Adult height after growth hormone treatment and its association with X chromosome dosage in Turner Syndrome : a cross-sectional database analysis of the French national rare disease network

Elodie Fiot [1], Delphine Zenaty [1], Priscilla Boizeau [4,5], Jeremy Haignere [4,5], Sophie Dos Santos [1], Juliane Léger [1,2,3] and the French Turner Study Group

1 Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, Service d'Endocrinologie et Diabétologie pédiatrique, Centre de Référence des Maladies Endocriniennes Rares de la Croissance, F-75019 Paris, France; 2 Université Paris Diderot,Sorbonne Paris Cité, F-75019 Paris, France; 3 Institut National de la Santé et de la recherche médicale (Inserm), Unité 1141, DHU Protect; F-75019 Paris, France ; 4 AP-HP, Hôpital Robert Debré, Unit of Clinical Epidemiology, F-75019, Paris, France; 5 Inserm, CIC-EC 1426, F-75019 Paris, France

INTRODUCTION

• Turner Syndrome (TS) is a condition in which all or part of one X chromosome is absent from some or all cells. It is characterized by growth retardation and gonadal dysgenesis, and may be associated with congenital malformations and acquired conditions, caused by various gene defects.

• Short stature is the cardinal finding. Patients have a spontaneous adult height (AH) approximately 20cm shorter than mid-parental target height (TH). SHOX haploinsufficiency accounts largely, but not entirely, for the height deficit of patients. Treatment with recombinant growth hormone (GH) has been shown to improve adult height, although individual outcomes vary markedly.

• **The effect of karyotype on growth is still a matter of debate** and **little is known about the contribution of other genes (than SHOX) to growth**.

AIM OF THE STUDY

To evaluate spontaneous postnatal growth and adult height after GH treatment as a function of karyotype subgroups

PATIENTS AND METHODS

• This **observational national multicenter study** included all patients with TS diagnosed up to January 2013 and followed within the French national rare disease network, **n=1536**. Patients were classified into **6 subgroups of karyotypes**: 45,X, isoXq, 45,X/46,XX, XrX, presence of Y and other karyotypes.

• Patients received a daily subcutaneous injection of GH at an initial median dose of 0.048 (0.040; 0.054) mg/kg/day during a median of 5.8 (3.6; 8.5) years.

• **Height deficit** was calculated as the difference between the patient's height and target height (SDS), and was evaluated in patients treated with GH **before the initiation of treatment (n=1075) and at the end of treatment in patients who had reached adult height (n=527),** by karyotype subgroups.

• Differences between groups were assessed by ANOVA or Kruskal Wallis tests for variables non normally distributed. Comparaison of height deficit before GH treatment was adjusted on age and after GH treatment for dose and duration of treatment.

RESULTS

Spontaneous postnatal growth before GH treatment, evaluated at a median age of 8.8 (5.3; 11.8) years and **adult height deficit after GH treatment**, evaluated at a median age of 19.3 (18.0; 21.8) years, were **significantly more affected in patients with XrX and isoXq**, and to a lesser extend 45,X karyotypes, than in patients with 45,X/46,XX or patients with a Y chromosome; $p<0.0001$ and 0.01, respectively (Figure 1 and Table 1).

Table 1:
Height deficit with respect to target height just before the initiation of GH therapy (n=1075) and after the cessation of GH treatment in patients who had reached adult height (n=527), according to karyotype.

	All patients	XrX	isoXq	45,X	45,X/46,XX	Presence Y	Other	*p* value
Height deficit at the beginning of GH (SDS)	2.38 (1.74; 3.09)	**2.74 (2.11; 3.57)**	**2.74 (2.17; 3.50)**	2.46 (1.78; 3.09)	2.10 (1.44; 2.68)	2.38 (1.63; 2.98)	2.03 (1.33; 2.73)	**<0.0001***
N	*847*	*39*	*96*	*187*	*35*	*28*	*56*	
Adult height (SDS)	-2.05 (-2.95; -1.20)	**-2.32 (-3.09 ; -1.59)**	**-2.23 (-2.98; -1.38)**	-2.05 (-2.94; -1.34)	-2.05 (-2.77; -1.00)	-1.34 (-2.23; -0.98)	-2.05 (-2.95; -1.14)	**0.05** *
N	*527*	*48*	*109*	*224*	*47*	*36*	*63*	
Target height - adult height (SDS)	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)	1.68 (0.96; 2.20)	**0.01****
N	*414*	*40*	*90*	*166*	*34*	*29*	*55*	

Data are expressed as median (25-75th percentiles). Data in bold highlight differences.
N: available data; * adjusted for age; ** adjusted for the dose and duration of GH treatment

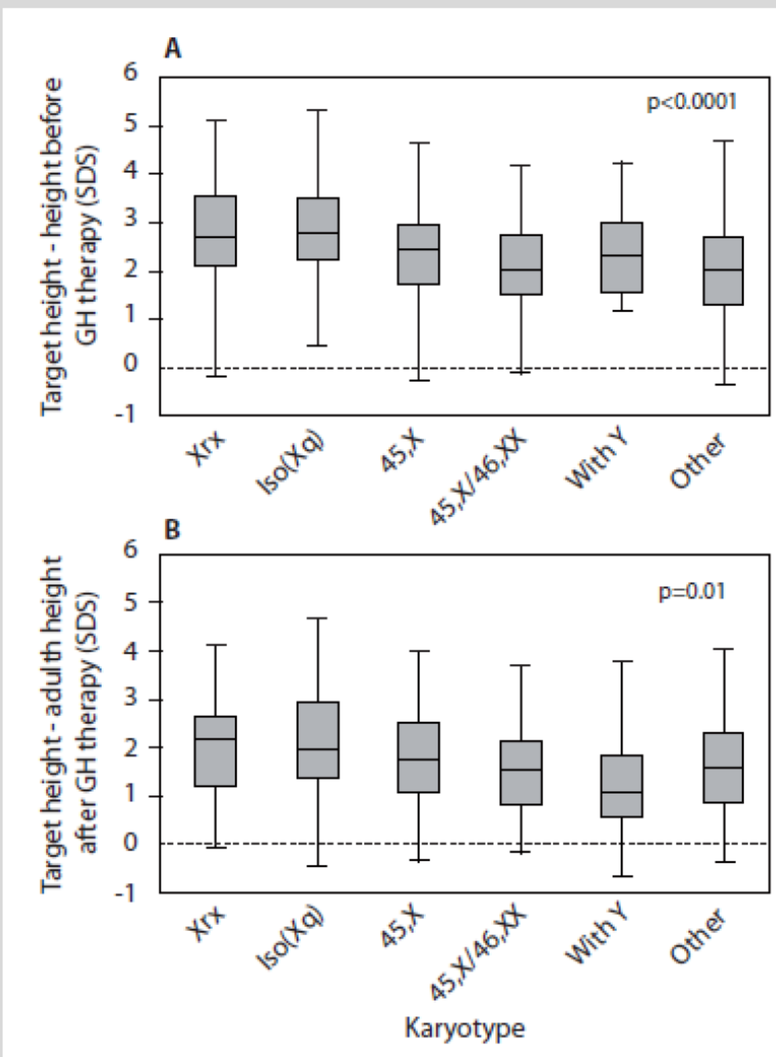

Figure 1:
Height deficit with respect to target height (SDS) before GH treatment (A) and after adult height has been achieved (B), by karyotype subgroups

CONCLUSION

•This study clearly demonstrates an **association between the karyotype subgroups and the spontaneous postnatal growth**. It also demonstrates for the first time that **GH therapy does not decrease the association between karyotype and height deficit**.

•These data highlight the **major role of X chromosome dosage in growth**, not only for spontaneous growth, but also after height improvement due to GH therapy.

• This suggest that **haploinsufficiency for as yet unidentified Xp gene increases the risk of a larger height deficit with respect to TH**, both before and after GH therapy in patients with TS.

French Turner Study Group

JC. Carel, S Cabrol, P. Chanson, S. Christin Maître, C. Courtillot, B. Donadille, J. Dulon, M. Houang, M.Nedelcu, I. Netchine, M. Polak, S. Salenave, D. Samara Boustani, D Simon, P. Touraine, M. Viaud (ParisH. Bony, R.Desailloud (Amiens); R.Coutant, P. Rodien (Angers); A.M Bertrand, F. Schillo (Besançon); P. Barat, A. Tabarin (Bordeaux); V. Kerlan, C. Metz (Brest); Y. Reznik, V. Ribault, (Caen); H. Carla, I.); Tauveron (Clermont Ferrand); C. Bensignor, F. Huet, B. Verges (Dijon); O. Chabre, C. Dupuis, A. Spiteri (Grenoble); J. Weill, JL. Wemeau (Lille); A.Lienhardt (Limoges); C. Naud Saudreau (Lorient) ; F. Borson-Chazot, M. Pugeat (Lyon); T. Brue, R. Reynaud, G. Simonin (Marseille); J. Bringer, F. Paris, C. Sultan (Montpellier); B. Leheup, G. Weryha (Nancy); S. Baron, B. Charbonnel (Nantes); E. Baechler, P. Fenichel, K. Wagner (Nice); F. Compain (Poitiers); H. Crosnier, C. Personnier (Poissy); B. Delemer, PF. Souchon (Reims); M. De Kerdanet, F. Galland, S. Nivot-Adamiak (Rennes); M. Castanet, (Rouen); O. Richard (Saint Etienne); N. Jeandidier, S. Soskin (Strasbourg); P. Lecomte, M. Pepin Donat, P. Pierre (Tours).

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Elodie Fiot
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