## ORIGINAL ARTICLE

# Association between Cardiac Malformations and Karyotype in Turner Syndrome - a Single Centre Study

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**ABSTRACT**

Turner syndrome is characterized by growth failure, pubertal delay and different skeletal, cardiovascular and renal malformations. In this study we investigated the prevalence of cardiac abnormalities and the correlation with the karyotype in girls with Turner syndrome.

**Methods.** We conducted a retrospective cohort study of 85 girls with TS aged 0-17 years, divided in two groups: monosomy X and other X chromosome abnormalities (mosaicism and structural X chromosome abnormalities). Echocardiography was performed in all patients. Karyotype was determined from peripheral blood lymphocytes using the G-banding technique. **Results.** Monosomy X was the most frequent karyotype (68.3%). 31% of patients presented different cardiac abnormalities. Bicuspid aortic valve and coarctation of the aorta were the most prevalent heart malformations (16.5% and 11.8% respectively). The girls with monosomy X had a higher prevalence of heart malformations than the girls with other chromosome abnormalities. Bicuspid aortic valve was more frequent in the monosomy X group.

**Conclusion.** Monosomy X is associated with a higher incidence of cardiac abnormalities. There were no differences in cardiovascular abnormalities between various karyotypes except the higher incidence of bicuspid aortic valve observed in patients with monosomy X comparing to those with mosaic karyotype and structural X chromosome aberrations.

**Keywords:** Turner syndrome, karyotype, cardiac abnormalities.

**REZUMAT**

Sindromul Turner este caracterizat prin deficit de creștere staturală, retard pubertar, anomalii scheletice, cardiovasculare și renale. Scopul studiului este de a stabili prevalența anomaliilor cardiovasculare și corelarea acestora cu cariograma la pacientele cu sindrom Turner.

**Metode.** Studiul a fost retrospectiv și a inclus 85 de paciente cu sindrom Turner, având vârsta cuprinsă între 0 și 17 ani, repartizate în două grupuri în funcție de cariogramă: monosomie X și alte anomalii cromozomiale (mozaicism și anomalii structurale ale cromozomului X). La toate pacientele s-a efectuat ecocardiografie Doppler. Pentru stabilirea formulei cromozomiale s-a folosit tehnica cariogramei bandate, utilizand limfocite din sangele periferic.

**Rezultate.** Monosomia X a fost cea mai frecventă formulă cromozomială depistată (68.3%). 31% dintre pacienți au prezentat diferite anomalii cardiace. Valva aortică bicuspidă și coarctația de aortă au fost cel mai frecvent diagnosticate (la 16.5% și respectiv 11.8% dintre paciente). Malformațiile cardiace au fost mai frecvente la pacientele cu monosomie X. Bicuspidia aortică a fost mai frecvent întalnită la pacientele din primul grup.

**Concluzii.** Monosomia X este asociată cu o incidență mai mare a malformațiilor cardiace. Nu au existat diferențe statistic semnificative între tipul malformațiilor cardiace diagnosticate la cele două grupuri, cu excepția bicuspidiei aortice, care a fost mai frecventă la pacientele cu monosomie X.

**Cuvinte cheie:** sindrom Turner, cariogramă, anomalii cardiace.

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## INTRODUCTION

Turner syndrome (TS), the most common sex chromosome abnormality in women is a developmental disorder characterized by complete or partial loss of the second sex chromosome. Turner syndrome was originally described by Henry Turner in 1938.[1] In 1959 Ford et al. identified the missing X chromosome.[2] The prevalence is approximately 1:2500 female births.[3] The classical presentation of the females diagnosed with TS includes short stature and delayed puberty. Additional features consist in characteristic dysmorphic features, webbed neck, low posterior hairline, multiple pigmented nevi, high arched palate, broad shield chest, cubitus valgus, short 4$^{th}$ metacarpal or metatarsal, lymphedema, diverse renal and cardiovascular abnormalities and autoimmune diseases. The most common cardiovascular abnormalities in females with TS are bicuspid aortic valve with 30-50 times higher prevalence than in the general population and coarctation of the aorta. Thoracic aorta aneurysm and dissection of the aorta represent the major cause of cardiovascular morbidity and mortality in TS adult patients.[4,5] Association of certain comorbidities in later-life as hypertension, diabetes mellitus, hyperlipidaemia and sleep apnea leads to an increased cardiovascular risk.[6] Approximately 50% of the patients with TS have a single X chromosome, 20-50% have mosaicism and other TS patients have isochromosomes, ring chromosome or various deletions.[6,7] Generally, the patients with mosaicism have a milder form of disease than the patients with monosomy X.[3] The severity of TS features was correlated with the number of cells that harbour Xp and a recent study has demonstrated that left-sided congenital heart defects are significantly associated with reduced dosage of Xp genes and increased dosage of Xq genes.[8,9] Associations between malformations and karyotype was also reported by other studies.[10,11]

Data related to cardiovascular manifestations in Romanian patients with TS are scarce, the only report that included 45 subjects refers more to clinical features.[12]

Considering these data, the aim of this study was to assess the prevalence of cardiac malformations and the correlation between the karyotype and cardiovascular malformations in 85 patients with TS.

## PATIENTS AND METHODS

### Study design

This was an exploratory, non-hypothesis testing analysis, using descriptive statistics, only single centre study.

### Study population

We performed full phenotypic/genotypic characterization in 85 consecutive patients with TS (mean age 8.6 ± 6.2 years; range 0 - 17), followed at Pediatrics I Clinic and Genetic Diseases Department, Emergency Paediatric Hospital Cluj-Napoca, during the period 2005-2020. Depending on the karyotype, the patients were divided in 2 groups. Group 1 comprised 58 patients with monosomy X and group 2 comprised 27 patients with mosaic karyotype and structural X chromosome aberrations (deletions of the long or short arm of the chromosome X and isochromosome X) – the non-monosomic group. The mosaicism included monosomy associated with cellular lines of normal female karyotype and trisomy X.

## METHODS

The following data were collected: age at diagnosis, actual age, medical history of cardiac disease, the presence of other different malformations and karyotype. Regular annual follow-up was performed in all patients.

Transthoracic echocardiography (TTE) was performed in all patients by the same physician, including Mmode, twodimensional (2D) and color Doppler techniques, using a commercially available system (Vivid S6, General Electric, Wauwatosa, WI, USA) with a transducer according to the age of patient. All cardiac measurements were conducted in accordance with the recommendations international cardiovascular imaging associations for cardiac chamber and valvular regurgitation quantification.[13,14] The standardized protocol included scanning in the parasternal long axis, parasternal short axis, apical, suprasternal and subcostal views.

The karyotype was determined from peripheral blood lymphocytes, using Lymphochrome (Lonza) culture medium. The analysis of metaphase chromosomes was done after performing G-banding technique. Sixteen metaphases were counted and analyzed in each patient and if a cell mosaic was strongly suggested, 32 metaphases were karyotyped.

### Statistical analysis

Statistical analyses were performed using the MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). Comparisons between the groups of continuous variables were performed using Student's *t* test and those of categorical variables was performed using the chi-squared test. Statistical significance was established by calculating the p value, with a statistical significance threshold of 0.05.[15]

### Ethics statement

Written informed consent was obtained from the patients aged more than 12 years and the guardians of paediatric patients and the study followed the ethical guidelines of the Declaration of Helsinki and the ethical standards of the national research committee.

## RESULTS

Baseline characteristics of patients with TS are depicted in Table 1. The mean age at diagnosis was 8.6 years. The mean age at diagnosis was 5.1 years for the patients with heart malformations and 9.9 years for the patients without heart malformations (t = 1.877; p = 0.031). Eighteen patients (21.1%) were diagnosed immediately after the birth and ten of them (55.5%) presented heart malformations. The most frequent malformations were the skeletal abnormalities, followed by cardiac malformations and renal malformations. Neuropsychological features consisted in intellectual disability, behavioural problems and neurosensorial deafness and were present in 17.6% of our group. Thyroid dysfunction was present in 21.2% of patients and cutaneous anomalies in 5.9% of patients. Twenty-one patients (24.8%) presented comorbidities recognized as cardiovascular risk factors (obesity, dyslipidaemia and insulin reistance). No hypertension was found in our cohort.

We identified a single chromosome X in 68.3% of cases and mosaicism in 22.4% of cases. In 9.3% of cases, other structural variants were present (isochromosome and deletions) – (Table 2).

26 patients (31%) presented different heart malformations (Table 3).

The most common malformation was bicuspid aortic valve (16.5%). This malformation was isolated in 4 girls (28.6%) and associated with other cardiac abnormalities in 10 patients (71.4%). Aortic disease (bicuspid aortic valve, coarctation of the aorta and aortic stenosis) was present in 18 patients (21.1%). 10 patients (11.8%) were diagnosed with coarctation of the aorta and 70% of them presented bicuspid aortic valve. Mitral valve disease (mitral valve prolapse and mitral regurgitation) was diagnosed in 3.5% of patients. In 6 patients a left-to-right shunt was diagnosed (4 patients with atrial septal defect, one patient with muscular ventricular septal defect and 1 patient with patent ductus arteriosus). Isolated heart malformations were diagnosed in 16 patients (18.8%): 5 patients with bicuspid aortic valve, 3 patients with coarctation of the aorta, 3 patients with atrial septal defect, 2 patients with mitral valve prolapse, 1 patient with patent ductus arteriosus, 1 patient with aortic stenosis and one patient with persistent left superior vena cava (Figures 1-4). 10 patients (11.7%) presented two or more heart malformations. Surgical intervention was required in 8 patients: 6 with coarctation of the aorta, one patient with atrial septal defect and one patient with patent ductus arteriosus.

The prevalence of heart malformations in the first group (monosomy X) was significantly higher than in the patients with non-monosomic karyotype (38%; p = 0.031). Bicuspid aortic valve had a significantly higher

**Table 1. Baseline characteristics of patients with TS**

| Patients n (%) | | Group 1<br>58 patients | Group 2<br>27 patients | Total<br>85 patients | p |
|---|---|---|---|---|---|
| Mean age at diagnosis (years) | | 8.6 | 8 | 8.6 | 0.077 |
| Malformations | Heart | 22 (38) | 4 (14.8) | 26 (31) | 0.031 |
| | Renal | 7 (12) | 7 (25.9) | 14 (16) | 0.108 |
| | Skeletal | 21 (36) | 6 (22.2) | 27 (32) | 0.197 |
| Neuropsychological manifestations | Intellectual disability | 7 (12) | 3 (11.1) | 10 (11.7) | 0.898 |
| | Behavioural problems | 1 (1.7) | 1 (3.7) | 2 (2.3) | 0.575 |
| | Neurosensorial deafness | 2 (3.4) | 1 (3.7) | 3 (3.5) | 0.952 |
| Cutaneous manifestations | Psoriasis | 2 (3.4) | 1 (3.7) | 3 (3.5) | 0.952 |
| | Vitiligo | 0 | 1 (3.7) | 1 (1.2) | NA |
| | Alopecia | 1 (1.7) | 0 | 1 (1.2) | NA |
| Thyroid dysfunction | | 13 (22.4) | 5 (18.5) | 18 (21.2) | 0.682 |
| Cardiovascular risk factors | Obesity | 11 (18.9) | 3 (11.1) | 14 (16.5) | 0.363 |
| | Dyslipidaemia | 5 (8.6) | 1 (3.7) | 6 (7.1) | 0.765 |
| | Insulin resistance | 1 (1.7) | 0 | 1 (1.2) | NA |

NA: not applicable

**Table 2. The karyotype in TS patients**

| Karyotype | Number | % |
|---|---|---|
| 45,X | 58 | 68.3 |
| 45,X/46,XX | 18 | 21.2 |
| 45,X/47,XXX | 1 | 1.2 |
| 46,Xi (Xq) | 3 | 3.5 |
| 46,del Xq | 3 | 3.5 |
| 46,del Xp | 2 | 2.3 |

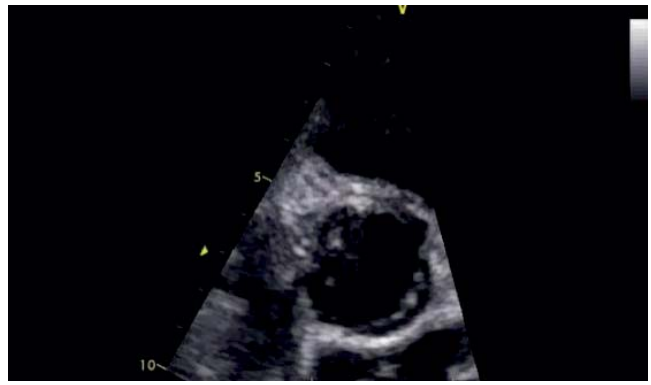

**Figure 1.** Transthoracic echocardiogram in parasternal short-axis view illustrating bicuspid aortic valve.

**Table 3. Types of cardiac abnormalities in patients with TS**

| Cardiac abnormalities n (%) | Group 1<br>58 patients | Group 2<br>27 patients | Total<br>85 patients | p |
|---|---|---|---|---|
| Bicuspid aortic valve | 13 (22.4) | 1 (3.7) | 14 (16.5) | 0.028 |
| Coarctation of the aorta | 9 (15.5) | 1 (3.7) | 10 (11.8) | 0.115 |
| Aortic stenosis | 3 (5.1) | 1 (3.7) | 4 (4.7) | 0.765 |
| Atrial septal defect | 4 (6.9) | 0 | 4 (4.7) | NA |
| Aortic regurgitation | 4 (6.9) | 1 (3.7) | 5 (5.8) | 0.560 |
| Mitral valve prolapse | 2 (3.4) | 1 (3.7) | 3 (3.5) | 0.952 |
| Ventricular septal defect | 1 (1.7) | 0 | 1 (1.2) | NA |
| Patent ductus arteriosus | 0 | 1 (3.7) | 1 (1.2) | NA |
| Persistent left superior vena cava | 0 | 1 (3.7) | 1 (1.2) | NA |

NA: not applicable

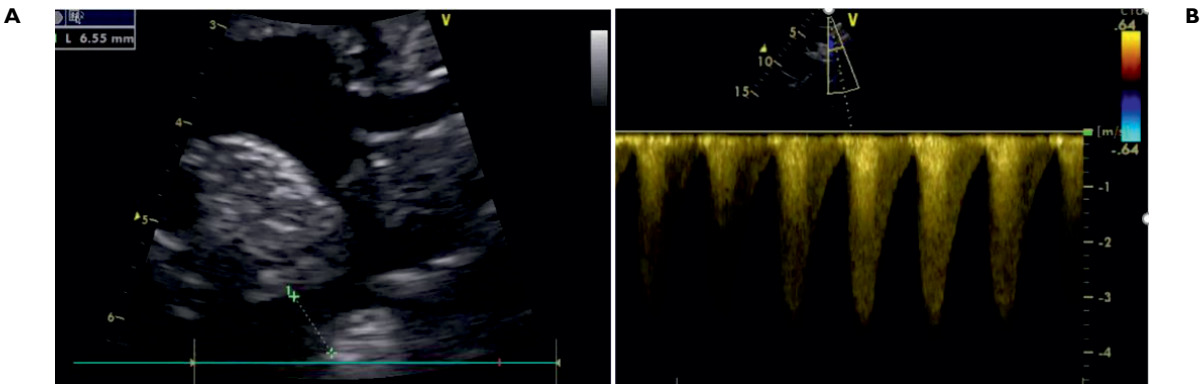


**Figure 2.** Transthoracic echocardiogram in suprasternal view illustrating narrow aortic isthmus (A) and high blood flow speed – continuous wave Doppler (B) in a patient with coarctation of the aorta.

prevalence in the group of patients with monosomy X, but no difference was found between the karyotype and the prevalence of aortic coarctation, aortic stenosis and mitral valve prolapse.

The mean age at diagnosis was 3.3 years in patients with coarctation of the aorta and 6.3 years in patients with other types of heart malformations (t = 0.784; p = 0.218).

## DISCUSSION

This study investigated cardiac abnormalities and karyotype-cardiac phenotype associations in a group

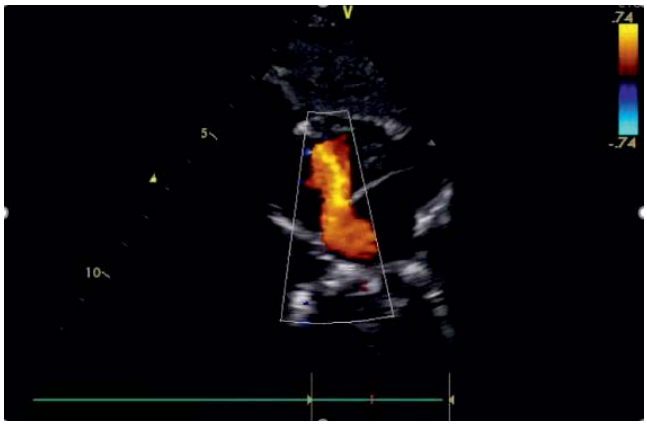

**Figure 3.** Transthoracic echocardiogram in subcostal long-axis view illustrating an ostium secundum atrial septal defect.

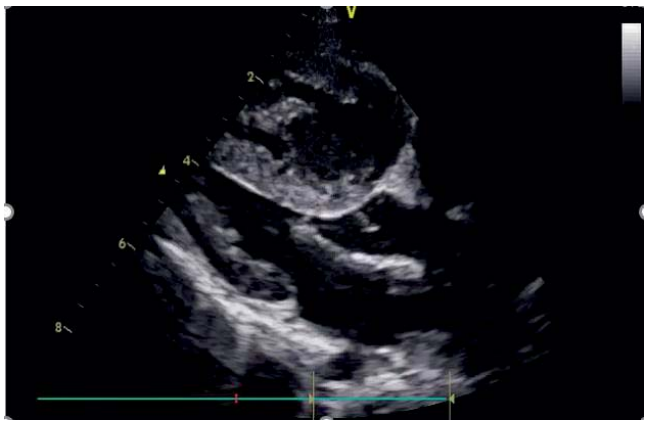

**Figure 4.** Transthoracic echocardiogram in parasternal long-axis view illustrating a dilated coronary sinus in a patient with persistent left superior vena cava.

of 85 girls with TS. We showed a higher prevalence of cardiac malformations in patients with monosomy X. Bicuspid aortic valve was more prevalent in patients with monosomy X. The most common karyotype in our group was monosomy X (45,X), followed by mosaicism (45,X/46,XX), deletions of the long arm and short arm of the chromosome X and isochromosome X. The proportion of monosomy X was higher in our group (68.3%) comparing to other studies where the monosomy X ranges between 31% and 65%.[3,16-20] This finding could be explained by the main reason of presentation of our patients for short stature and pubertal delay, findings that are more prevalent in patients with monosomy X than in those with mosaicism.[21,22] If all girls with short stature would be screened for TS, even in the absence of characteristic dysmorphic features, a more frequent diagnosis of mosaicism could be established.

The frequency of cardiac abnormalities in our study (31%) is in accordance with other studies which ranges from 19% to 40%.[6,16,19] Bicuspid aortic valve and coarctation of aorta were the leading heart malformations.

Bicuspid aortic valve was the predominant cardiac abnormality in our cohort study (16.5%), comprising 53.8% of total cardiac defects. The incidence of this malformation in TS varies between 6% and 41% in other studies.[6,8,16,23-28] Increased prevalence of bicuspid aortic valve in individuals with monosomy X was demonstrated by other authors.[29,30] In TS the prevalence of bicuspid aortic valve is 30-50 higher than in general population and complete or partial loss of the second sex chromosome is the most likely predisposing factor.[31] However, it has been demonstrated that monosomy X is not always a sufficient factor causing aortic disease and a second factor which interacts with monosomy X, as autosomal variants affecting cardiac developmental genes leads to an increased prevalence of the left-sided congenital heart lesions in TS.[8]

Coarctation of the aorta was present in 10 patients (11.8%), representing 38.5% of total cardiac defects. The prevalence in our cohort study was within the limits reported by other authors (3.4-18.1%).[6,8,16,23-28] In our group, in four of ten patients with coarctation of the aorta the diagnosis of TS was established late, after the age of 5 years, when the patients presented for endocrinological assessment for short stature. The mean age at diagnosis of TS in patients with coarctation of the aorta seemed to be lower compared to the patients with other various heart malformations (3.3 years vs. 6.3 years), although this association was not statistically significant. However, is noteworthy that in six patients with coarctation of the aorta the diagnosis of TS was established in the first month of life due to the coexistence of the heart malformation. All these patients associated characteristic dysmorphic features and one girl presented neonatal lymphedema. Therefore, karyotype should be required in female neonates with coarctation of the aorta, especially in those with associated characteristic phenotypic features as webbed neck or peripheral lymphedema.[32] On the other hand, Wong et al. diagnosed TS by routine karyotype in 5.3% of females with coarctation of the aorta and Eckhauser et al. in 12.6% of them, recommending immediately TS screening after the diagnosis for all patients with coarctation of the aorta.[33,34]

In our cohort study we found a statistically significant difference between the mean age at TS diagnosis

in patients with congenital heart malformations (5.1 years) and those without congenital heart defects (9.9 years). This finding could be explained by earlier referral of the patients with clinical signs suggesting a congenital heart disease to a tertiary centre where a complete diagnostic evaluation (including genetic diagnosis) is performed.

The prevalence of mitral valve prolapse in our cohort study was 3.5%, higher than in healthy young women which is assumed to be 1% to 2%, but lower than in other studies.[35]

Six patients (7%) from our TS group had left-to-right shunts (four patients with atrial septal defect, one patient with ventricular septal defect and one patient with patent ductus arteriosus), of which 2 required surgery (one for atrial septal defect and one for patent ductus arteriosus), in contrast to other studies where these malformations are reported incidentally.[36-38]

One patient of our group (representing 1.2%) presented persistent left superior vena cava. This cardiac abnormality is generally rarely associated with TS, the only reports are limited to studies involving catheter implantation candidates. The studies using other imaging methods than echocardiography as magnetic resonance or computed tomography angiography have reported a consistent prevalence of 13%.[39,40] In normal neonates, Nagasawa et al. reported an incidence of 0.21%, while a higher incidence (more than 7 times) was observed in patients with congenital heart defects.[41] Although other studies reported additional vascular anomalies, including coronary arteries anomalies and partial anomalous pulmonary venous return, we have not found these abnormalities in our group.[42,43]

We found a higher prevalence of cardiac abnormalities in the group with monosomy X comparing the group with mosaicism and structural chromosomal abnormalities (38% vs. 14.8%), suggesting a correlation between cardiac abnormalities and karyotype. This correlation has been showed by Mazzanti et al. in a group of 594 TS patients, Gøtzsche et al. in a group of 393 patients and Noordman et al. in a group of 202 patients, who demonstrated a higher incidence of more severe cardiac abnormalities, especially coarctation of the aorta in monosomy X and association with skeletal and lymphatic phenotype.[44-46] In our second group, only one patient presented aortic disease, in accordance with other studies which have demonstrated that mosaicism seems to mitigate the TS phenotype.[22]

The prevalence of bicuspid aortic valve in our cohort group was significantly higher than in the first group (22.4% vs. 3.7%), according to other studies.[27,46] Coarctation of the aorta seemed to have a higher incidence in monosomy X group, although the association was not statistically significant. Yeşilkaya et al. studied a large group of 842 TS patients and demonstrated that coarctation of the aorta predominates in patients with the karyotype of 45,X.[47] This finding was also confirmed by Mondal et al. in a group of 103 patients.[28]

Turner syndrome is associated with a high risk of subsequent comorbidities. Obesity, dyslipidaemia, diabetes mellitus and hypertension contribute to an increased cardiovascular risk. The prevalence of overweight and obesity in our group was 16.5%, lower than the prevalence reported by Chiriță-Emandi et al. 2016 who found a prevalence of obesity and overweight in Romanian girls of 20.9% and Pop et al. who reported in 2021 a higher prevalence, of 22.7%.[48,49] The lower prevalence of obesity in patients with TS can be explained by the fact that their parents are much better informed than general population about the risks of obesity and they are more concerned about the health of their children and adopt a healthier lifestyle. Dyslipidaemia and insulin resistance in our group had a lower prevalence (7.1%, 1.2% respectively) compared to that reported by Yeşilkaya et al., the difference could be attributed to younger age of the patients from our group.[47] The absence of hypertension in our cohort group could also be attributed to the younger age of our patients and early correction of cardiac abnormalities.

This study has several limitations. The study was retrospective with variable follow-up durations for patients and the number of patients was also limited. The non-monosomy group was heterogeneous and composed of patients with many different karyotypes. Echocardiography has its limits in the diagnosis of certain vascular abnormalities. No data on healthy controls regarding the prevalence of different heart malformations were available. There is no national program of screening for TS in our country, so the number of patients may be higher. We did not evaluate the presence of acquired cardiac abnormalities, which may affect these patients. Finally, our cohort included pediatric patients and further studies are required to detect changes with aging.

## CONCLUSION

Our results suggest that the prevalence of cardiac abnormalities is higher in TS patients with monosomy X primarily due to a significant difference in the pre-

valence of aortic valve abnormalities and aortic coarctation.

## Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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