Different ascending aortic phenotypes with similar mutations in 2 patients with Loeys-Dietz syndrome type 2

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INTRODUCTION

Loeys-Dietz syndrome (LDS) is an autosomal-dominant connective tissue disorder due to pathogenic variants that affect the transforming growth factor β receptors I and II, SMAD 2 and 3 and the transforming growth factors β I and II. Its clinical manifestations include arterial aneurysms and tortuosity with skeletal manifestations such as cleft palate or pectus excavatum. Intrafamilial variations in phenotypes and their severity are common [1]. The independent factor for increased mortality is an aortic dissection that can lead to sudden aortic rupture [2]. Frequent monitoring of aneurysm progression and adequate timing of surgery to prevent adverse outcomes are mandatory. Valve-sparing aortic root surgery is the treatment of choice in the young affected cohort [3]. This case series, we present 2 infants with confirmed Loeys-Dietz syndrome type 2. The missense mutations in exon 7 of the TGFBR2 gene are only 5 codons apart (c.1597T>C and c.1582C>G). Phenotypically, the aneurysms of the ascending aorta were restricted to different segments of the aorta: the suprajunctional segment in 1 patient and the aortic root in another. These cases highlight the complexity of signaling pathways and gene expression in the pathogenesis of aortic aneurysms.

Keywords: Great vessel anomaly • Aortic Surgery • Loeys-Dietz syndrome

Abstract

Our goal was to present 2 infants with confirmed Loeys-Dietz syndrome. The missense mutations in exon 7 of the TGFBR2 gene are only 5 codons apart (c.1597T>C and c.1582C>G). Phenotypically, the aneurysms of the ascending aorta were restricted to different segments of the aorta: the suprajunctional segment in 1 patient and the aortic root in another. These cases highlight the complexity of signaling pathways and gene expression in the pathogenesis of aortic aneurysms.

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INTRODUCTION

Loeys-Dietz syndrome (LDS) is an autosomal-dominant connective tissue disorder due to pathogenic variants that affect the transforming growth factor β receptors I and II, SMAD 2 and 3 and the transforming growth factors β I and II. Its clinical manifestations include arterial aneurysms and tortuosity with skeletal manifestations such as cleft palate or pectus excavatum. Intrafamilial variations in phenotypes and their severity are common [1]. The independent factor for increased mortality is an aortic dissection that can lead to sudden aortic rupture [2]. Frequent monitoring of aneurysm progression and adequate timing of surgery to prevent adverse outcomes are mandatory. Valve-sparing aortic root surgery is the treatment of choice in the young affected cohort [3]. In this case series, we present 2 infants with genetically confirmed Loeys-Dietz syndrome (OMIM# LDS2 610168) due to pathogenic variants in TGFBR2 on chromosome 3p24.1, encoding the transforming growth factor β receptor 2. The identified missense variants affect the TGFBR2 polypeptide at positions p.(Arg528Gly) and p.(Cys533Arg), respectively, lying only 5 codons apart. Phenotypically, the aneurysms of the ascending aorta were restricted to different segments of the aorta: the suprajunctional segment in patient A and the aortic root in patient B (Fig. 1). These cases highlight the complexity of the phenotype due to similar genetic alterations. The ethics committee of the Charité – Universitätsmedizin Berlin approved this investigation (application number: EA2/120/16).

PATIENT A

The first presentation of the female patient in our aortic outpatient department at the age of 22 months was due to a suspected connective tissue disorder. She already had surgically fixed club feet, unstable pes/talipes calcaneus, pectus excavatum (sunken chest), high-arched palate, uvula bifida, tooth malposition, arachnodactyly, scoliosis, positive wrist and thumb sign, joint contraction elbow, hypertelorism, ambylopia, anisometropia and psychomotor delay (physical and speech development disorders). A missense variant in exon 7 of TGFBR2 (NM_003242.6: c.1597T>C (p.Cys533Arg) was identified using Sanger sequencing. Cysteine was exchanged with arginine at position 533; this variant is listed in the Human Gene Mutation Database (CM064332) as a disease mutation. Co-segregation analyses revealed this variant to be absent in the parents; thus we considered it to be a de novo alteration. A highly conserved kinase domain was affected, so the function of the receptor should be modified. The aortic diameters were assessed frequently. From 25 mm (z-score: +5.16) at the time of her first presentation, the diameter of her ascending aorta increased to 39 mm (z-score: +10.1) over a 24-month...
period \[4\]. Additionally, echocardiography showed aortic regurgitation grade II\[2\], a dilated pulmonary trunk and a multisegment mitral valve prolapse with mild regurgitation (grade I\[2\]) (Table 1).

**PATIENT B**

The first presentation of the male patient in our aortic outpatient department at the age of 36 months was due to typical skeletal anomalies that led to the identification of a suspected connective tissue disorder. At the physical examination, pectus excavatum, craniosynostosis, Chiari I malformation with low tonsillar and medulla compression, cleft palate, pes valgus and planus, scoliosis, positive wrist and thumb sign, increased arm range/height ratio, reduced upper segment/lower segment ratio, striae distensae, easy bruising, translucent skin, strabismus divergens, high myopia (-4.5 diopters) and dural ectasia (lumbar) were diagnosed. A missense variant in exon 7 within TGFBR2 (NM_003242.6: c.1582C>G (p.Arg528Gly)) was also detected by Sanger sequencing. Arginine was exchanged with glycine at position 528. ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/) and the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php) do not cite this variant, but other missense alterations affecting arginine528 are listed as pathogenic variants. Unfortunately, genetics testing could

### Table 1: Clinical and imaging parameters of the 2 observed patients

|                        | Patient A | Patient B |
|------------------------|-----------|-----------|
| **Demographics**       |           |           |
| Age, years             | 4         | 5         |
| Sex                    | Female    | Male      |
| Height, cm             | 103       | 107       |
| Weight, kg             | 16.4      | 15.6      |
| **Echocardiography**   |           |           |
| Aortic regurgitation   | 2\[2\]    | 1\[2\]    |
| Mitral regurgitation   | 1\[2\]    | 1\[2\]    |
| Mitral valve prolapse  | Yes       | Yes       |
| Left ventricular ejection fraction | 57\%       | 55\%       |
| Left ventricular end-diastolic diameter | 38        | 44        |
| Bicuspid aortic valve  | Yes       | No        |
| **Aortic dimensions**  |           |           |
| Aortic annulus         | 20        | 23        |
| Bulbus aortae          | 30        | 46        |
| Sinotubular junction   | 38        | 22        |
| Ascending aortae       | 39        | 19        |
| Z-scores               |           |           |
| Aortic annulus         | 4.06      | 5.33      |
| Bulbus aortae          | 5.35      | 9.48      |
| Sinotubular junction   | 8.94      | 3.88      |
| Ascending aortae       | 10.11     | 2.14      |
| **Congenital heart defects** |         |           |
| Persistent foramen ovale | Yes      | Yes      |
| Persistent ductus arteriosus | Yes      | Yes      |
| **Vascular disorders** |           |           |
| Arterial tortuosity of arch vessels | Yes      | Yes      |
| Arterial tortuosity of cranial vessels | No      | No       |
| **Skeletal disorders** |           |           |
| Pectus excavatum       | Yes       | Yes       |
| Upper-to-lower segment ratio < 0.85 or arm span-to-height ratio > 1.05 | Yes | Yes |
| Pes planus             | Yes       | Yes       |
| Scoliosis >20\[\]    | Yes       | Yes       |
| Extension at elbows <170\[\] | Yes | No |
| Dural ectasia          | Yes       | Yes       |
| Facial appearance      |           |           |
| Craniosynostosis       | Yes       | Yes       |
| Hypertelorism           | Yes       | No        |
| High-arched palate     | Yes       | Yes       |
| Uvula bifida/cleft palate | Yes  | Yes      |
| Tooth malposition      | Yes       | No        |
| Arachnodactyly         | Yes       | Yes       |
| Ocular manifestations  |           |           |
| Amblyopia              | Yes       | Yes       |
| Anisometropia          | Yes       | Yes       |
| Physical and speech development disorders | Yes | Yes |
| Exotropia, exophoria   | Yes       | Yes       |

![Figure 1](https://example.com/figure1.png)

**Figure 1**: (A) Family tree of the 2 patients. (B) Preoperative 3-dimensional computed tomography of the suprajunctional ascending aortic aneurysm of patient A. (C) Preoperative 3-dimensional computed tomography of the aortic root aneurysm of patient B.
not be performed on the clinically unaffected parents to prove the de novo status of this variant. The highly conserved kinase domain was also affected. The function of the receptor should be modified. The aortic diameters were assessed frequently. From 39 mm (z-score: +7.86) at the time of his first presentation, the diameter of his sinus of Valsalva increased to 46 mm (z-score: +9.5) over a period of 22 months [4]. Additionally, a persistent ductus arteriosus, sinus arrhythmia and an enlarged heart were seen. The aortic and mitral valves showed mild regurgitation (Table 1).

**FOLLOW-UP**

According to the current recommendations, the 2 young patients in our series underwent valve-sparing aortic root replacement at the ages of 4 and 5 years, respectively. The 2 patients are free from reoperation, adverse neurological events or aortic regurgitation after 8 years (patient A) and 2 years (patient B), respectively.

**DISCUSSION**

We present 2 patients with LDS, whose missense alterations in exon 7 of TGFBR2 lie very close to each other, only 5 codons apart (p.Arg528Gly and p.Cys533Arg). Both alterations of the corresponding protein affect the highly conserved kinase domain. Unfortunately, no skin biopsy was taken from either affected individual, which made it impossible to further investigate changes of TGF-β signaling due to the observed variants in the cultivated fibroblasts. The genetic proximity, however, did not reflect the significant variation of aneurysm location in the ascending aorta. From an embryological point of view, the thoracic aorta is a heterogeneous structure whose segments develop one after the other with a specific set of signaling pathways and genes. The 2 presented cases depict the independence with which their contrary aneurysms are formed despite their similar genotypes. TGFBR2 missense variants leading to LDS alter amino acids in the intracellular domain of the receptor and are predicted to disrupt kinase activity of the receptors and thus likely prevent proper signaling, thereby disrupting the differentiation of the neural crest and the mesenchymal cells into vascular smooth muscle cells (SMC). SMCs from LDS may instead increase TGF-β activity in different parts of the ascending aorta, may be part of future investigations.

The literature contains a relative paucity of information regarding the identification of the genetic and molecular factors that influence the development and differentiation of the aortic root and the ascending aorta. However, a single gene, receptor or signaling pathway does not seem to have a generalized effect on the development of specific segments of the aortic tree. We agree with the authors of previous investigations that, for the precise identification of specific segments of the aortic tree, we need to agree with the authors of previous investigations that, for the precise identification of specific segments of the aortic tree, we need to determine the dependence of different signaling pathways in different parts of the ascending aorta, may be part of future investigations.

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