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CASE REPORT

A Heterozygous Variant of *TGFB3* in a Patient With an Atypical Presentation of Loeys–Dietz Syndrome: A Case Report

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Abstract
Loeys–Dietz syndrome (LDS) 5 is characterized by aortic aneurysms, hypertelorism, and cleft palate/bifid uvula. We describe a woman with a transforming growth factor beta3 (TGFβ3) mutation who displays a *forme fruste* phenotype of LDS5. A 43-year-old woman with joint pain and hypermobile joints underwent evaluation for hypermobile Ehlers–Danlos syndrome. Her features included pes planus, treated high-arched palate, and increased joint mobility. Genetic analysis identified a pathogenic TGFβ3 variant (c.427A>T, p.Arg143*), clarifying the diagnosis of LDS5. Comparing our patient with others with TGFB3 mutations illustrated the diversity of LDS5 features, often a milder *forme fruste* form, which warrants more investigation due to insufficient characterization.

Background
Loeys–Dietz syndrome (LDS) is an autosomal-dominant connective tissue disorder with vascular, skeletal, and craniofacial features similar to Marfan syndrome and Ehlers–Danlos syndrome (EDS) (1). The clinical triad includes hypertelorism, bifid uvula/cleft palate, and aortic aneurysm (2). Mutations of genes comprising the transforming growth factor beta (TGFβ) signaling pathway are implicated in LDS (1).

LDS5 (Rienhoff syndrome), caused by *TGFβ3* mutations located on chromosome 14q24.3, has the syndromic presentation of early-onset aortic aneurysms prone to dissections and rupture. Patients may have features resembling other LDS types such as spinal instability and craniofacial abnormalities (3, 4). However, clinical features vary among patients.

Objective
We describe a woman found to have a previously described heterozygous nonsense variant in *TGFB3* during an evaluation for joint hypermobility and back pain. She did not display the diagnostic features of LDS5 but rather a mild, *forme fruste* phenotype of LDS5, which is poorly characterized.

Case Report
A 43-year-old woman of Northern European ancestry, born to nonconsanguineous parents, was referred to rheumatology for persistent back and bilateral hip pain. Despite multiple therapy sessions and hip bracing, her discomfort persisted. She had a spine fusion at age 12 years for a hemivertebrae that led to cervical scoliosis. Recent imaging showed thoracolumbar spinal scoliosis (Figure 1A and B). Additional scans revealed sacroiliac joint degeneration without inflammatory arthritis (Figure 1C and D). The rheumatologist noted her hypermobile joints and referred her to genetics for a connective tissue disorder evaluation.

When seen by the geneticist, the patient did not report a history of joint dislocation, pectus excavatum, wound dehiscence, hip dislocation, club feet, or heart murmurs. At birth, she

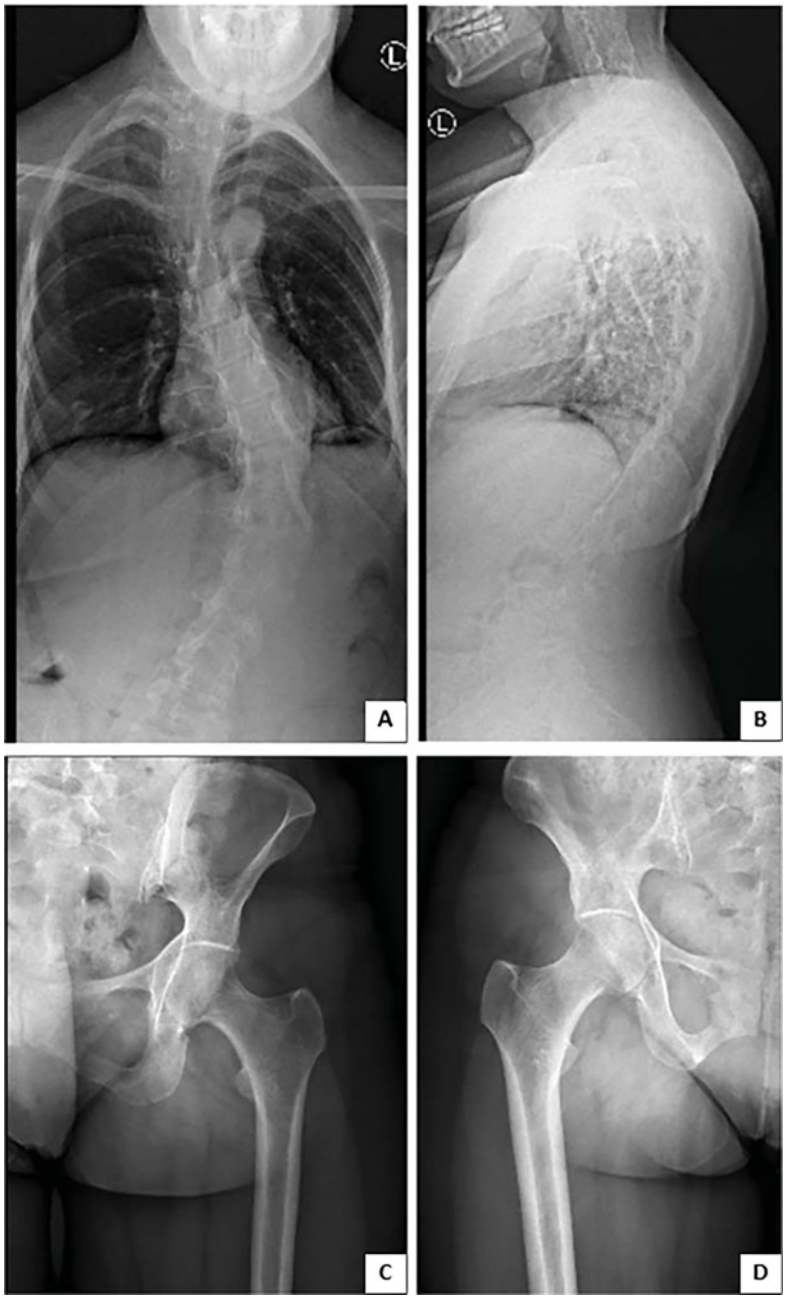

Figure 1. **Radiographic findings. (A–B) 2020 posteroanterior and lateral x-rays, respectively, demonstrating left convex curvature of the thoracolumbar spine with Cobb angle of 53 degrees. (C–D) 2021 left hip and right hip x-rays, respectively, demonstrating sacroiliac joint and pubic symphysis degenerative changes and bilateral mild femoral head–neck junction osteophytosis without significant joint space loss. Right posterior iliac bone has deformity related to bone graft harvest for spinal fusion.**

was in the ninth percentile for weight, 58th percentile for length, and fourth percentile for head circumference. Developmentally appropriate milestones were met, but hospitalization occurred at age 2 years due to failure to thrive. As a child, Marfan syndrome criteria were not met. She has *pes planus*, an untreated umbilical hernia, and moderate myopia (right eye –2.25, left eye –5.25). A benign uvular growth was removed with her wisdom teeth. Palate expanders with orthodonture treated high and arched palate with dental crowding. Due to enlarged sinuses, a tooth became embedded in her palate and was guided down. In addition, her sinuses frequently ache, and she self-soothes through teeth grinding. At 42 years, cataract repair of the right eye was completed, and she was diagnosed with keratoconus. Despite 2 uncomplicated pregnancies, a septate uterus was identified, leading to a hysterectomy at 42 years due to ablation complications and excessive bleeding.

Findings of a physical examination revealed an arm span-to-height ratio of 1.07, high-arched palate with crowding, and left corneal clouding. She had an increased range of motion but normal strength in the elbows, hips, and knees and decreased motion with surgical scarring in the lower

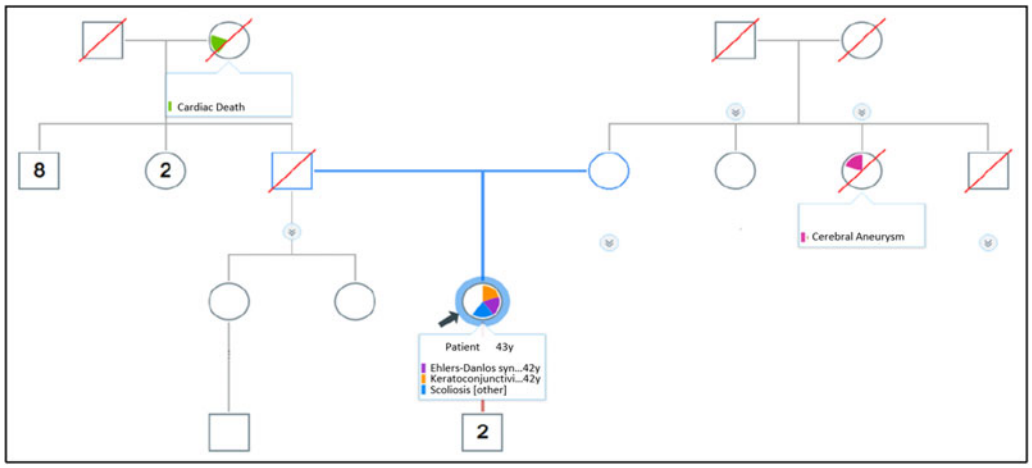

Figure 2. **Four-generation pedigree. The *arrow* represents the proband. *Circles* represent female relatives and squares represent male relatives. A *red diagonal slash* indicates a deceased family member. A pertinent positive in this patient's family genetic history is a maternal aunt with a cerebral aneurysm.**

back. The patient's skin was doughy, with palpable bilateral piezogenic papules. Other physical examination findings were normal.

An echocardiogram at age 42 years revealed normal aortic measurements and a tricuspid aortic valve. Computed tomography of the brain at age 30 years was likewise normal. Magnetic resonance angiography scans at age 43 years of the neck, brain, chest, and abdomen were all unremarkable, with no evidence of aneurysms.

A 4-generation pedigree showed a maternal aunt with a history of a hemorrhagic stroke from a cerebral aneurysm but no family history of aortic aneurysms, dissections, or other presentations of connective tissue disorders (Figure 2). The patient was evaluated using the 2017 diagnostic criteria for hypermobile EDS (5). She met criteria 1 and 2 with a Beighton score of 8 of 9 and 6 of 12 objective Criterion 2A but did not satisfy criterion 3. The presence of unique features not normally appreciated in patients with hypermobile EDS, including a septate uterus and severe scoliosis, triggered molecular genetic evaluation. Sequence analysis and deletion/duplication testing of 92 connective-tissue genes revealed a pathogenic variant, c.427A>T (p.Arg143*), in the *TGFB3* gene, clarifying LDS5 as the diagnosis.

A referral to a center with expertise in LDS was made, with the expectation of close vascular monitoring and aggressive blood pressure control. She was encouraged to follow up with ophthalmology. No symptoms suggesting inflammatory bowel disease or severe allergies were identified. Supportive, adjunctive pain control options also were discussed.

Discussion

LDS is a newly identified disease, and the features that characterize the condition, therapeutic management, and outcome are all still being explored. There are 5 subtypes of LDS, defined by the presence of pathogenic variants in one of the genes of the TGFβ signaling pathway.

As described by Rienhoff and colleagues (6), LDS5 is the latest subtype. The subtypes represent a spectrum of severity, with subtype one being the most severe (7). After an extensive literature search, few studies report patients with LDS5. The patient's pathogenic variant was previously discovered by Ziganshin and colleagues in a 58-year-old man (8) with an aortic root aneurysm and trileaflet aortic valve. Our patient is younger with a trileaflet aortic valve and recent unremarkable vascular imaging.

TGFB3 mutations display reduced penetrance with variable expressivity among families and unrelated probands (9–12). In fact, most patients manifest with *forme fruste* phenotypes of LDS5. Many patients had 2 or fewer features of the clinical triad, with varying combinations. Of 68 reported patients, only 6 had all 3 triad features: Marsili (patient 22), Matyas, and Bertoli–Avella (patients 2-III:7, 4-II:2, 5-II:1, 10-III:2). In LDS, *forme fruste* is not very well characterized; however, it could refer to a milder variant with fewer features or that the progression of the syndrome occurs more slowly with late onset of symptoms.

In general, 2 clinical triad features, hypertelorism and bifid uvula/cleft palate, were observed in 40% of patients. Arachnodactyly, *pes planus*, joint laxity, scoliosis, and dental crowding are observed frequently in LDS5 (Table 1) (3, 4, 6, 8, 9, 11–13).

The presentation of aortic aneurysms, the third component of the clinical triad, varies among patients. Aortic dilation was seen in 42%, aneurysms in 16%, and dissections in 12% (Table 1) (3, 4, 6, 8, 9, 11–13). Reports of patients with LDS5 without cardiac or vascular involvement are enriched for children (Table 2) (3, 4, 6, 8, 9, 11–13). Our patient, at 43 years, shows no vascular changes. It is unclear whether our current estimates are biased by enrichment for cohorts of patients with aortic dilation, or whether children in other studies are too young to have developed cardiac involvement. This patient might experience future cardiac involvement, similar to another patient with the same *TGFB3* gene variant (8).

Table 1. ***TGFB3*** **Phenotype Frequency in Reported Patients (*n* = 69)***

Feature	Frequency of feature, %
Aortic dilation	42
Aneurysm	16
Dissection	12
Dental crowding	13
Bifid uvula	39
Cleft palate	13
Hypertelorism	39
Micrognathia/retrognathia	30
Myopia	20
Tall stature, overgrowth, marfanoid habitus	51
Scoliosis	27.5
Pectus carinatum/excavatum	38
Pes planus	48
Arachnodactyly	54
Decreased muscle mass/muscular hypotonia	21
Reduced subcutaneous fat	16
Hernia	22
Joint laxity	48

*Features in bold represent the clinical triad.

Management for patients with LDS includes baseline vascular imaging with head-to-pelvis magnetic resonance angiography or computed tomography angiography and echocardiogram every 1 to 2 years (1). Strict control of hypertension and exercise are also recommended to reduce arterial stress (1). Whether to modify such intensive monitoring may warrant further exploration, especially given the variable cardiac involvement seen in patients with LDS5.

When evaluating a patient for hypermobility, referral to genetics and the use of molecular sequencing help to clarify the diagnosis in people with unique and atypical symptoms. The comparison of our patient with other individuals with *TGFB3* mutations illustrates that LDS5 can manifest with various clinical features, with *forme fruste* phenotypes being more common than a true LDS5 syndromic presentation. This highlights the value of more investigations to define the wide-range of phenotypes seen with LDS5 and further advance patient management in clinical practice.

Table 2. **Frequency of Cardiac and Vascular Involvement Categorized by Age of** ***TGFB3*** **Mutation Report**

Age at Report, y	Frequency of Dilation (%)	Frequency of Aneurysm (%)	Frequency of Dissection (%)
0–10	1/11 (9)	1/11 (9)	0/11 (0)
11–20	4/9 (44)	0/9 (0)	0/9 (0)
21–30	6/10 (60)	0/10 (0)	0/10 (0)
31–40	2/6 (33)	2/6 (33)	2/6 (33)
41–50	5/14 (36)	4/14 (29)	3/14 (21)
>50	11/19 (58)	4/18 (22)	3/18 (17)

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