

# Novel Association of a Familial *TGFBR1* Mutation in Loeys-Dietz Syndrome with Concomitant Hematologic Malignancy

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Concomitant Loeys-Dietz syndrome (LDS) and hematologic malignancies are exceptionally rare. This is the first report of a patient operated on for aortic root dilation who had been previously diagnosed with LDS and B-cell-lymphoma. After completion of chemotherapy and complete remission, an elective valve-sparing aortic root replacement (using the David-V method) was performed. Due to the positive family history, pre-operative genetic counseling was conducted, and revealed LDS with a *TGFBR1* (transforming growth factor beta receptor type I) mutation in 6 probands of the family, albeit in 1 of them posthumously. This missense mutation has been previously described in relation to aortic dissection, but a causative relationship to malignancy has so far neither been proposed nor proven.

**Key words:** 1. Loeys-Dietz syndrome  
2. B-cell lymphoma  
3. Aortic aneurysm, thoracic

## Case report

A 54-year-old man was referred to our clinic to undergo elective surgery for an aortic root dilation measuring 54 mm in diameter (Fig. 1A). Routine echocardiography had been performed as a screening examination due to newly diagnosed sleep apnea/hypopnea syndrome 6 months previously and revealed aortic root dilation with a concomitant mild aortic regurgitation. The diagnosis was confirmed by means of a subsequent aortic computed tomography (CT) scan. The otherwise asymptomatic patient revealed a positive familial history of 2 female second-degree

cousins. Both cousins had been previously diagnosed with Loeys-Dietz syndrome (LDS) with a heterozygous missense mutation, c.759G>A, p.(Met253Ile), in exon 4 of the transforming growth factor beta receptor type I (*TGFBR1*) gene. Unfortunately, the first cousin was diagnosed only postmortem after passing away from a ruptured aortic root aneurysm at the age of 30, just hours after giving birth to triplets. The other cousin (sister of the deceased) underwent genetic counseling, which revealed exactly the same mutation as well as clinical signs of arachnodactyly, dolichocephaly, scoliosis, and hypermobility, thus establishing the diagnosis of LDS. Furthermore, the

Received: March 12, 2019, Revised: August 6, 2019, Accepted: August 28, 2019, Published online: October 5, 2019

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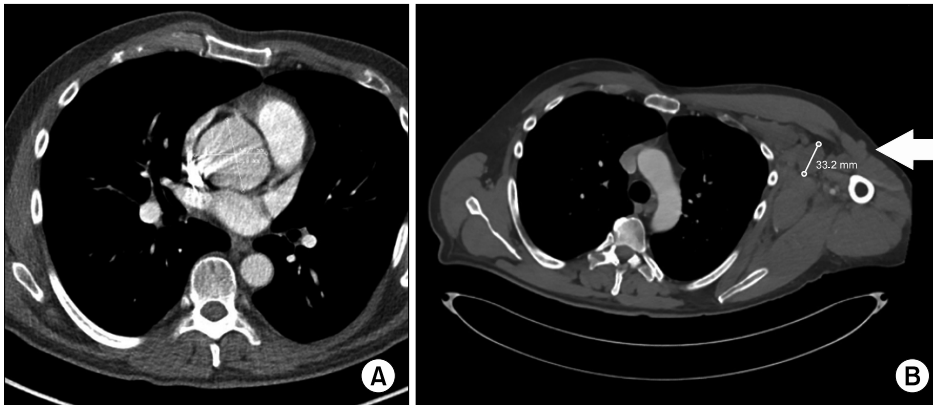


Fig. 1. Preoperative multi-slice computed tomographic scan of the chest showing: (A) the dilated aortic root and (B) pronounced left-axillary lymphadenopathy with conglomerates of lymph nodes measuring up to 33 mm (white arrow).

triplets of the deceased sister were subsequently screened and 2 of them were detected to have the same missense mutation and various concomitant clinical manifestations, ranging from general hypermobility, hypermobile fingers, and arachnodactyly to mild cerebral palsy in 1 of them. Targeted genetic counseling of our patient also revealed the above-mentioned mutation in the *TGFBR1* gene, as well as mild scoliosis, dolichocephaly, and arachnodactyly. Therefore, LDS type 1 was diagnosed. Moreover, one of the patient's offspring (a 25-year-old son) also tested positive for the same mutation. Noteworthy, all probands were negative for *FBN1* gene mutations.

Prior to the writing of this case report, the patient was verbally informed and he declared his willingness for his case to be published.

While on the waiting list for elective surgery of the aortic root, the patient presented to the emergency unit of our hospital with an unclear swelling of the left axilla and left arm. Consecutive CT imaging of the chest revealed a pronounced left axillar and infraclavicular lymphadenopathy, with conglomerates of lymph nodes measuring up to 33 mm (Fig. 1B). Lymph node biopsy revealed diffuse large-cell B-cell lymphoma in stage IIA (according to the Ann Arbor staging classification, aaIPI [low risk]). A pre-phase treatment with vincristine/prednisolone and 1 course of the R-CHOP protocol (rituximab, doxorubicin, mesna, cyclophosphamide, vincristine, and pegfilgrastim) were initiated. After receiving a total of 6 courses of the R-CHOP protocol within 5 months, complete clinical and imaging remission was established.

Two months after completing the R-CHOP protocol, an elective aortic root operation was performed, us-

ing a standard median sternotomy approach. Inspection of the aortic root showed symmetrical root dilation combined with a significant thinning of the aortic wall tissue. The aortic valve consisted of 3 cusps without signs of calcific degeneration or any other structural deterioration. Valve-sparing aortic root replacement (using the David-V method) was conducted with subsequent reimplantation of both coronary ostia. Intraoperative transesophageal echocardiography showed a competent aortic valve. The entire postoperative course was uneventful and the patient was discharged on postoperative day 9.

The postoperative management of the patient included  $\beta$ -blockers and an angiotensin-receptor antagonist (losartan). The latter category of medications is beneficial due to their effects on the TGF- $\beta$  signaling cascade. Moreover, exercise restrictions to reduce stress on the aortic and arterial tissue included avoidance of competitive sports and isometric exercises.

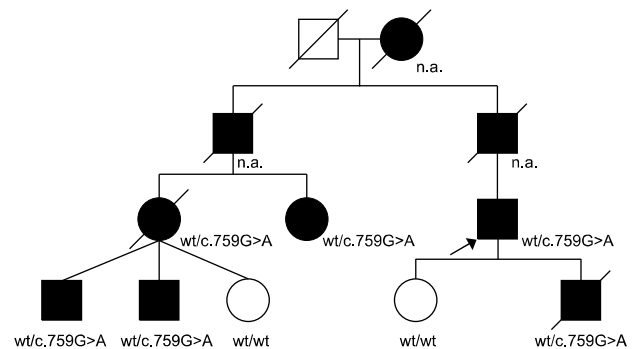
## Discussion

Since its first description, LDS has been the subject of intense research due to its deleterious cardiovascular manifestations, such as aortic dissection and cerebral hemorrhage [1,2]. It may present with diverse craniofacial, skeletal, cardiovascular, and cutaneous clinical features [1]. The majority of LDS patients die of aortic dissection and cerebral hemorrhage, at a very early mean age of 26 years [1]. However, the survival of affected individuals can be improved by early detection, surveillance, and early treatment [3]. Since LDS represents a rather new genotypic and phenotypic entity, the spectrum of concomitant multisystemic manifestations is still a

topic of research. Furthermore, to date, little is known about potential associations of LDS with malignancies.

Transforming growth factor-beta receptor I and II (*TGFBR1* and *TGFBR2*) mutations were the first genetic abnormalities diagnosed in LDS, which were later expanded to include other genes, such as *SMAD3* and *TGFB2*, which were also found to cause LDS [3]. However, significant phenotypic variability within and between individuals affected 4 LDS have been reported [3]. Due to the multisystemic manifestations of LDS, along with its aggressive clinical course and the need for intense life-long surveillance, an interdisciplinary team approach is strongly recommended in the care of these patients. Moreover, aortic dimensions alone are not a good predictor of adverse aortic events in LDS patients, as aortic dissection has been reported to occur in aortas with a diameter of less than 4.0 cm [1]. This is quite different from patients presenting with Marfan syndrome, in whom aortic risk increases significantly as aortic root dimensions exceed 5.0 cm. Surgical correction by means of valve-sparing root surgery is a very reasonable treatment option for LDS patients, which distinguishes LDS patients from those presenting with vascular Ehlers-Danlos syndrome, who are prone to fatal perioperative complications [4]. Although there are many overlapping features between patients with Marfan syndrome and those with LDS, patients with LDS most often present with cardiovascular features first, while this is not the case for Marfan syndrome.

The concomitant occurrence of LDS and malignancy is a very rare manifestation, and no systematic data exist regarding such an association. Reports of concomitant LDS and hematologic malignancies are exceptionally rare, which furthermore hinders the possibility of establishing a causative relationship between both phenomena. To the best of our knowledge, this is the first report of a clinically apparent association between LDS and B-cell lymphoma. Furthermore, this particular mutation has been previously found in a family with several individuals affected by aortic dissection [5], but the possibility of a causative relationship with malignancies has not yet been established. Although the life-long risk of malignancy in LDS patients has not been well established, TGF- $\beta$  signaling has been proposed to play a role in the initial stage of oncogenesis, as well as in the lat-



**Fig. 2.** Pedigree of a family with Loey-Dietz syndrome associated with c.759G>A p.(Met253Ile) in the *TGFBR1* gene. The index patient is indicated by an arrow. n.a., no DNA available; Wt, wild type (no mutation detected); *TGFBR1*, transforming growth factor beta receptor type I.

er stages, by promoting tumor progression and metastasis formation [6]. Our patient was diagnosed with a heterozygous missense mutation, c.759G>A, p.(Met253Ile) in exon 4 of the *TGFBR1* gene. This sequence alteration in exon 4 (from G to A at codon 759) resulted in the amino acid methionine being replaced with isoleucine (i.e., p.(Met253Ile)). Consequently, a highly conserved hydrophobic amino acid was replaced by one with similar physical and chemical properties. This, in turn, may have contributed to destabilization of the protein structure, with potential impairment of *TGFBR1* function that would interfere with the TGF- $\beta$  pathway. Hematologic malignancies, especially B-cell lymphoma, have received relatively little attention regarding TGF- $\beta$  signaling. It was reported that B-cell lymphoma cell lines displayed less sensitivity to TGF- $\beta$  than primary B cells. This has important implications for the development of B-cell lymphoma, as it indicates a loss of sensitivity towards the growth-inhibitory effects of TGF- $\beta$  [7]. Furthermore, a meta-analysis found that certain polymorphisms of *TGFBR1* were associated with an increased risk of carcinogenesis [8]. To what extent *TGFBR1* mutations in patients with LDS contribute to oncogenesis remains incompletely elucidated. At present, no specific cancer pattern has emerged, and it remains unknown whether patients with LDS are at an increased risk of developing malignancies [3]. Therefore, thorough interdisciplinary clinical and basic research is needed in order to fully clarify the risk of oncogenesis in patients with LDS. Our patient was the oldest repre-

sentative of all known family members with this mutation, which in part may explain the singular occurrence of such a malignancy in the analyzed family. Six family members who were tested for this mutation were diagnosed positive (Fig. 2). Considering the high penetrance and the variable expression of the genetic defect in this family, along with the documented aggressive clinical course of LDS and the excellent long-term results of valve-sparing root surgery, increased alertness and timely aortic root intervention should be strongly considered in patients who test positive for this *TGFBR1* mutation.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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### References

1. Loeys BL, Schwarze U, Holm T, et al. *Aneurysm syndromes caused by mutations in the TGF-beta receptor*. N Engl J Med 2006;355:788-98.
2. Loeys BL, Chen J, Neptune ER, et al. *A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2*. Nat Genet 2005;37:275-81.
3. MacCarrick G, Black JH 3rd, Bowdin S, et al. *Loeys-Dietz syndrome: a primer for diagnosis and management*. Genet Med 2014;16:576-87.
4. Oderich GS, Panneton JM, Bower TC, et al. *The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience*. J Vasc Surg 2005;42:98-106.
5. Singh KK, Rommel K, Mishra A, et al. *TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loeys-Dietz syndrome*. Hum Mutat 2006;27:770-7.
6. Akhurst RJ, Derynck R. *TGF-beta signaling in cancer: a double-edged sword*. Trends Cell Biol 2001;11:S44-51.
7. Bakkebo M, Huse K, Hilden VI, Smeland EB, Oksvold MP. *TGF-β-induced growth inhibition in B-cell lymphoma correlates with Smad1/5 signalling and constitutively active p38 MAPK*. BMC Immunol 2010;11:57.
8. Wang YQ, Qi XW, Wang F, Jiang J, Guo QN. *Association between TGFBR1 polymorphisms and cancer risk: a meta-analysis of 35 case-control studies*. PLoS One 2012;7:e42899.