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Original Article

Impact of Genotype-Phenotype Interactions on Cardiovascular Function in Paediatric Loeys-Dietz Syndrome

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ABSTRACT

Background: The relationship between genotype and phenotypical vascular and cardiac properties in paediatric Loeys-Dietz syndrome (LDS) patients are not well characterized. This study explores the phenotypical differences in aortic properties and cardiac structural and functional parameters between paediatric LDS patients with *TGFBR1* and *TGFBR2* mutations.

Methods: We included 32 LDS patients with either *TGFBR1* (n = 17) or *TGFBR2* (n = 15) mutations. Echocardiographic data included aortic dimensions, distensibility, strain, and stiffness at the level of the annulus, sinuses of Valsalva, sinotubular junction, ascending aorta,

RÉSUMÉ

Contexte : Les liens entre le génotype des enfants atteints du syndrome de Loeys-Dietz (SLD) et les particularités phénotypiques vasculaires et cardiaques n'ont pas encore été bien caractérisés. La présente étude vise à explorer les différences phénotypiques entre les propriétés de l'aorte et les paramètres cardiaques structuraux et fonctionnels des enfants atteints du SLD qui présentent une mutation du gène *TGFBR1* et ceux qui présentent une mutation du gène *TGFBR2*.

Méthodologie : Nous avons inclus dans notre analyse 32 patients atteints du SLD présentant une mutation de *TGFBR1* (n = 17) ou de

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder caused by mutations in any of the following 6 genes: *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2*, or *SMAD3*.[1] One of the major contributors to morbidity and mortality in LDS is aortic pathology including aortic aneurysms, dissection, and rupture.[2] Clinical management is complicated by the significant phenotypic heterogeneity between patients. LDS-causing mutations have been associated with phenotypes ranging from normal to severe cardiovascular involvement in childhood requiring multiple surgical interventions.[3]

Recent studies highlighted important phenotypic differences between LDS genotypes, especially between the 2 most common LDS genotypes (*TGFBR1* and *TGFBR2*). Aortic features differ between the 2 populations, with more aggressive aortic disease identified in patients with *TGFBR2* mutations.[4-6] These data are mainly based on adult LDS cohorts and suggest that there may be gene-dependent differences in the impact on aortic wall architecture and biophysical properties. LDS-associated mutations can also alter the cardiac extracellular matrix composition, which plays an important role in cardiac structure and function, but less is known about the impact of genotypical variation on cardiac structure and function.[7]

In this study, we aimed to further explore the relationship between genotype and cardiovascular phenotype in a paediatric cohort of LDS patients with *TGFBR1* and *TGFBR2* mutations.

Methods

Study population

Paediatric patients followed by our institution with a genetically confirmed diagnosis of LDS between January 2006 and June 2020 were included. Inclusion criteria were a clinically confirmed pathogenic or likely pathogenic variant of an LDS-associated mutation (*TGFBR1* or *TGFBR2*) and at least 1 echocardiographic assessment with blood pressure, height, and weight measurements on the day of imaging. Current medications, family history, and the presence of other

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and descending aorta. Parameters for left ventricular size and function were also recorded.

Results: Demographics were similar between the groups. Patients with *TGFBR2* were more likely to have undergone aortic surgery (47% vs 12%, $P = 0.057$) and use angiotensin receptor blockers (93% vs 47%, $P = 0.015$). Aortic *z* scores were significantly larger in the *TGFBR2* group at the level of the aortic valve annulus ($P = 0.007$), sinuses of Valsalva ($P = 0.001$), sinotubular junction ($P = 0.001$), and ascending aorta ($P = 0.054$). Patients with *TGFBR2* also had significantly lower aortic distensibility and strain coupled with higher stiffness index at the level of the annulus, sinotubular junction, and ascending aorta. Parameters for the descending aorta, cardiac morphology, and cardiac function were similar between the groups.

Conclusions: Paediatric LDS patients with *TGFBR2* present with more severe cardiovascular phenotypes than patients with *TGFBR1* with larger aortic dimensions and increased aortic stiffness. Our findings suggest that genotypes should be taken into consideration in the clinical management of paediatric LDS patients.

TGFBR2 (n = 15). Les données échocardiographiques colligées incluaient les dimensions de l'aorte, sa distensibilité, sa déformation (*strain*) et sa rigidité au niveau de l'anneau aortique, des sinus de Valsalva, de la jonction sinotubulaire, de l'aorte ascendante et de l'aorte descendante. Les paramètres ayant trait à la taille et à la fonction du ventricule gauche ont également été consignés.

Résultats : Les caractéristiques démographiques étaient comparables dans les deux groupes. Les patients présentant une mutation du gène *TGFBR2* étaient plus susceptibles d'avoir subi une intervention chirurgicale de l'aorte (47 % *vs* 12 %, $p = 0{,}057$) et de prendre un antagoniste des récepteurs de l'angiotensine (93 % *vs* 47 %, $p = 0{,}015$). Les scores z aortiques étaient significativement plus élevés chez les patients présentant une mutation de *TGFBR2* pour les dimensions de l'anneau de la valve aortique ($p = 0{,}007$), des sinus of Valsalva ($p = 0{,}001$), de la jonction sinotubulaire ($p = 0{,}001$) et de l'aorte ascendante ($p = 0{,}054$). Les patients avec une mutation de *TGFBR2* présentaient aussi une élasticité et une déformation aortiques significativement plus faibles ainsi qu'une rigidité accrue au niveau de l'anneau aortique, de la jonction sinotubulaire et de l'aorte ascendante. Les paramètres de l'aorte descendante, les caractéristiques morphologiques cardiaques et la fonction cardiaque étaient comparables pour les deux groupes.

Conclusions : Chez les enfants atteints du SLD, une mutation du gène *TGFBR2* se traduisait par des phénotypes plus défavorables que dans le cas d'une mutation du gène *TGFBR1* et se caractérisait par des dimensions et une rigidité aortiques accrues. Nos observations indiquent qu'il convient de prendre le génotype des patients en considération lors de la prise en charge clinique des enfants atteints du SLD.

phenotypic presentations at the time of echocardiography were also collected. In applicable cases, echocardiographic assessment performed after surgical aortic repair or replacement was excluded. Children were excluded from the study if they had clinical features of LDS without genetic confirmation or had LDS with non-*TGFBR1* or non-*TGFBR2* mutations.

Echocardiographic assessments

Echocardiograms were performed according to a standardized clinical protocol based on the American Society of Echocardiography guidelines, including standard measurements of aortic dimensions, cardiac chamber dimensions, and systolic and diastolic function.[8] The most recent echocardiographic measurements (presurgical, when applicable) were abstracted from clinical reports or measured from digitally stored images (SyngoDynamics; Siemens, Munich, Germany). Echocardiograms that had missing measurements in the reports were measured offline by a trained observer who was blinded to the participants' clinical and genetic information. If multiple measurements of the same parameter were collected from the same echocardiogram, the average of these measurements was used in the analysis. Using standardized and validated methods,[9] aortic measurements were collected from the parasternal short-axis view. Measurements of the descending aorta were collected from the suprasternal long-axis view. Aortic measurements and associated calculations of biophysical properties were obtained based on inner edge-to-inner edge measurements for the aortic root, sinuses of Valsalva, sinotubular junction, and ascending aorta. Left ventricular structural and functional measurements were collected from M-mode echocardiograms. Aortic biophysical properties were assessed by the calculating aortic distensibility, strain, and stiffness index based on the following formulae:[9,10]

$$\text{Aortic distensibility} = (2(\text{AOs}-\text{AOd}))/(\text{AOd}(\text{SBP}-\text{DBP})$$
$$\text{Aortic strain} = 100((\text{AOs}-\text{AOd})/\text{AOd}))$$
$$\text{Aortic stiffness index} = (\ln(\text{SBP}/\text{DBP}))/((\text{AOs}-\text{AOd})/\text{AOd})$$

where AOs is the systolic aortic dimension, AOd is the diastolic aortic dimension, ln is the natural logarithm, and SBP and DBP are the systolic and diastolic blood pressure, respectively.

Measurements of left ventricular dimensions included left ventricular end-diastolic dimension (LVEDD), left ventricular posterior wall end-diastole (LVPWD), and interventricular septum end-diastole (IVSD) were taken in M-mode. Left ventricular mass (LVM) was calculated using the following American Society of Echocardiography—recommended formula:[11]

$$\text{LVM} = 0.8(1.04((\text{LVEDD}+\text{IVSD}+\text{LVPWD})^3 - \text{LVEDD}^3)) + 0.6$$

Parameters of systolic function included ejection fraction (M-mode), fractional shortening, and mitral annulus tissue Doppler S′-velocity. Parameters of diastolic function included mitral valve E-wave velocity, A-wave velocity, A-wave time, and E-wave

Table 1. Demographic, pharmacologic, and phenotypic parameters in 32 paediatric Loeys-Dietz syndrome (LDS) patients

General characteristics	TGFBR1 (n = 17)	TGFBR2 (n = 15)	*P*
Demographics			
Age at echo (y)	11.0 (4.7-16.2)	10.0 (6.6-14.3)	0.478
Sex, male	11 (65)	8 (53)	0.769
Height (cm)	159 (111.5-174.0)	143 (116.2-167.5)	0.427
Weight (kg)	45.3 ± 30.2	35.7 ± 24.9	0.332
BSA (m^2)	1.33 ± 0.57	1.15 ± 0.54	0.362
Aortic surgery			
History of aortic surgery	2 (12)	7 (47)	**0.057**
Aortic dissection	0 (0)	1 (14)	—
Age at aortic surgery (y)	13.5 (12.3-14.7)	6.0 (2.3-12.0)	0.222
ARB	8 (47)	14 (93)	**0.015**
β-Blocker	7 (41)	12 (80)	0.061
ACEi	0 (0)	1 (7)	0.949
None	6 (35)	1 (7)	0.127
Family history			
Positive family history for LDS	9 (53)	4 (27)	0.250
Presence of other phenotypic characteristics			
Arterial tortuosity	12 (71)	13 (87)	0.272
Craniofacial features	3 (18)	7 (47)	0.077
Pectus deformities	3 (18)	7 (47)	0.077
Dural ectasia	4 (24)	5 (33)	0.538
Scoliosis	3 (18)	5 (33)	0.307

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).
Bold values indicate $P < 0.05$.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area.

deceleration time. Isovolumetric relaxation time and septal and lateral mitral annulus tissue Doppler velocities (E′ and A′) were measured. The mitral E/A ratio and lateral and septal E/E′ ratio were calculated. *z* scores were calculated based on the formulas and values published by the Pediatric Heart Network (PHN).[12]

Statistical analyses

Continuous data were reported as means (±standard deviation) or medians (interquartile range [IQR]), depending on the distribution. Categorical data are presented as proportions (percentages) and were compared using Pearson's χ^2 test. Aortic measurements and left ventricular structural and functional measurements were compared using the unpaired Student *t* test or the Mann-Whitney Wilcoxon test, depending on the distribution. A *P* value of <0.05 was considered statistically significant. All statistical analyses were conducted using RStudio version 2023.03.1+446.

Results

Study population

In total, 32 patients met the eligibility criteria. According to the available genetic testing, patients were divided into either *TGFBR1* (n = 17) or *TGFBR2* (n = 15). Characteristics of each group are shown in Table 1. The median age at the time of echocardiographic imaging was 11.0 (IQR: 4.7-16.2) and 10.0 (IQR: 6.6-14.3) in the *TGFBR1* and *TGFBR2*, respectively ($P = 0.478$). Both groups comprised more males (65% and 53%, respectively). Body mass index was not significantly different between the groups ($P = 0.315$).

Significantly more patients in the *TGFBR2* group had a history of aortic surgery than those in the *TGFBR1* group (47% vs 12%, $P = 0.057$). One patient in the *TGFBR2* group experienced an aortic dissection. Patients with *TGFBR1* were more likely to undergo aortic surgery in late childhood, whereas the age at aortic surgery in patients with *TGFBR2* was more variable (IQR: 12.3-14.7 years vs 2.3-12.0 years, respectively). Significantly more patients in the *TGFBR2* group were treated with angiotensin receptor blockers (93% vs 47%, $P = 0.015$).

The presence of arterial tortuosity, craniofacial features, pectus deformities, dural ectasia, and scoliosis was similar between the groups. The list of each patient's individual genetic variants is shown in Supplemental Table S1.

Aortic dimensions

Aortic dimension results are summarized in Figure 1. Patients in the *TGFBR2* group had significantly larger systolic diameters for the sinuses of Valsalva and sinotubular junction. The systolic dimensions were similar at the aortic valve annulus, ascending aorta, and descending aorta between the patients with *TGFBR1* and *TGFBR2*.

Patients in the *TGFBR2* group had significantly larger diastolic diameters for the sinuses of Valsalva and sinotubular junction. The diastolic diameter was similar for the ascending and descending aorta between patients with *TGFBR1* and *TGFBR2*. The diastolic diameter of the aortic annulus was excluded as it is not clinically considered.

The PHN *z* score was significantly larger for patients with *TGFBR2* at the level of the aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta. There are no PHN *z* scores for the descending aorta to report.

Aortic biophysical properties

The results of aortic biophysical properties are summarized in Figure 2. Patients in the *TGFBR2* group had significantly lower distensibility at the level of the sinotubular junction and ascending aorta. Distensibility was similar at the level of the

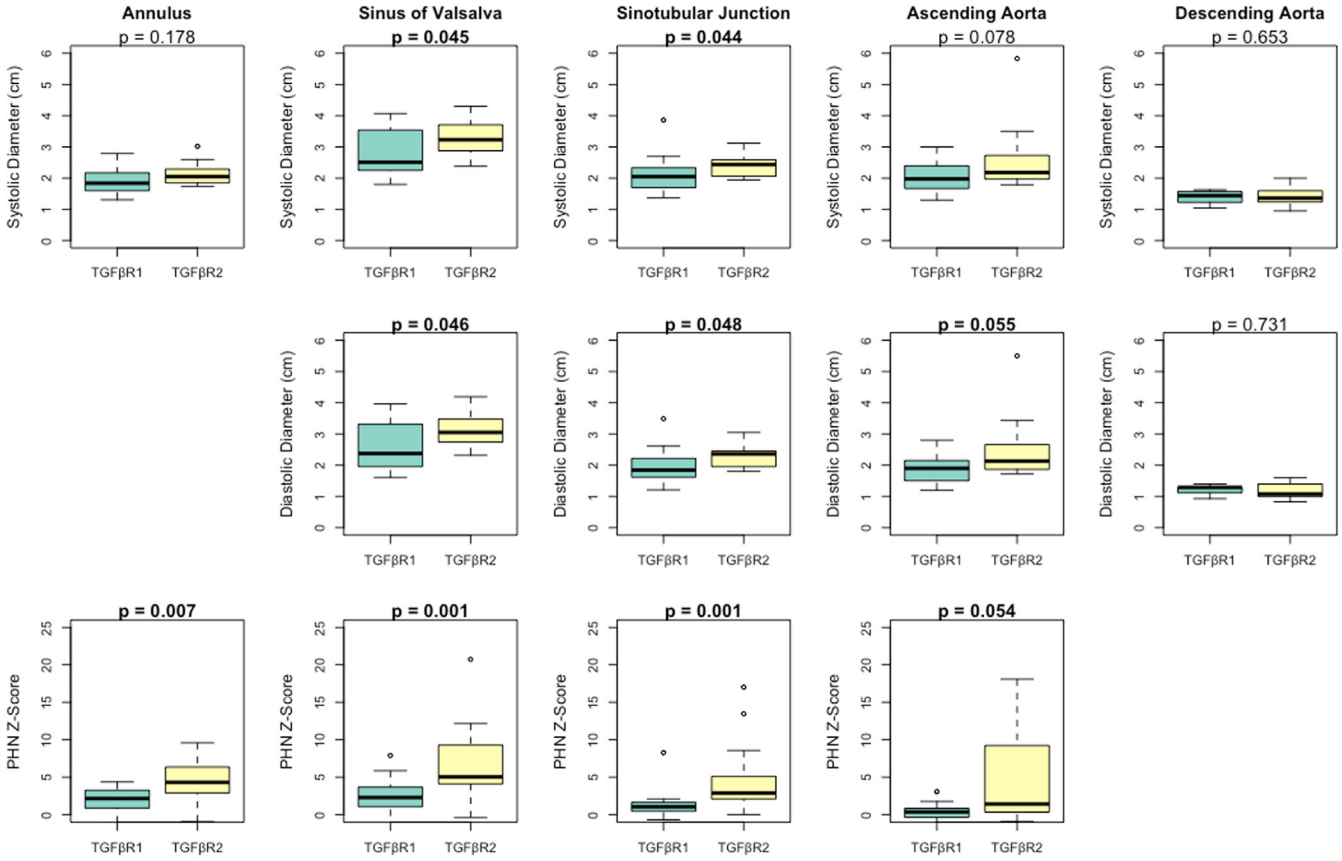

Figure 1. Aortic dimensions at the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta in 32 paediatric Loeys-Dietz syndrome patients. PHN, Pediatric Heart Network.

sinuses of Valsalva and descending aorta between patients with *TGFBR1* and *TGFBR2*.

Patients in the *TGFBR2* group had significantly lower strain in the sinotubular junction and ascending aorta. Strain was similar at the level of the sinuses of Valsalva and descending aorta between patients with *TGFBR1* and *TGFBR2*.

Patients in the *TGFBR2* group had significantly higher stiffness at the level of the sinotubular junction and ascending aorta. The stiffness index of the sinuses of Valsalva and descending aorta was similar between patients with *TGFBR1* and *TGFBR2*.

Left ventricular structural and functional parameters

Our results did not show statistically significant differences for left ventricular dimensions between the *TGFBR1* and *TGFBR2* mutation groups (Table 2). The LVPWD *z* score was significantly higher for patients with *TGFBR2* but was within a normal clinical range. Significantly more patients in the *TGFBR2* group had aortic regurgitation when compared with the *TGFBR1* group. There were no significant differences in left ventricular diastolic or systolic functional parameters between the 2 groups (Table 3).

Discussion

In this study, we report the genotype-phenotype interactions in aortic dimensions and biophysical properties, left ventricular morphology, and left ventricle functional parameters in paediatric LDS patients with either *TGFBR1* or *TGFBR2* mutations. We demonstrate that at a young age, patients with *TGFBR2* mutations have a more clinically unfavourable course requiring earlier surgical interventions and have significant differences in aortic dimensions and biophysical properties.

Genotype considerations in cardiac clinical management

Recent studies have highlighted important phenotypic differences between the 2 most commonly detected LDS genotypes (*TGFBR1* and *TGFBR2*). In comparing the largest international cohort of adult LDS patients with either a *TGFBR1* or *TGFBR2* mutation, the Montalcino Aortic Consortium suggests that aortic features may differ between the 2 populations, with more aggressive aortic disease in patients with *TGFBR2* mutations.[4] Another group reported that aortic dissections occurred with minimal aortic root enlargement in patients with *TGFBR2* mutations, whereas in patients with *TGFBR1* mutation, dissections were only reported in association with significant aortic enlargement.[6] When compared with patients with *TGFBR1*, adult LDS patients with the *TGFBR2* mutation also have significantly higher cumulative risk of aortic events.[5] These studies suggest that LDS patients harbouring *TGFBR2* mutations manifest a distinct trajectory of disease progression, underscoring the

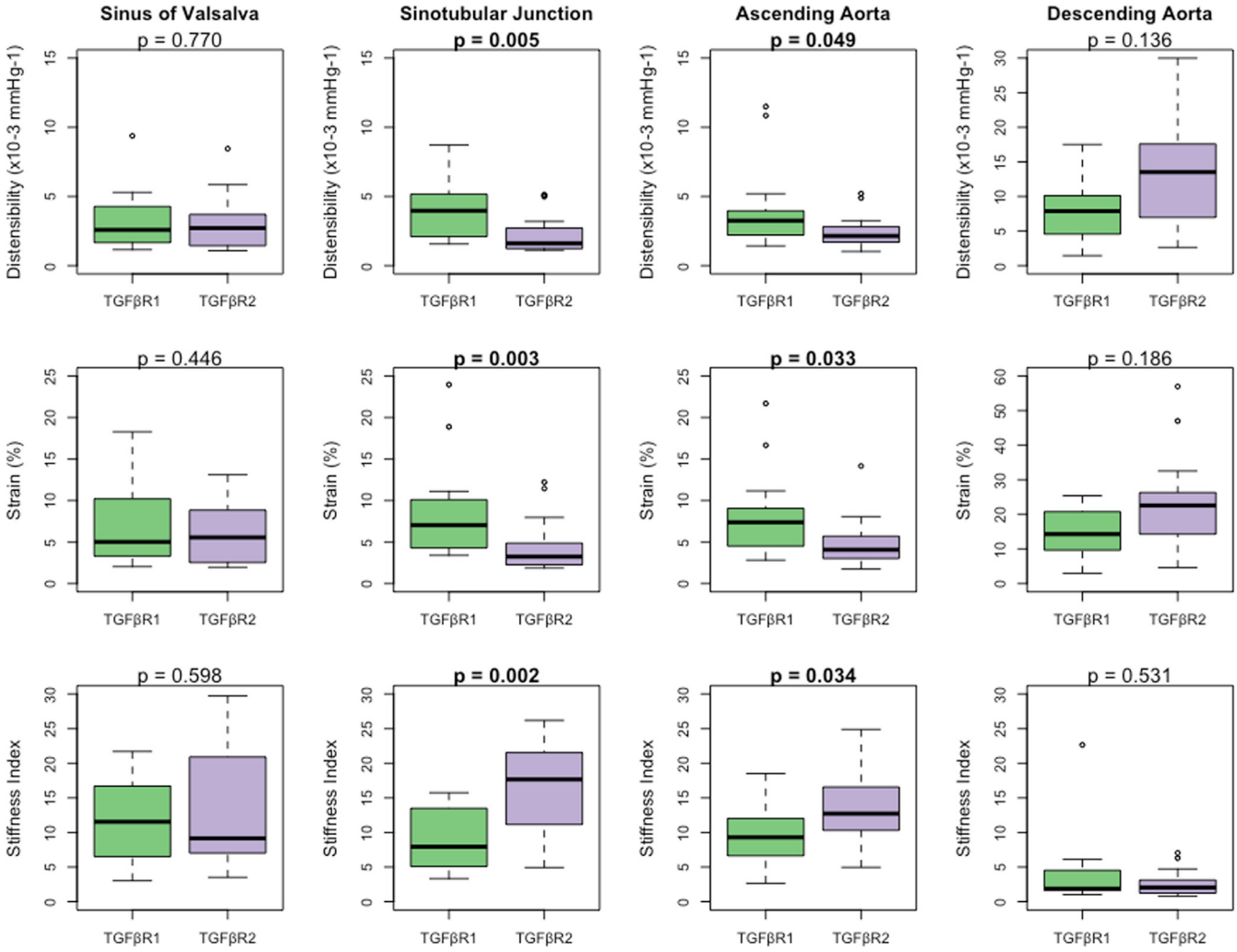

Figure 2. Aortic biophysical properties at the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta in 32 paediatric Loeys-Dietz syndrome patients.

imperative need for tailored and genotype-specific cardiac clinical management recommendations.

Our findings in a paediatric cohort are consistent with the existing literature. Our study illustrates that intrinsic variations in disease progression among LDS genotypes are extendable to paediatric populations, with a pronounced impact on the prevalence of aortic surgery, pharmacologic management, aortic dimensions, and aortic biophysical properties. This underscores the concept that distinct disease trajectories begin to manifest at an early age in individuals with LDS, emphasizing the significance of initiating genotype-specific clinical management strategies during the paediatric phase of care. Furthermore, our findings highlight the necessity for more close clinical monitoring of LDS patients with *TGFBR2* mutations, even when their aortic measurements seemingly align with clinically accepted ranges. This approach to clinical management is warranted given our findings, coupled with previous research, which suggests that patients with *TGFBR2* mutations may deviate from the conventional disease progression trends currently postulated for LDS patients.

Aortic dimensions and biophysical properties in prophylactic surgical planning

In this study, we delineated based on genotypes (*TGFBR1* or *TGFBR2* mutations) in LDS patients. First, considering only structural dimensions and using *z* scores to account for differences in body surface area, our findings show that PHN *z* scores were significantly higher in *TGFBR2* patients compared with *TGFBR1* at the level of the aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta. These findings confirm a more unfavourable aortic disease progression as previously reported in LDS patients with *TGFBR2* mutations.[4-6]

Aortic biophysical properties differed between the LDS genotypes. Previous studies comparing heterogeneous cohorts of Marfan syndrome and/or LDS patients with healthy controls have reported differences in aortic biophysical properties including lower aortic wall distensibility and increased aortic stiffness.[13-15] Our data showed that these differences are applicable even when delineating between LDS genotypes. The differences in aortic distensibility, strain, and stiffness between the mutation types were observed at the level of the

Table 2. Left ventricular structural parameters in 32 paediatric Loeys-Dietz syndrome patients

Left ventricular structural parameters	TGFBR1 (n = 17)	TGFBR2 (n = 15)	*P*
Structural measurements			
LVEDD (cm)	4.32 ± 0.80	4.33 ± 0.78	0.958
LVEDD, PHN *z* score	0.08 ± 0.93	1.12 ± 1.92	0.071
LVPWD (cm)	0.58 ± 0.17	0.65 ± 0.12	0.204
LVPWD, PHN *z* score	−0.26 (−1.36 to 0.62)	0.52 (−0.05 to 1.01)	**0.011**
IVSD (cm)	0.65 ± 0.14	0.63 ± 0.19	0.721
IVSD, PHN *z* score	0.20 ± 0.89	0.29 ± 1	0.806
LVM (g)	87.14 ± 46.76	89.24 ± 53.88	0.453
LVM, PHN *z* score	−5.79 ± 0.03	−5.79 ± 0.03	0.824
LVM indexed to BSA (g/m^2)	63.41 (56.7-72.7)	68.54 (60.9-87.7)	0.278
LVM indexed to height (g/mm^2)	0.56 ± 0.21	0.62 ± 0.28	0.515
Valve function			
Aortic regurgitation	2 (12)	8 (53)	**0.032**
Mitral valve regurgitation	0	2 (13)	0.410
Mitral valve prolapse	0	2 (13)	0.410

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).

Bold values indicate $P < 0.05$.

BSA, body surface area; IVSD, interventricular septum end-diastole; LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; LVPWD, left ventricular posterior wall end-diastole; PHN, Pediatric Heart Network.

sinotubular junction and ascending aorta, but not at the level of the sinuses of Valsalva despite clinically significant increases in PHN *z* scores. This indicates that changes to aortic mechanical properties may precede aortic remodelling, suggesting that aortic biophysical properties may have independent predictive value for aortic disease progression. Indeed, lower aortic root strain and high aortic root stiffness are associated with a higher rate of aortic root dilation and surgical aortic root replacement. These associations are independent of the aortic root *z* score.[16] It is important to note that our conclusions are speculative for 2 reasons. First, the biophysical properties are calculated using the same aortic dimensions and thus are innately correlated. Second, measuring larger and/or effaced aortic structures may lead to increased measurement variability. Longitudinal data are needed to evaluate the clinical applicability and significance of our observations.

Existing evidence suggests that the phenotypic manifestations of LDS in adults extend beyond the confines of the aortic root and sinuses of Valsalva, encompassing the sinotubular junction and ascending aorta as well.[17,18] Our study demonstrates that the persistence of such manifestations extends to paediatric cohorts. This is consistent with previous paediatric surgical case reports.[19,20] In the absence of paediatric-specific directives, the clinical management of paediatric LDS patients currently relies on adult guidelines, which focus predominantly on the surveillance of aortic root and sinus of Valsalva dimensions. Clinical guidelines by the American Heart Association and American College of Cardiology Joint Committee recommend prophylactic surgical interventions at aortic root diameters of ≥4.0 cm or 4.5 cm depending on the presence of other high-risk features.[21] Although the risk for aortic dissection escalates at or beyond these dimensions in LDS, instances of aortic dissection have been documented in patients with aortic root dimensions ranging from 3.9 to 4.0 cm.[22] Data from a single American centre on 11 adult LDS patients who experienced acute type A aortic dissections reported preoperative aortic root measurements ranging from 3.2 to 6.8 cm.[23] Evidently, aortic dissections can occur in a broad range of aortic root diameters, and clinical guidelines for the risk stratification of LDS patients should not be primarily size dependent.

Although *TGFBR1* and *TGFBR2* mutations both impact the intracellular domain of their respective receptors and result in TGFβ oversignalling, nuanced variations in their downstream molecular pathogenesis result in distinct phenotypic presentations.[24] Medial degeneration of the aorta, known as

Table 3. Left ventricular diastolic and systolic parameters in 32 paediatric Loeys-Dietz syndrome patients

Left ventricular functional parameters	TGFBR1 (n = 17)	TGFBR2 (n = 15)	*P*
Diastolic function			
Mitral valve E-velocity (cm/s)	83 (72.6-90.8)	75 (72.0-89.5)	0.850
Mitral valve A-velocity (cm/s)	43.8 ± 7.38	45.2 ± 12.7	0.733
Mitral valve E/A ratio	1.96 ± 0.56	1.97 ± 0.77	0.967
Mitral valve E′-velocity (cm/s)	16.3 ± 3.09	14.9 ± 3.52	0.279
Mitral valve A′-velocity (cm/s)	5.0 (4.2-7.0)	6.5 (5.6-7.3)	0.129
Mitral valve E/E′ ratio	4.81 (4.5-5.8)	5.29 (4.8-5.5)	0.451
Isovolumetric relaxation time (ms)	65.9 ± 15.4	57.9 ± 16.1	0.208
Mitral valve deceleration time (ms)	134 (116-169)	143 (119.2-176.0)	0.905
Mitral valve A-wave time (ms)	106.5 (96.5-148.5)	106 (92.0-139.5)	0.828
Systolic function			
Mitral valve S′-velocity (cm/s)	10.0 (8.0-11.5)	10.5 (8.1-12.1)	0.380
Ejection fraction (%)	66.1 ± 5.41	67.7 ± 4.90	0.362
Shortening fraction (%)	35.1 (32.2-38.5)	36.4 (33.6-39.4)	0.484

Data are presented as mean ± standard deviation or median (interquartile range).

cystic medial necrosis, leads to pathological remodelling of aortic structure and is associated with a higher risk of aortic events.[25] Indeed, pathohistologic analysis of aortic specimens from LDS patients demonstrated that patients with *TGFBR2* mutations had significantly higher grades of cystic medial necrosis than those with *TGFBR1* mutations.[26] Considering these differential genetic mechanisms impacting aortic disease progression in LDS, it is likely that our patients in the *TGFBR1* and *TGFBR2* cohorts present distinct aortic structural arrangements that impact aortic biophysical properties and consequently the rate of dilatation. Our findings underscore the need for genotype-specific clinical management strategies of paediatric patients that extend beyond aortic root dimensions, encompassing a complete evaluation from the root to the ascending aorta and considering the inclusion of aortic biophysical properties. Such a comprehensive approach could be useful in the clinical management of aortopathy populations. Further research is required to determine whether aortic biophysical properties can improve long-term outcomes by accurately predicting and reducing the incidents of aortic events.

Impact of genotype on left ventricle morphologic and functional parameters

In the adult LDS population, there have been reports of impaired systolic function, cardiomyopathy, and/or heart failure.[27,28] There is ongoing debate on whether primary cardiomyopathy exists in LDS patients, as cardiac remodelling can be attributed secondary to aortic dilation and/or valvular disease.[29] Cardiac magnetic resonance imaging studies in LDS patients found increased extracellular volume, suggesting increased diffuse myocardial fibrosis in both paediatric and adult patients.[27,30]

Despite more frequent aortic regurgitation in patients with *TGFBR2* compared with those with *TGFBR1* mutations, we report no significant differences in left ventricular size and wall thickness between the groups. Furthermore, there were no echocardiographic differences in systolic and diastolic function between the groups. The occurrence of mitral valve prolapse was also similar between the groups. Further longitudinal studies will need to determine the impact of the 2 different genotypes on myocardial phenotype.

Limitations

The retrospective, single-centre design of the present study combined with the small sample size of the mutation groups is an inherent limitation. In addition, measuring larger and/or effaced aortic structures may lead to increased measurement variability and/or altered measurement accuracy. Finally, patients in this study were diagnosed and treated over a span of 14 years (2006-2020), during which standards of care and echocardiographic techniques were (and still are) evolving.

Conclusions

Our study demonstrates that during childhood, LDS patients with *TGFBR2* mutations exhibit a more severe aortic phenotype than those with *TGFBR1* mutations. This is evidenced by increased likelihood of aortic surgery, increased use of pharmacologic therapy, larger aortic dimensions, and differences in aortic biophysical properties. We did not observe differences in left ventricular morphology or function between the groups.

These findings underscore the importance of tailored LDS clinical management strategies based on genotypes, especially for patients with *TGFBR2*. Future research with larger paediatric cohorts and longitudinal follow-up is needed to better understand the role of aortic biophysical properties in the cardiovascular disease progression in paediatric LDS patients.

Ethics Statement

This study was approved by the institutional research ethics board (approval number: 1000071940).

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective study using de-identified data with a waiver of consent approved by the Research Ethics Board (REB).

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Pediatric and Congenital Heart Disease* at https://www.cjcpc.ca// and at https://doi.org/10.1016/j.cjcpc.2023.12.003