e1004127. (doi:10.1371/journal.pgen.1004127)

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