International Medical Case Reports Journal

Dovepress
Taylor & Francis Group

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CASE REPORT

A Novel Mutation of *TGFB2* Gene Responsible of Loeys-Dietz 4 Syndrome

Erika Di Zazzo[1,2], Autilia Tommasina Buonagura[3,4], Veronica Palladino[5], Michele Pinelli[3,4], Silvio Garofalo[1,2]

[1]Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy; [2]Unit of Laboratory Medicine, Cardarelli Hospital, Campobasso, Italy; [3]Department of Molecular Medicine and Medical Biotechnology, University of Naples "Federico II", Naples, Italy; [4]Unit of Medical Genetics, University Hospital Federico II, Naples, Italy; [5]Unit of Transfusion Medicine, Cardarelli Hospital, Campobasso, Italy

Correspondence: Erika Di Zazzo, Email erika.dizazzo@unimol.it

Background: Loeys-Dietz syndrome (LDS) is a connective tissue disorder that is characterized by vascular and skeletal abnormalities. LDS, classified into six subtypes (LDS1–6), is caused by mutations in the genes encoding proteins involved in the transforming growth factor-beta (TGF-β) signaling pathway. LDS4 is the mild form of the LDS spectrum, considering that aneurysms are observed in the fourth decade and the disease progression is slower than the other forms.

Case Presentation: We reported the case of a novel *TGFB2* variant c.280_298del p.(Ser94Profs*7), NM_001135599.2 responsible of LDS4 in a family with sudden death and vascular lesions.

Conclusion: The pedigree analysis highlighted the high clinical variability of LDS signs even within the same family. In addition, *TGFB2* mutations which do not always lead to vascular phenotype and skeletal signs can be prevalent. We emphasize the relevance of genetic counseling and molecular analysis to identify genetic diseases subtending sudden deaths and to distinguishing heritable connective tissue disorders with phenotypic overlap. Genetic testing can be used to guide clinical management and provide valuable prognostic information.

Keywords: Loeys-Dietz syndrome, TGF-β, next generation sequencing

Background

Heritable connective tissue disorders that affect the connective tissue of various organ systems, including heart, blood vessels, bones, eyes, skin, joints, and lungs, are characterized by alterations in the extracellular matrix (ECM). The ECM provides structure and support to the surrounding cells and is endowed with a regulatory role by sequestering cytokines, such as transforming growth factor-beta (TGF-β).[1] Heritable connective tissue disorders such as Loeys-Dietz syndrome (LDS) and Marfan syndrome (MFS) show similar cardiovascular, skeletal, and cutaneous alterations. Thus, the clinical diagnosis is critical and molecular analyses are required. Both LDS and MFS are involved in TGF-β signaling. The *FBN1* gene, mutated in MFS, encodes for Fibrillin-1 that binds to the latent TGF-β complex and regulates the release of active molecules into the extracellular environment.[2,3]

LDS is an autosomal dominant heritable connective tissue disorder whose clinical triad includes hypertelorism, bifid uvula, cleft palate, and aortic aneurysms with vessel tortuosity.[4] LDS is caused by pathogenic variants of one of the several genes that encode proteins involved in the TGF-β signaling pathway. Accordingly, LDS is classified into six subtypes based on mutations of the following genes: *TGFBR1* (LDS1), *TGFBR2* (LDS2), *SMAD3* (LDS3), *TGFB2* (LDS4), *TGFB3* (LDS5), and *SMAD2* (LDS6).[5]

LDS subtypes induce cardiovascular complications, including arterial tortuosity, aortic aneurysms and dissections, mitral valve prolapse, and arthritis.[5,6] Several pieces of evidence suggest that TGF-β signaling plays a major role in the pathogenesis of aneurysms.[7–10] Hence, several loss of function mutations of the TGF-β pathway genes increasing TGF-β signaling in LDS aortic tissues have been described. Alteration of TGF-β signaling modifies the ECM in different manners in different organs, thus resulting in a variable clinical expressivity of LDS in individuals with the same genetic

Received: 12 June 2025
Accepted: 17 September 2025
Published: 25 October 2025

condition, even within the same family. Thus, the severity and specific features of LDS vary significantly between studies.

The LDS4, caused by mutations in the *TGFB2* gene encoding for the TGF-β2 ligand, shows milder symptoms among the LDS types, since aneurysms are usually observed in the fourth decade and the disease progression is slower than the other forms. The LDS4 is characterized by aneurysms, dissections, and tortuosity throughout the arterial tree, in association with mitral valve disease, mild craniofacial features, and skeletal and cutaneous alterations. LDS4 is the most similar to MFS. Therefore, a high rate of similarities in the musculoskeletal alterations affecting MFS and LDS4 patients has been underlined, as pes planus. In addition, both LDS4 and MFS patients have proteoglycan and collagen deposition and elastin fragmentation in the aortic tissue. However, in LDS4, unlike MFS, aortic aneurysm involves mainly, but not exclusively, the sinus of Valsalva and shows a later onset.[9,11,12]

In this report we describe a new LDS4 family with a 12 year-old proband without thoracic aortic aneurysms and other major vascular complications, with pes planus caused by a novel mutation in *TGFB2* gene.

Case Presentation

We describe a LDS4 family with a novel *TGFB2* mutation in three members: the proband, one of his father's asymptomatic cousins, and one of her children.

A 12-year-old Italian proband came to our attention not for cardiovascular complaints, but mainly for pes planus.

Genetic counselling conducted on November 27, 2021, revealed a notable family history of aneurysms on the paternal side of his family. Specifically, his father (III.3) died suddenly at the age of 44 without a post-mortem diagnosis, his paternal grandmother (II.2) died following aortic aneurysm rupture at 69 years of age, and the sister of his paternal grandmother (II.1) died of dilated cardiomyopathy at 69 years of age. Additionally, his paternal aunt (III.5) had an aortic aneurysm and underwent genetic counselling, followed by Next Generation Sequencing (NGS) analysis using the Illumina MiSeq platform (Illumina Inc, San Diego, CA) and Agilent SureSelect kit (Agilent Technologies, Los Angeles, CA). The NGS analysis included the following genes involved in connective tissue disorders that could be linked to aneurysms: *ACTA2*, *BGN*, *COL3A1*, *FBN1*, *FOXE3*, *LOX*, *MAT2A*, *MFAP5*, *MYH11*, *MYLK*, *NOTCH1*, *PRKG1*, *ROBO4*, *SLC2A10*, *SMAD2*, *SMAD3*, *SMAD6*, *SKI*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2*. The analysis was performed at the Medical Genetics Laboratory of the University of Padua, Italy. This analysis identified a heterozygous 280–298nt deletion in the *TGFB2* gene. The *TGFB2* variant c.280_298del p. (Ser94Profs*7), NM_001135599.2, was predicted as a likely pathogenic variant according to the American College of Medical Genetics (ACMG) criteria (PVS1, PM2). This deletion led to a shift in the open reading frame, resulting in a Ser94Pro substitution and a premature translation termination seven amino acids after Pro94. The truncated TGFB2 protein lacked biological activity. A plausible diagnosis of LDS4 was conducted. Based on this evidence, we investigated the familial variant in the proband (IV.3), the paternal uncle (III.4), and two children (III.1 and III.2) of a sister of the maternal grandmother, who died from complications of dilated cardiomyopathy (II.1). One of them (III.1), who is asymptomatic, was found to be a carrier of the variant. A consent form signed by the mother after genetic counselling and before genetic testing was collected. Consequently, genetic testing was extended to her two children. The variant was identified in one of them (IV.2), who presents with joint laxity and bilateral pes planovalgus (Figure 1). Since a late-onset aneurysmatic vasculopathy remains possible, a periodical follow-up with vascular imaging was scheduled for the carriers that are participating to a dedicated surveillance program. In particular, proband, monitored by a pediatric vascular surgeon initiated a prophylactic antihypertensive regimen with sartans. The patient followed a healthy lifestyle and maintained a balanced diet to avoid obesity and other risk factors such as major cardiovascular complications.

Discussion and Conclusions

LDS4 is a connective tissue disorder with autosomal dominant transmission that depends on *TGFB2* mutations, which result in deregulation of the TGF-β signaling pathway. In addition to skeletal alterations, LDS4 shows vascular abnormalities, including arterial tortuosity and aneurysms throughout the arterial tree such as thoracic aortic and cerebral aneurysms.[4] Although the precise and relative contribution of *TGFB2* mutations in aortic aneurysm is underscored and controversial,[9] we identified a family with autosomal dominant transmission of a *TGFB2* mutation, pes planovalgus, and

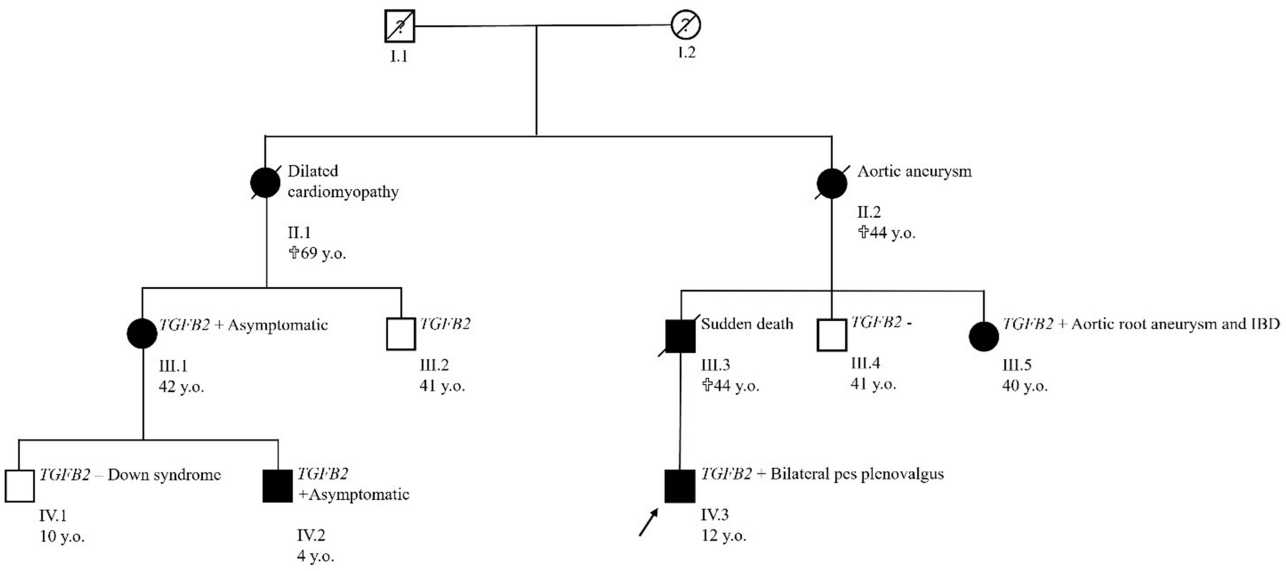

Figure 1 Pedigree of the LDS4 family. The arrow indicates the proband. Squares represent male individuals; circles represent female individuals; barred squares and circles indicate died males and females, respectively. Filled squares and circles indicate carriers of the familial *TGFB2* variant c.280_298del p.(Ser94Profs*7); empty squares indicate individuals who tested negative for the genetic variant. Individuals II.1, II.2, and III.3 are obligate carriers of the *TGFB2* variant. NGS marks the patients who underwent gene-panel sequencing. The question mark indicates a patient with unknown diseases status (I.1). †Indicates the age of death of the patients. For living patients, the age at the time of the visit is reported below the symbol.

an aortic aneurysm phenotype with variable clinical expression. The variant identified, c.280_298del in *TGFB2*, is a deletion, whereas most variants described in *TGFB2* are missense or nonsense mutations.

This evidence confirms that proactive consideration of LDS in patients presenting with connective tissue disorders is essential. Identifying causative mutations in LDS not only confirms the diagnosis but also prompts surveillance for vascular abnormalities, particularly aortic alterations, which significantly contribute to morbidity and mortality. This surveillance is particularly relevant for LDS4, where baseline manifestations may be milder than those of LDS 1 and 2, but still carry a risk of life-threatening aortic dissections or ruptures. The identification of mutations, such as those in *TGFB2* gene associated with LDS4, facilitates regular vascular imaging and prophylactic management, including antihypertensive therapies that may slow disease progression and prevent acute events.[13,14]

Our findings describe a novel *TGFB2* gene mutation responsible for the LDS4 variant. Moreover, our observations suggest that heterozygous mutations in the gene encoding for TGF-β2 are sufficient to cause a syndromic presentation of aortic aneurysm. The reported pedigree also highlights the clinical variability of LDS even within the same family. Indeed, the awareness of the variable expressivity of that conditions led the clinician to suspect an underlying autosomal dominant disease – connecting the proband's mild arthropathy (pes planus) to the severe family history of sudden death and aneurysm. Here, we emphasize the relevance of genetic counseling and testing in patients of all ages with sparse signs of MFS; LDS and related connective tissue disorders, even though major cardiovascular events are absent, as with our proband. Genetic testing plays a crucial role in clinical management and offers valuable prognostic insights. In addition, molecular analysis allows the early identification of patients and relatives at risk of major cardiovascular complications that are subjected to further screening for silent vasculopathies that may require drug treatment or elective intervention to avoid significant complications. Moreover, we highlight the strong need to develop gene panels largely employed in genetic laboratories for the screening of multiple candidate genes by NGS techniques, taking advantage of this time and cost-efficient technique. In conclusion, LDS and MFS show several phenotypic overlaps, resulting in a difficult clinical diagnosis. However, the associated cardiovascular complications show different degrees of severity, and some of them have a high mortality rate, thus watchful clinical surveillance is highly recommended. LDS patients, indeed, can have aneurysms anywhere throughout the vascular tree and, although LDS coronary artery aneurysm is rare, it can occur. Thus, timely genetic diagnosis is crucial for the identification of LDS.

Abbreviations

ACMG, American College of Medical Genetics; ECM, Extracellular matrix; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; NGS, Next Generation Sequencing; TGF-β, transforming growth factor-beta.

Data Sharing Statement

All data and materials are available upon request to the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the appropriate Ethics Committee of A.S.R.e.M. (Azienda Sanitaria Regionale del Molise) and registered as protocol n. 68 of 5/11/2015 in the Trail Register. According to institutional policies, this approval covers the entire research process, including the preparation and publication of case reports. Therefore, no additional institutional approval was required for publication.

Consent for Publication

Written informed consent for publication of this manuscript has been obtained by all LDS4 family members. A consent for publication has been obtained from the patient's legal guardian. A copy of the written consent is available for review by the Editor-in-Chief of this journal. A consent form signed by the mother after genetic counseling and before genetic testing was collected.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no competing interests in this work.

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