



**HAL**  
open science

## **Aortic tissue analysis in Turner syndrome**

Bruno Donadille, Alexander Valent, Kisaki Amemiya, Nicolas Rive Le Gouard, Laurence Iserin, Paul Achouh, Tatiana Lecot-Connan, Patrick Bruneval, Jean-Pierre Siffroi, Sophie Christin-Maitre

► **To cite this version:**

Bruno Donadille, Alexander Valent, Kisaki Amemiya, Nicolas Rive Le Gouard, Laurence Iserin, et al.. Aortic tissue analysis in Turner syndrome. *Journal of the American College of Cardiology*, 2022, 80 (13), pp.1284-1285. 10.1016/j.jacc.2022.07.017 . hal-03855805

**HAL Id: hal-03855805**

**<https://hal.sorbonne-universite.fr/hal-03855805v1>**

Submitted on 16 Nov 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Title: Aortic tissue analysis in Turner syndrome**

2  
3 **Authors:** Bruno Donadille, MD<sup>a</sup>; Alexander Valent, MD, PhD<sup>b</sup>; Kisaki Amemiya, MD,  
4 PhD<sup>c,d</sup>; Nicolas Rive le Gouard, MD<sup>e</sup>; Laurence Iserin, MD<sup>f</sup>; Paul Achouh, MD, PhD<sup>g,h</sup>;  
5 Tatiana Lecot-Connan, MD<sup>a</sup>; Patrick Bruneval, MD<sup>c,h</sup>; Jean-Pierre Siffroi, MD, PhD<sup>e,i</sup> ;  
6 Sophie Christin-Maitre, MD, PhD<sup>a,i</sup>

7  
8 **Total word count:** 800

9  
10 **Affiliations:**

- 11 a) Department of Endocrinology, Saint Antoine Hospital, Assistance Publique-Hôpitaux de  
12 Paris, Sorbonne Université. *Centre de Référence des Maladies Endocriniennes Rares de la*  
13 *Croissance et du Développement* (CRMERCDC), Filière FIRENDO, Endo-ERN [739527],  
14 Paris, France.  
15 b) Department of Molecular Pathology, Cytogenetics and Medical Biology, Institut Gustave  
16 Roussy, Villejuif, France.  
17 c) Department of Pathology, European Georges Pompidou Hospital, Assistance Publique-  
18 Hôpitaux de Paris, Paris, France.  
19 d) Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Osaka,  
20 Japan.  
21 e) Département de Cytogenetics, Armand Trousseau Hospital, Assistance Publique-Hôpitaux  
22 de Paris, Sorbonne Université, Paris, France.  
23 f) Department of Adult Congenital Cardiopathies, European Hospital Georges Pompidou,  
24 Assistance Publique-Hôpitaux de Paris, Paris, France.  
25 g) Department of Cardiovascular Surgery, European Hospital Georges Pompidou, Assistance  
26 Publique-Hôpitaux de Paris, Paris, France.  
27 h) Université Paris Cité, INSERM U970 PARCC, Paris, France.  
28 i) Sorbonne Université, INSERM U933, Paris, France

29  
30 **Sources of Funding:** Dr Kisaki Amemiya was supported in part by the «Programme pour la  
31 formation des résidents étrangers des hôpitaux de Paris à l'Assistance Publique-Hôpitaux de  
32 Paris».

33  
34 **Disclosures:** None.

35  
36 **Corresponding author:** (E-mail): [bruno.donadille@aphp.fr](mailto:bruno.donadille@aphp.fr); Reference Center for Rare  
37 Endocrine Growth Diseases; Saint Antoine Hospital, Sorbonne Université; AP-HP; 187 rue  
38 du Faubourg St Antoine, 75012 PARIS, France. (Phone): +331 49 28 24 00

39  
40 **Keywords:** Turner syndrome; Aortic dilatation; Aortic Aneurysm; FISH analysis; Karyotype.

41  
42 **Non-standard Abbreviations and Acronyms:**

43 AD: Aortic dilatation;  
44 ASI: Aortic size index;  
45 BAV: Bicuspid aortic valve;  
46 ERCB: Ethics Review Committee for Biomedical research  
47 FFPE: Formalin-fixed and paraffin-embedded;  
48 MDC: Media degenerative changes;  
49 MEMA: Mucoïd extracellular matrix accumulation (-I: Intralamellar and -T: Translamellar);  
50 TAA: Thoracic aorta aneurysm.

51 Prevention of aortic dissection is difficult in patients with Turner syndrome (TS). The aim of  
52 our study was to describe aortic walls' cytogenetics and histology in patients having a  
53 prophylactic surgery for a thoracic aorta aneurysm (TAA).

54  
55 TS affects 1/2500 female at birth <sup>1</sup>. In half of cases, a complete loss of one X-chromosome is  
56 found in blood lymphocyte karyotype. A 45,X/ 46,XX mosaicism is present in 15-20% of  
57 patients. A structural anomaly of the X chromosome (isochromosome, ring) is present in the  
58 remaining patients.

59  
60 Congenital heart abnormalities in TS include bicuspid aortic valve (BAV) and aortic  
61 coarctation, in 20-30% and 15-20% of patients, respectively <sup>2</sup>. Aortic dilatation (AD) is  
62 common in TS <sup>3</sup>. The risk factors for aortic dissection are BAV, aortic coarctation, AD,  
63 hypertension, a 45,X karyotype and pregnancy. According to the current guidelines <sup>1,2</sup>,  
64 prophylactic surgery is recommended to prevent any dissection event, when the ascending  
65 aortic size index (ASI) is higher than 25 mm/m<sup>2</sup>.

66  
67 TS patients were recruited from our Reference Center for Rare Diseases ([Endo-ERN](#)). This  
68 study was approved by the Paris North ERCB (N°12-029). Aortic histology and media  
69 degenerative changes (MDC) score were assessed using a semi quantitative score <sup>4</sup>. The X  
70 monosomy was searched in blood karyotype, buccal smear and aortic media using  
71 Fluorescence *in Situ* Hybridization (FISH). For each aortic tissue, one hundred cells  
72 (media/adventice) were analyzed. These results were compared to data obtained from the  
73 blood karyotype and buccal smears FISH results, when available. For one mosaic patient, an  
74 additional FISH with TFE3 probe (Xp11.23) was performed on 50 nuclei to confirm the aortic  
75 mosaicism.

76  
77 Eleven aortic tissues from 11 patients were included. The patients' median age at prophylactic  
78 aortic surgery was 39.0 years (IQR: 29.5-46.5). Their median age at TS diagnosis was 8.0  
79 years (IQR: 2.8-13.0). BAV was present in 10/11 cases. According to Sievers' classification <sup>5</sup>,  
80 6/11 patients had a type 1 BAV, with one raphe and fusion of both coronary cusps (L-R).

81  
82 The median ascending aortic diameter and ASI at surgery were 44 mm (IQR: 39.0-45.5) and  
83 29.0 mm/m<sup>2</sup> (IQR: 26.7-30.1), respectively. The aortic surgical techniques were as follows:  
84 Yacoub (5/11), Bentall (5/11) and Tyron-David (1/11).

85  
86 The blood karyotypes showed: an homogenous X monosomy in 7/11 cases, a 45,X/46,XX  
87 mosaicism in 1/11 and a structurally abnormal X chromosome in 3/11 cases (two X ring and  
88 one Xq isochromosome).

89  
90 An early MDC (**Figure 1A**) was found in all patients. The MDC score was 9.0 (IQR: 7-10.5).  
91 It was characterized by a loss of smooth muscle cells, a mucoid extracellular matrix  
92 accumulation (MEMA-I or/and MEMA-T), as well as loss and/or fragmentation of elastic  
93 fibers.

94  
95 In aortic media walls, the X monosomy was frequent, as it was present in 7/11 of cases. The  
96 level of 45, X mosaicism was otherwise higher than 60%.

97  
98 Interestingly, one patient (**Figure 1B**) with a low 45,X mosaicism in blood (5%), had a higher  
99 rate of X monosomy (70%) in endothelial and muscle components of her ascending aortic  
100 media.

101 To our knowledge, this is the first aortic FISH description in patients with TS having  
102 prophylactic surgery. Histology revealed an early MDC in all cases, even in young TS  
103 patients. Our group previously identified similar levels of MDC in the aorta of non-TS  
104 patients with TAA, with or without BAV<sup>4</sup>. In TS patients, MDC was present, even with a low  
105 percentage of 45,X monosomy in blood. Therefore, a low level of 45,X monosomy in blood  
106 should not be reassuring concerning an aortic dissection risk.

107  
108

## 109 **References**

110

111 1. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women  
112 with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur. J.*  
113 *Endocrinol.* 2017; 177:G1–G70.

114

115 2. Silberbach M, Roos-Hesselink JW, Andersen NH, et al. Cardiovascular Health in Turner Syndrome: A  
116 Scientific Statement From the American Heart Association. *Circ. Genomic Precis. Med.* 2018; 11:e000048.

117

118 3. Donadille B, Tuffet S, Cholet C, et al. Prevalence and progression of aortic dilatation in adult patients with  
119 Turner syndrome: a cohort study. *Eur. J. Endocrinol.* 2020; 183:463–470.

120

121 4. Amemiya K, Mousseaux E, Ishibashi-Ueda H, Achouh P, Ochiai M, Bruneval P. Impact of histopathological  
122 changes in ascending aortic diseases. *Int. J. Cardiol.* 2020; 311:91–96.

123

124 5. Sievers H-H, Stierle U, Mohamed SA, et al. Toward individualized management of the ascending aorta in  
125 bicuspid aortic valve surgery: the role of valve phenotype in 1362 patients. *J. Thorac. Cardiovasc. Surg.* 2014;  
126 148:2072–2080.

127

128

## 129 **Figure 1:**

130

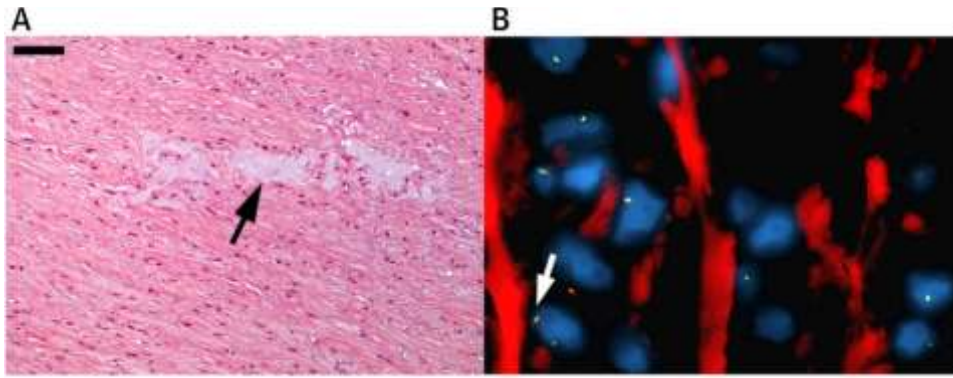
131 **1A:** Histology of an aortic wall showing a MEMA-T (arrow) and an aortic media multifocal  
132 extension. Bar = 200 micrometers.

133

134 **1B:** FISH analysis on the FFPE section of an aortic tissue: A 45,X monosomy is found in the  
135 majority of the nuclei of the aortic media (single green signal ; DXZ1 probe). In rare nuclei, 2  
136 green signals are present (arrow).

137

138



139