Does X-chromosome gene dosage a determinant of growth and phenotypic features in Turner syndrome with 45,X/46,XX mosaicism on standard karyotyping? A cross-sectional analysis of the French national rare disease network database

Elodie Fiot, Delphine Zenaty, Paul Picq, Priscilla Boizeau, Jeremie Haigneré, Sophie Dos Santos, Sophie Christin-Maitre, Jean-Claude Carel, Juliane Léger and the French Turner Study Group

Robert Debré University Hospital, Pediatric Endocrinology Diabetology Department and Unit of Clinical Epidemiology, Paris Diderot University,, Inserm 1141 and CIC-EC 1426
Saint Antoine University Hospital, Endocrinology Department, Paris Sorbonne University,
Assistance Publique-Hôpitaux de Paris. Reference centre for Endocrine Growth and Development Disorders, Paris, France

Centre de Référence des Maladies Endocriniennes de la Croissance et du Développement

BACKGROUND

• 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. Haploinsufficiency of various genes situated in the X chromosome would be responsible for most of clinical traits.

• The most frequently observed karyotypes are 45,X (45-50%) and the mosaic karyotype 45,X/46,XX (45%). A standard karyotype is recommended to make the diagnosis of TS and can detect 10% mosaicism with 95% confidence.

• **The phenotype of patients with a 45,X karyotype is generally more severe than patients with mosaicism, but the potential role of the degree of mosaicism in modulating TS phenotype has never been investigated.**

AIM OF THE STUDY

To assess the impact of various degrees of 45,X/46,XX mosaicism on phenotypic features in a cohort of TS patients.

PATIENTS AND METHODS

• In an **observational national multicenter study** of patients with TS (n=1536, 45,X : 36%, 45,X/46,isoXq : 19%, 45,X/46,XX : 15%, XrX : 7%, presence of Y : 6%, others karyotypes : 17%), we analysed patients with 45,X/46,XX karyotype for whom the **percentage of mosaicism was known (*n* = 183/221).**

• Patients were classified **according to the degree of mosaicism: low (<10%), moderate (10-30%), or high (>30%).**

• The genetic analyses carried out included standard karyotype analyses of more than 20 cells or fluorescence *in situ* hybridization on about 100 cells.

• Auxological data, prevalence of congenital malformations and acquired conditions were recorded from medical records.

RESULTS

- A trend towards association with the degree of mosaicism was observed for birth weight SDS, birth length SDS and height deficit with respect to target height SDS before growth hormone treatment, the **patients with lower levels of mosaicism being less likely to be affected**.
- High levels of mosaicism were associated with a **higher frequency of malformations of the kidneys (*p*=0.02)** but not of the heart. A trend towards an association with the degree of mosaicism was observed for autoimmune thyroid disease, hearing impairment, overweight/obesity and spontaneous puberty.

Auxological data, congenital malformations and acquired conditions according to the percentage of mosaicism

	45X/46XX patients (n=183)			p
	45X <10% (*n*=28)	45X : 10-30% (*n*=72)	45X ≥ 31% (*n*=83)	
Birth weight (SDS)	-0.42 (-0.96; 0.56)	-0.51 (-1.12; 0.12)	-0.77 (-1.65; 0.11)	0.29
Birth length (SDS)	-0.42 (-1.49; 0.43)	-0.72 (-1.38; 0.22)	-0.93 (-1.75; -0.14)	0.54
Median age (years) before GH	11.1 (4.4; 13.9)	9.8 (6.5; 12.2)	9.6 (7.2; 12.7)	0.68
Height deficit (SDS) before GH	1.44 (0.89; 2.37)	2.08 (1.40; 2.39)	2.33 (1.52; 2.89)	0.30
Congenital heart malformation	3 (11%)	9 (13%)	7 (8%)	0.71
Congenital kidney malformation *	**0 (0%)**	**6 (8%)**	**15 (18%)**	**0.02**
Median age (years) at last evaluation	12.3 (1.9; 22.6)	12.4 (5.6; 16.1)	13.9 (9.0; 21.6)	0.07
Autoimmune thyroid disease	1 (7%)	10 (33%)	20 (42%)	0.06
Hearing impairment	1 (10%)	5 (21%)	12 (28%)	0.45
Overweight/obese	3 (13%)	9 (17%)	22 (31%)	0.10
Spontaneous onset of puberty	11 (79%)	26 (68%)	29 (58%)	0.30

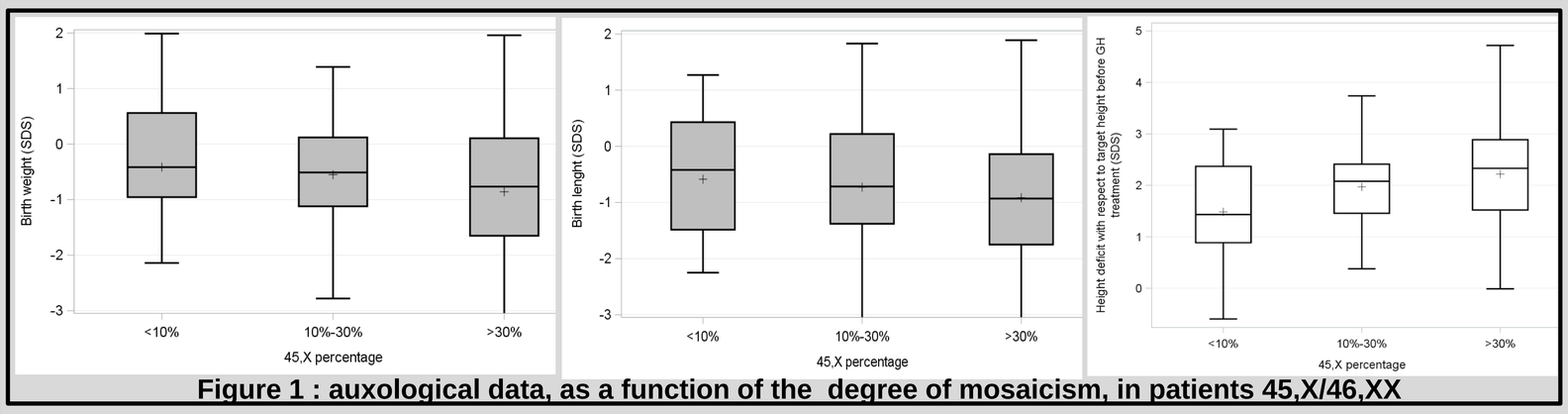

Figure 1 : auxological data, as a function of the degree of mosaicism, in patients 45,X/46,XX

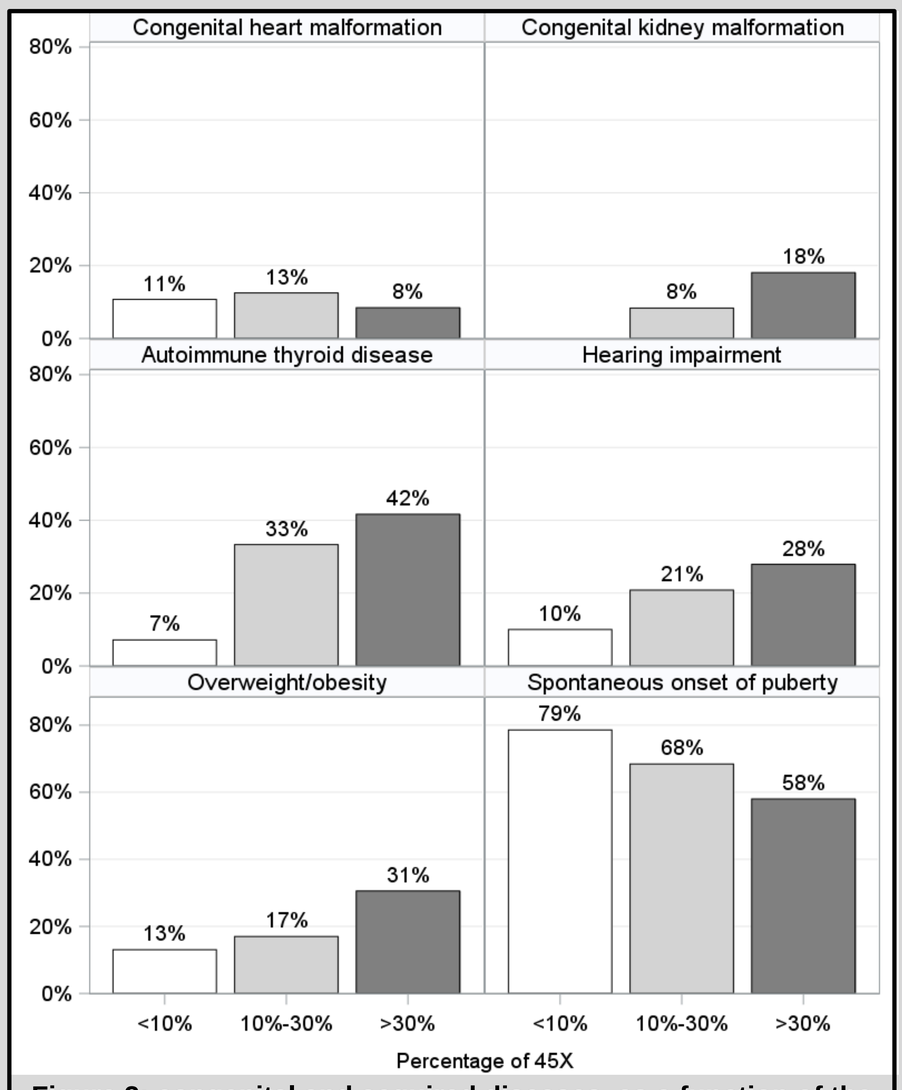

Figure 2: congenital and acquired diseases, as a function of the degree of mosaicism, in patients 45,X/46,XX

CONCLUSION

• In TS patients with 45,X/46,XX mosaicism, high levels of mosaicism was significantly associated with a higher rate of congenital kidney malformations. Patients with lower levels of mosaicism seemed to be less severely affected for auxological data including birth weight/length SDS and height deficit with respect to target height SDS. Autoimmune thyroid disease, hearing impairment and overweight/obesity seemed to be more frequent in patients with higher levels of mosaicism whereas spontaneous puberty seemed more frequent in patients with lower levels of mosaicism.

•This results highlight the **major role of X chromosome dosage in the severity of the phenotype of TS patients**, **with a milder phenotype in patients with lower levels of mosaicism.**

• Further studies on larger cohorts are required to confirm these results and to improve our understanding of these associations.

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).

The authors declare no conflicts of interest

57ESPE
159--P1
Growth and syndromes (to include Turner syndrome)
Elodie Fiot
Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018
PosterSessionOnline.com