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Loeys-Dietz Syndrome

Synonym: Loeys-Dietz Aortic Aneurysm Syndrome

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Summary

Clinical characteristics

Loeys-Dietz syndrome (LDS) is characterized by vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections), skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus, and cervical spine malformation and/or instability), craniofacial features (hypertelorism, strabismus, bifid uvula / cleft palate, and craniosynostosis that can involve any sutures), and cutaneous findings (velvety and translucent skin, easy bruising, and dystrophic scars). Individuals with LDS are predisposed to widespread and aggressive arterial aneurysms and pregnancy-related complications including uterine rupture and death. Individuals with LDS can show a strong predisposition for allergic/inflammatory disease including asthma, eczema, and reactions to food or environmental allergens. There is also an increased incidence of gastrointestinal inflammation including eosinophilic esophagitis and gastritis or inflammatory bowel disease. Wide variation in the distribution and severity of clinical features can be seen in individuals with LDS, even among affected individuals within a family who have the same pathogenic variant.

Diagnosis/testing

The diagnosis of LDS is established in (1) a proband with characteristic clinical findings or (2) by the identification of a heterozygous pathogenic variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* or biallelic pathogenic variants in *IPO8* in a proband with aortic root enlargement, type A dissection, other characteristic clinical features of LDS, or a family history of an established diagnosis of LDS.

Management

Treatment of manifestations: Important considerations when managing cardiovascular features of LDS include the following: aortic dissection can occur at smaller aortic diameters and at younger ages than observed in Marfan syndrome; vascular disease is not limited to the aortic root; angiotensin receptor blockers, beta-adrenergic receptor blockers, or other medications are used to reduce hemodynamic stress; and aneurysms are

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amenable to early and aggressive surgical intervention. Consider subacute bacterial endocarditis prophylaxis in those undergoing dental work or other procedures expected to contaminate the bloodstream with bacteria. Management of orthopedic manifestations per orthopedist. Surgical fixation of cervical spine instability may be necessary to prevent spinal cord damage. Management by a craniofacial team is preferred for treatment of cleft palate and craniosynostosis. Hernias tend to recur after surgical intervention; a supporting mesh can be used during surgical repair to minimize recurrence risk. Standard treatment for allergic complications with consideration of referral to an allergy/immunology specialist in those with severe disease. Careful and aggressive refraction and visual correction is mandatory in young children at risk for amblyopia. Optimal management of pneumothorax to prevent recurrence may require chemical or surgical pleurodesis or surgical removal of pulmonary blebs. Counseling regarding risk and clinical manifestations of organ rupture.

Surveillance: Echocardiography to monitor the status of the aortic root and ascending aorta (at least annually) and magnetic resonance angiography or computerized tomography angiography to assess the entire arterial tree (at least every other year); more frequent imaging may be indicated based on genotype, family history, absolute vessel size or growth rate, or vascular pathology. Assess for skeletal deformity, joint manifestations, pes planus, hernia, and allergic and inflammatory manifestations at each visit or as needed. Individuals with cervical spine instability and severe or progressive scoliosis should be followed by an orthopedist. Eye examination per ophthalmologist.

Agents/circumstances to avoid: Contact sports, competitive sports, and isometric exercise; agents that stimulate the cardiovascular system including routine use of decongestants or triptan medications for the management of migraine headache; activities that cause joint injury or pain; for individuals at risk for recurrent pneumothorax, breathing against a resistance (e.g., playing a brass instrument) or positive pressure ventilation (e.g., scuba diving).

Evaluation of relatives at risk: Clarify the genetic status of at-risk relatives of any age either by molecular genetic testing (if the LDS-related pathogenic variant[s] in the family are known) or by clinical examination including echocardiography and extensive vascular imaging if findings suggest LDS or if findings were subtle in the index case (if the pathogenic variant[s] in the family are not known) so that affected individuals can undergo regular cardiovascular screening to detect aortic aneurysms and initiate appropriate medical or surgical intervention.

Pregnancy management: Pregnancy and the postpartum period can be dangerous for women with LDS because of increased risk of aortic dissection/rupture and uterine rupture. Increased frequency of aortic imaging is recommended, both during pregnancy and in the weeks following delivery.

Genetic counseling

LDS caused by a pathogenic variant in *SMAD2*, *SMAD3*, T*GFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* is inherited in an autosomal dominant manner. *IPO8*-related LDS is inherited in an autosomal recessive manner.

Autosomal dominant inheritance: Approximately 75% of probands diagnosed with LDS have the disorder as the result of a *de novo* pathogenic variant; approximately 25% of individuals diagnosed with LDS have an affected parent. Each child of an individual with LDS has a 50% chance of inheriting the pathogenic variant and the disorder.

Autosomal recessive inheritance: The parents of a child with *IPO8*-related LDS are presumed to be heterozygous for an *IPO8* pathogenic variant. If both parents are known to be heterozygous for an *IPO8* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives requires prior identification of the *IPO8* pathogenic variants in the family.

If the LDS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Loeys-Dietz syndrome (LDS) have been published.

Suggestive Findings

LDS **should be suspected** in individuals with the following vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, ocular, and family history findings [Loeys et al 2005].

Vascular

- **Dilatation or dissection of the aorta and other arteries.** Aortic root dilatation is seen in more than 95% of probands; the aortic root is the most common site for a dissection to occur. In rare circumstances, aneurysms or dissections can be seen in other arteries in the head, chest, abdomen, or extremities in the absence of aortic involvement.
- **Other arterial aneurysms and tortuosity**
  - Evaluation is best done with magnetic resonance angiography (MRA) or CT angiogram (CTA) with 3D reconstruction from head to pelvis to identify arterial aneurysms or dissections and arterial tortuosity throughout the arterial tree.
  - Tortuosity is often most prominent in head and neck vessels.
  - Approximately 50% of individuals with LDS studied had an aneurysm distant from the aortic root that would not have been detected by echocardiography.

Skeletal

- Pectus excavatum or pectus carinatum
- Scoliosis
- Joint laxity or contracture (typically involving the fingers)
- Arachnodactyly
- Talipes equinovarus
- Cervical spine malformation and/or instability
- Osteoarthritis

Craniofacial

- Hypertelorism
- Bifid uvula / cleft palate
- Craniosynostosis, in which any sutures can be involved

Cutaneous

- Soft and velvety skin
- Translucent skin with easily visible underlying veins
- Easy bruising
- Dystrophic scars
- Milia, predominantly on the face

Allergic/inflammatory disease

- Food allergies
- Seasonal allergies

- Asthma / chronic sinusitis
- Eczema
- Eosinophilic esophagitis/gastritis
- Inflammatory bowel disease

Ocular. Blue or dusky sclerae

Family history is most often consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations), except in those with *IPO8*-related LDS (LDS7), which is inherited in an autosomal recessive manner. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Clinical diagnosis. The clinical diagnosis of LDS **can be established** in a proband with suggestive findings. Note: No consensus clinical diagnostic criteria are published.

Molecular diagnosis. The molecular diagnosis of LDS **can be established** in a proband who has a heterozygous pathogenic (or likely pathogenic) variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* or biallelic pathogenic (or likely pathogenic) variants in *IPO8* (see Table 1) AND any of the following [MacCarrick et al 2014]:

- Aortic root enlargement (defined as an aortic root z score ≥2 standard deviations above the mean) or type A dissection
- Other characteristic clinical features of LDS: craniofacial, skeletal, cutaneous, and/or vascular manifestations (especially arterial tortuosity, prominently including the head and neck vessels, and aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree)
- Family history of established diagnosis of LDS

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A multigene Marfan syndrome / Loeys-Dietz syndrome / familial thoracic aortic aneurysms and dissections panel that includes *IPO8*, *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*,*TGFBR1*, and *TGFBR2* as well as other genes associated with disorders that include aortic aneurysms and dissections (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from other inherited disorders with features observed in LDS, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Loeys-Dietz Syndrome

Gene [1, 2]	Proportion of LDS Attributed to Pathogenic Variants in Gene [3]	MOI	Proportion of Pathogenic Variants [4] Identified by Method	
			Sequence analysis [5]	Gene-targeted deletion/duplication analysis [6]
IPO8	~1%	AR	~100%	None reported [7]
SMAD2	~1%-5%	AD	90%-95%	None reported [7]
SMAD3	~5%-10%	AD	90%-95%	Rare [8]
TGFB2	~5%-10%	AD	90%-95%	Rare [9]
TGFB3	~1%-5%	AD	90%-95%	Rare [10]
TGFBR1	~20%-25%	AD	~100%	See footnote 11.
TGFBR2	~55%-60%	AD	~100%	See footnote 11.
Unknown [12]	5%-10%	NA		

LDS = Loeys-Dietz syndrome; MOI = mode of inheritance

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. Meester et al [2017b]

4. See Molecular Genetics for information on variants detected in this gene.

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

8. Hilhorst-Hofstee et al [2013], Schepers et al [2018]

9. Lindsay et al [2012], Gaspar et al [2017], Schepers et al [2018]

10. Deletion of *TGFB3* has been observed [BL Loeys & HC Dietz, personal observations].

11. Whole-gene deletion of *TGFBR2* [Campbell et al 2011] or *TGFBR1* [Redon et al 2006] and duplication of a 14.6-Mb region surrounding *TGFBR1* [Breckpot et al 2010] have been reported; however, these individuals lacked aortic involvement. Several other persons with deletions of *TGFBR1* or *TGFBR2* have not developed aortic aneurysms to date, suggesting that at least some mutated protein needs to be present [Lindsay & Dietz 2011]. As such, whole deletion/duplication of *TGFBR1* or *TGFBR2* do not present with clear features of LDS. Smaller deletions/duplications that lead to in-frame events are likely to cause an LDS phenotype, whereas those leading to out-of-frame events are not.

12. Based on rare individuals with discriminating features of LDS who show no pathogenic variants in the known genes, additional LDS-associated genes remain to be identified [BL Loeys & HC Dietz, personal observations].

Clinical Characteristics

Clinical Description

Loeys-Dietz syndrome (LDS) represents a wide phenotypic spectrum in which affected individuals may have various combinations of clinical features ranging from a severe syndromic presentation with significant extravascular systemic findings in young children to predominantly thoracic aortic aneurysm/dissection occurring in adults. Clinical variability is also observed among individuals in the same family who have the same pathogenic variant. The most common findings involve the vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, and ocular systems [Loeys et al 2005, Loeys et al 2006].

Cardiovascular

The major sources of morbidity and early mortality in LDS are dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic dissection and rupture, mitral valve prolapse (MVP) with or without regurgitation, and enlargement of the proximal pulmonary artery.

Individuals with LDS have more severe vascular disease (with frequent involvement of vascular segments distant from the aortic root) than that observed in Marfan syndrome. Attias et al [2009] reported that the proportion of individuals with aortic dilatation, the age at dissection, and the need for surgery were similar in those with a heterozygous *TGFBR2* pathogenic variant and those with a heterozygous *FBN1* pathogenic variant causative of Marfan syndrome; however, the rate of dissection leading to death was greater in affected individuals with a heterozygous *TGFBR2* pathogenic variant. In a systematic review of 3,896 individuals with LDS, the range of rate of aortic dissections were reported as follows: *TGFBR1*-related LDS, 17%-25%; *TGFBR2*-related LDS, 16%-35%; *SMAD3*-related LDS, 0%-33%; *TGFB2*-related LDS, 9%-11%; TGFB3-related LDS, 23% [Gouda et al 2022].

Arterial aneurysms have been observed in almost all side branches of the aorta including (but not limited to) the subclavian, renal, superior mesenteric, hepatic, and coronary arteries.

Aortic dissection has been observed in early childhood (age ≥6 months) and/or at aortic dimensions that do not confer risk of dissection in other connective tissue disorders such as Marfan syndrome.

Arterial tortuosity can be generalized but most commonly involves the head and neck vessels.

- The arterial involvement is widespread, and arterial tortuosity is present in a majority of affected individuals.
- Most affected individuals have multiple arterial anomalies.
- Vertebral and carotid artery dissection and cerebral bleeding have been described; rarely, isolated carotid artery dissection in the absence of aortic root involvement has been observed [Huguenard et al 2022].

MVP with mitral regurgitation has been observed in individuals with LDS, although less frequently than in Marfan syndrome.

Other recurrent cardiovascular findings include patent ductus arteriosus, atrial septal defects, and bicuspid aortic valve. Although all these findings are common in individuals who do not have LDS, the incidence in LDS exceeds by at least five times that seen in the general population.

Aortic histopathology. Histologic examination of aortic tissue reveals fragmentation of elastic fibers, loss of elastin content, and accumulation of amorphous matrix components in the aortic media. Structural analysis shows loss of the intimate spatial association between elastin deposits and vascular smooth muscle cells and a marked excess of aortic wall collagen. These characteristics are observed in young children and in the absence of inflammation, suggesting a severe defect in elastogenesis rather than secondary elastic fiber destruction.

Aortic samples from individuals with LDS had significantly more diffuse medial degeneration than did samples from individuals with Marfan syndrome or control individuals. The changes are not entirely specific for LDS, but in the appropriate clinicopathologic setting help differentiate it from other vascular diseases [Maleszewski et al 2009].

Skeletal

The skeletal findings are characterized by Marfan syndrome-like skeletal features and joint laxity or contractures [Erkula et al 2010].

Skeletal overgrowth in LDS is less pronounced than in Marfan syndrome and usually affects the digits (arachnodactyly) more prominently than the long bones.

Combined thumb and wrist signs were present in one third of individuals with LDS. Note: (1) The Walker-Murdoch wrist sign is the overlapping of the complete distal phalanx of the thumb and fifth finger when wrapped around the opposite wrist. (2) The "thumb sign" (Steinberg) is an extension of the entire distal phalanx of the thumb beyond the ulnar border of the hand when apposed across the palm.

Dolichostenomelia (leading to an increase in the arm span-to-height ratio and a decrease in the upper-to-lower segment ratio) is less common in LDS than in Marfan syndrome.

Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum).

Joint hypermobility is common and can include congenital hip dislocation and recurrent joint subluxations. Paradoxically, some individuals can show reduced joint mobility, especially of the hands (camptodactyly) and feet (clubfeet).

Spine anomalies, including congenital malformations of the cervical vertebrae and cervical spine instability, are common, especially in individuals with more severe craniofacial features.

Preliminary data suggest that approximately 15% (or more) of affected individuals have structural cervical spine anomalies and at least 25% have cervical spine instability.

Other skeletal findings

- Spondylolisthesis and scoliosis can be mild or severe and progressive.
- Acetabular protrusion, present in one third of individuals, is usually mild but can be associated with pain or functional limitations.
- Pes planus, often associated with inward rotation at the ankle, contributes to difficulty with ambulation, leg fatigue, and muscle cramps.
- Preliminary evidence suggests that individuals with LDS have an increased incidence of osteoporosis with increased fracture incidence and delayed bone healing [Kirmani et al 2010].

Note: Musculoskeletal findings, including hypotonia, have been observed in neonates with LDS [Yetman et al 2007].

Craniofacial

In their most severe presentation, craniofacial anomalies in individuals with LDS are characterized by hypertelorism and craniosynostosis. Craniosynostosis most commonly involves premature fusion of the sagittal suture (resulting in dolichocephaly). Coronal suture synostosis (resulting in brachycephaly) and metopic suture synostosis (resulting in trigonocephaly) have also been described.

Bifid uvula is considered the mildest expression of a cleft palate. Sometimes the uvula has an unusual broad appearance with or without a midline raphe.

Other craniofacial characteristics include malar flattening and retrognathia.

Cutaneous

The skin findings, similar to those seen in vascular Ehlers-Danlos syndrome (see Differential Diagnosis), include velvety, thin, translucent skin with visible veins on the chest wall, easy bruising (occurring in locations more than just the lower legs), slower scar formation, and dystrophic scarring. Inguinal, umbilical, and surgical hernias are common in individuals with LDS, although precise incidence estimates have not been determined.

Allergy and Gastrointestinal Disease

Individuals with LDS are predisposed to developing allergic disease including asthma, food allergy, eczema, allergic rhinitis, and eosinophilic gastrointestinal disease. Some affected individuals have exhibited elevated immunoglobulin E levels, eosinophil counts, and T helper 2 (TH2) cytokines in plasma [Frischmeyer-Guerrerio et al 2013, Felgentreff et al 2014].

Ocular

Myopia is less frequent and less severe than that seen in Marfan syndrome. Significant refractive errors can lead to amblyopia. Other common ocular features include strabismus and blue sclerae. Retinal detachment has been reported rarely. Ectopia lentis is not observed except in exceedingly rare case reports of unclear significance.

Other

As in other connective tissue disorders, **pneumothorax** occurs at increased frequency. Precise incidence estimates have not been determined.

Life-threatening manifestations include **spontaneous rupture** of the spleen and bowel, and uterine rupture during pregnancy.

The two most common neuroradiologic findings are dural ectasia (the precise incidence of which is unknown, as only a minority of affected individuals have undergone appropriate examination) and Arnold-Chiari type I malformation, which may be relatively rare.

A minority of affected individuals have **developmental delay**. When present, developmental delay is most often associated with craniosynostosis and/or hydrocephalus, suggesting that developmental delay and/or learning disability is an extremely rare primary manifestation of LDS. Motor developmental delay is related to muscle hypotonia.

Less common associated findings requiring further exploration include submandibular branchial cysts and defective tooth enamel.

Pregnancy. Pregnancy can be dangerous for women with LDS due to increased risk of aortic dissection/rupture and uterine rupture; see Pregnancy Management.

Phenotype Correlations by Gene

Genes are listed in Table 2 in order of phenotypic severity (from those genes associated with the most severe phenotype to the least severe phenotype).

Table 2. Loeys-Dietz Syndrome (LDS): Associated Genes and Subtypes

Gene	Subtype of LDS	Comment	Reference
TGFBR1	LDS1	Most severe phenotype; phenotype for *TGFBR1*- & *TGFBR2*-related LDS is similar in severity.	Loeys et al [2005], Loeys et al [2006]
TGFBR2	LDS2		

Table 2. continued from previous page.

Gene	Subtype of LDS	Comment	Reference
SMAD3	LDS3	Severity of aortic disease in *SMAD3*-related LDS is similar to *TGFBR1*- or *TGFBR2*-related LDS; strong predisposition for osteoarthritis [1]	van de Laar et al [2011]
IPO8	LDS7	Very severe aneurysms at young age; no dissections described	Van Gucht et al [2021b]
TGFB2	LDS4	Systemic findings possibly less severe & more like Marfan syndrome	Boileau et al [2012], Lindsay et al [2012], Bertoli-Avella et al [2015]
SMAD2	LDS6	Variable cardiovascular phenotype, incl congenital heart disease	Granadillo et al [2018], Cannaerts et al [2019]
TGFB3	LDS5	Mildest form of LDS	Boileau et al [2012], Lindsay et al [2012], Bertoli-Avella et al [2015]

LDS = Loeys-Dietz syndrome
1. Several individuals with *SMAD3*-related LDS do not have osteoarthritis [Wischmeijer et al 2013].

Genotype-Phenotype Correlations

While the implicated gene can correlate broadly with disease severity (see Phenotype Correlations by Gene), there are few specific genotype-phenotype correlations in LDS. Wide intrafamilial and interfamilial phenotypic variability has been reported. The identical pathogenic variant has also been described in unrelated affected individuals with phenotypes ranging from predominantly thoracic aortic disease to classic and severe LDS.

Penetrance

Rare examples of non-penetrance in LDS have been documented. In some instances, non-penetrance is explained by mosaicism [Baban et al 2018].

Nomenclature

While various clinical presentations have in the past been labeled as LDS type I (craniofacial features present), LDS type II (minimal to absent craniofacial features), and LDS type III (presence of osteoarthritis), it is now recognized that LDS caused by a heterozygous pathogenic variant in any of the seven known genes (see Table 1) is a continuum in which affected individuals may have various combinations of clinical features.

Marfan syndrome type 2 was a designation initially applied by Mizuguchi et al [2004] to describe individuals with "classic" Marfan syndrome caused by a heterozygous pathogenic variant in *TGFBR2*. At the time of the report other discriminating features of LDS had not yet been described. There has not been documentation of individuals with a heterozygous pathogenic variant in*TGFBR1* or *TGFBR2* that satisfied diagnostic criteria for Marfan syndrome, including the stipulation requiring absence of discriminating features of LDS [Loeys et al 2006, Van Hemelrijk et al 2010]. The term "Marfan syndrome type 2" should not be used to refer to LDS.

TGFB3-related LDS may also be referred to as Rienhoff syndrome.

Prevalence

The exact prevalence of LDS is unknown but estimated to be 1:50,000. More than 1,000 families with LDS have been described in the literature.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *IPO8*.

Other phenotypes associated with germline pathogenic variants in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Disorder
SMAD2	2 pathogenic variants in *SMAD2* have been reported in a series of 362 persons w/severe congenital heart disease [Zaidi et al 2013]. These 2 persons presented w/dextrocardia assoc w/multiple other congenital heart defects.
	Nonsyndromic heritable thoracic aortic disease
SMAD3	Nonsyndromic heritable thoracic aortic disease
TGFB2	Nonsyndromic heritable thoracic aortic disease
TGFB3	Nonsyndromic heritable thoracic aortic disease
TGFBR1	Heterozygous loss-of-function variants in *TGFBR1* are assoc w/multiple self-healing squamous epithelioma, also known as Ferguson-Smith disease (OMIM 132800).
	Nonsyndromic heritable thoracic aortic disease
TGFBR2	Nonsyndromic heritable thoracic aortic disease

Differential Diagnosis

Marfan Syndrome and Shprintzen-Goldberg Syndrome

***FBN1*-related Marfan syndrome** is a systemic disorder with a high degree of clinical variability. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems. Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. Marfan syndrome is caused by pathogenic variants in *FBN1* and inherited in an autosomal dominant manner.

Shprintzen-Goldberg syndrome (SGS) is characterized by craniosynostosis, distinctive craniofacial features, skeletal changes, neurologic abnormalities, mild-to-moderate intellectual disability, and brain anomalies. Cardiovascular anomalies (mitral valve prolapse, mitral regurgitation, and aortic regurgitation) may occur, but aortic root dilatation is less commonly observed than in Loeys-Dietz syndrome (LDS) and can be mild. An important feature distinguishing SGS from LDS is the near-uniform incidence of developmental delay in individuals with SGS. SGS is caused by heterozygous pathogenic variants in *SKI* and most individuals have a *de novo* pathogenic variant. The protein encoded by SKI, ski oncogene, is a known repressor of transforming growth factor beta signaling.

Table 4. Comparison of Clinical Features in Loeys-Dietz Syndrome, Marfan Syndrome, and Shprintzen-Goldberg Syndrome

Clinical Feature	Marfan syndrome	Loeys-Dietz Syndrome						Shprintzen-Goldberg Syndrome
	FBN1	*TGFBR1*/ *TGFBR2*	*SMAD3*	*TGFB2*	*TGFB3*	*SMAD2*	*IPO8*	*SKI*
Developmental delay	–	–	–	–	–	–	+ [1]	++

Table 4. continued from previous page.

Clinical Feature	Marfan syndrome	Loeys-Dietz Syndrome						Shprintzen-Goldberg Syndrome
	FBN1	*TGFBR1/ TGFBR2*	*SMAD3*	*TGFB2*	*TGFB3*	*SMAD2*	*IPO8*	*SKI*
Ectopia lentis	+++	–	–	–	–	–	–	–
Cleft palate / bifid uvula	–	++	+	+	+	+	+	+
Hypertelorism	–	++	+	+	+	+	++	++
Craniosynostosis	–	++	+	–	–	–	–	+++
Tall stature	+++	+	+	++	+	+	–	+
Arachnodactyly	+++	++	+	+	+	+	++	++
Pectus deformity	++	++	++	++	+	+	++	++
Clubfoot	–	++	+	++	+	–	+	+
Osteoarthritis	+	+	+++	+	+	+	?	–
Aortic root aneurysm	+++	++	++	++	+	+	+++	+
Arterial aneurysm	–	++	+	+	+	+	++	+
Arterial tortuosity	–	++	++	+	+	+	+	+
Early-onset aortic dissection	+	+++	++	+	+	+	–	–
Bicuspid aortic valve	–	++	+	+	+	+	+	+
Mitral valve insufficiency	++	+	+	++	+	+	+	+
Striae	++	+	+	+	+	+	+	+
Dural ectasia	+	+	+	+	–	–	?	+

+ = feature is present (presence of more than one "+" indicates that a feature is more common, with "+++" indicating most common); – = feature is absent; ? = unknown if clinical feature is associated with *IPO8*-related LDS

1. Developmental delays are primarily motor delays.

Genes of Interest in the Differential Diagnosis of Loeys-Dietz Syndrome

Table 5. Genes of Interest in the Differential Diagnosis of Loeys-Dietz Syndrome

Gene	Disorder	MOI	Clinical Characteristics
Syndromic forms of thoracic aortic aneurysms			
BGN	BGN-assoc aortic aneurysm syndrome (Meester-Loeys syndrome) (OMIM 300989)	XL	Clinical features significantly overlap Marfan syndrome & LDS, incl early-onset aortic root dilatation & dissection, hypertelorism, joint hypermobility, contractures, bifid uvula, & pectus deformities. In some families, heterozygous females are also affected.
COL1A2	Cardiac-valvular EDS (OMIM 225320)	AR	Joint hypermobility, skin hyperextensibility, & severe cardiac-valvular defects.
COL3A1 (*COL1A1*) [1]	Vascular EDS (vEDS)	AD [2]	If vEDS is clinically suspected, collagen biochemistry normal, & no *COL3A1* or *COL1A1* pathogenic variant is present, consider LDS molecular analysis of *SMAD2*, *SMAD3*, TGFB2, *TGFB3*, *TGFBR1*, & *TGFBR2*.

Table 5. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
COL5A1 *COL5A2* *COL1A1* [3]	Classic EDS (cEDS)	AD	Aortic root dilatation has been reported in persons w/cEDS. [4] It appears to be more common in young persons & rarely progresses. [5] Persons w/cEDS are at risk for spontaneous rupture of large arteries, although the prevalence of such complications is much lower than in those w/vEDS.
FBN1	*FBN1*-related Marfan syndrome	AD	See Table 4.
	MASS syndrome (OMIM 604308)	AD	Mitral valve prolapse, myopia, borderline & non-progressive aortic enlargement, & nonspecific skin & skeletal findings that overlap w/those seen in Marfan syndrome
FBN2	Congenital contractural arachnodactyly (CCA)	AD	Marfan-like appearance (tall, slender habitus in which arm span exceeds height) & arachnodactyly. Aortic root dilatation has been documented in persons w/CCA w/a confirmed *FBN2* pathogenic variant; progression is rare. A severe/lethal infantile form is characterized by multiple cardiovascular & gastrointestinal anomalies in addition to typical skeletal findings.
FKBP14	*FKBP14*-related kyphoscoliotic EDS	AR	Risk for rupture of medium-sized arteries & respiratory compromise if kyphoscoliosis is severe. Aortic dilatation & rupture variably seen.
PLOD1	*PLOD1*-related kyphoscoliotic EDS	AR	
FLNA	FLNA deficiency	XL	Connective tissue findings, mitral valve disease, & aortic aneurysm/dissection in some affected persons
PMEPA1 (*TMEPAI*)	Marfan/LDS-like syndrome	AD	Variable aortic aneurysm/dissection w/marfanoid habitus [6]
SKI	Shprintzen-Goldberg syndrome	AD	See Table 4.
SLC2A10	Arterial tortuosity syndrome	AR	Rare connective tissue disorder characterized by severe tortuosity, stenosis, & aneurysms of aorta & middle-sized arteries. Skeletal & skin involvement is also common.
Syndromes assoc w/ascending aortic aneurysms			
BRAF *KRAS* *LZTR1* *MAP2K1* *MRAS* *NRAS* *PTPN11* *RAF1* *RASA2* *RIT1* *RRAS2* *SOS1* *SOS2*	Noonan syndrome	AD (AR) [7]	Short stature, congenital heart defect, & developmental delay of variable degree. Congenital heart disease (e.g., pulmonary valve stenosis, hypertrophic cardiomyopathy, atrial & ventricular septal defects) occurs in 50%-80% of affected persons. Rarely, aortic aneurysms have been described. [8]
EFEMP2	*EFEMP2*-related cutis laxa	AR	Arterial/aortic aneurysms are reported in >90% of persons w/ *EFEMP2*-related cutis laxa.
ELN	*ELN*-related cutis laxa	AD	Aortic dissection has been reported in multiple persons w/*ELN*-related cutis laxa, as early as the 3rd decade; the risk for aortic dissection has not been established.
Nonsyndromic familial thoracic aortic aneurysms & dissections			

Table 5. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
ACTA2 *FBN1* *LOX* [9] *MYH11* *MYLK* *PRKG1* *SMAD3* *TGFB2* *TGFBR1* *TGFBR2* (selected HTAD-related genes [10])	Nonsyndromic heritable thoracic aortic disease (HTAD)	AD	Often asymptomatic thoracic aortic aneurysms of the aortic root & ascending aorta can lead to life-threatening acute type A aortic dissections. Although aneurysms involving the ascending aorta often precede type A dissections, aortic dissection can occur in the absence of aortic enlargement. A genetic cause of HTAD is identified in only approximately 20%-30% of persons w/a family history of thoracic aortic disease who do not have syndromic manifestations. Patent ductus arteriosus has been described in *ACTA2*- & *MYH11*-related HTAD. [11]

AD = autosomal dominant; AR = autosomal recessive; LDS = Loeys-Dietz syndrome; MOI = mode of inheritance; XL = X-linked

1. Arginine-to-cysteine pathogenic variants in *COL1A1* have been identified in a subset of affected individuals who typically present with aneurysms of the abdominal aorta and iliac arteries reminiscent of vEDS. Distinct abnormalities on collagen electrophoresis are observed [Malfait et al 2007]. Pathogenic variants in *COL1A1* are listed as a rare cause of vEDS in the 2017 International Classification of the Ehlers-Danlos Syndromes [Malfait et al 2017].

2. Vascular EDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported.

3. Pathogenic variants in *COL1A1* are not a major cause of cEDS.

4. Wenstrup et al [2002], McDonnell et al [2006], Atzinger et al [2011]

5. Bowen et al [2017]

6. Greene et al [2023]

7. Noonan syndrome is most often inherited in an autosomal dominant manner. Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

8. Cornwall et al [2014]

9. Heterozygous *LOX* pathogenic variants have been reported in individuals with aortic aneurysm/dissection with variable connective tissue findings [Van Gucht et al 2021a].

10. Listed genes are reported to have a definitive or strong HTAD association by the Clinical Genome Resource (ClinGen) HTAD Gene Curation Expert Panel (see Heritable Thoracic Aortic Disease Overview, Table 1).

11. Glancy et al [2001], Khau Van Kien et al [2004], Khau Van Kien et al [2005], Zhu et al [2006], Pannu et al [2007]

Other Considerations

Bicuspid aortic valve (BAV) with thoracic aortic aneurysm. A dilated ascending aorta may be associated with an underlying BAV (a BAV is present in 1%-2% of the general population). Among persons with aortic dissection detected at postmortem examination, 8% have BAVs. Histologic studies show elastin degradation and cystic medial necrosis in the aorta above the valve. Echocardiography of young persons with normally functioning BAVs shows that aortic root dilatation is common (52%) [Nistri et al 1999]. Importantly, the aortic dilatation often occurs above the sinuses of Valsalva. BAVs cluster in families. *MIB1*, *NOTCH1*, *ROBO4*, and *SMAD6* pathogenic variants have been identified in rare (<1%) individuals with a BAV with or without ascending aortic aneurysm [Gould et al 2019, Luyckx et al 2019, Tessler et al 2023].

Turner syndrome, one of the most common sex chromosome aneuploidy syndromes, is caused by the loss of one of the X chromosomes (45,X). The most important phenotypic features are short stature, gonadal dysgenesis, neck webbing, and an increased incidence of renal and cardiovascular abnormalities. The latter include bicuspid aortic valve (BAV), coarctation of the aorta, and thoracic aortic aneurysms. Aortic root dilatation is observed in up to 30% of women with Turner syndrome, but the frequency with which it leads to aortic dissection is unknown. Current health surveillance recommendations for Turner syndrome include echocardiography or MRI for evaluation of the diameter of the aortic root and ascending aorta at least every five years.

Fibromuscular dysplasia (FMD) (OMIM 135580) is a non-atherosclerotic, non-inflammatory vascular disease that can affect almost every artery, but most frequently affects the renal and internal carotid arteries. Most commonly, medial hyperplasia leads to a classic "strings of beads" stenotic arterial appearance. Macroaneurysms and dissections are complications. It is possible that genetic factors play a role in the pathogenesis: the disease is observed among the first-degree relatives of persons with fibromuscular dysplasia of the renal arteries. The underlying genetic cause for nonsyndromic FMD has not been identified, although *PHACTR1* has been reported as a genetic susceptibility locus for FMD [Kiando et al 2016].

Management

An extensive review of management guidelines for Loeys-Dietz syndrome (LDS) has been published [MacCarrick et al 2014] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with LDS, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Loeys-Dietz Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Cardiovascular	• Echocardiography • MRA or CT w/3D reconstruction from head to pelvis to identify arterial aneurysms & arterial tortuosity throughout the arterial tree • Select findings (e.g., severe aortic dilatation) may require immediate attention of cardiologist or cardiothoracic surgeon.	Aortic root measurements must be interpreted based on consideration of normal values for age & body size. Approximately half of persons w/LDS studied had an aneurysm distant from the aortic root that would not have been detected by echocardiography. [1]
Skeletal	• Clinical assessment for pectus deformity, clubfoot, scoliosis, pes planus • Assessment for congenital hip dislocation & abnormal joint mobility • Spine radiographs (incl flexion & extension views of cervical spine) to detect skeletal manifestations that may require attention by an orthopedist (e.g., severe scoliosis, cervical spine instability)	
Craniofacial	Craniofacial exam for evidence of cleft palate & craniosynostosis	
Allergy / Gastrointestinal disease	Assessment for clinical manifestations of asthma, food allergy, eczema, allergic rhinitis, &/or eosinophilic gastrointestinal disease	
Ocular	Exam by ophthalmologist w/expertise in connective tissue disorders incl: • Assessment for refractive errors • Specific assessment for retinal detachment	
Genetic counseling	By genetics professionals [2]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of LDS to facilitate medical & personal decision making

LDS = Loeys-Dietz syndrome; MOI = mode of inheritance; MRA = magnetic resonance angiography

1. Roman et al [1989]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management of LDS is most effective through the coordinated input of a multidisciplinary team of specialists including a clinical geneticist, cardiologist, cardiothoracic surgeon, orthopedist, and ophthalmologist (see Table 7).

Table 7. Loeys-Dietz Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cardiovascular	Persons should be managed in a medical center familiar w/LDS.	
	Beta-adrenergic blockers or angiotensin receptor blockers (ARBs) to ↓ hemodynamic stress	No clinical trials evaluating efficacy of beta-blockers vs ARBs have been completed in persons w/LDS.
	Aneurysms are amenable to early & aggressive surgical intervention: • **For young children w/*TGFBR1*- & *TGFBR2*-related LDS (LDS1 & 2)** & severe craniofacial manifestations of LDS, consider surgical repair of ascending aorta once maximal dimension is >99th centile & aortic annulus is >1.8-2.0 cm, allowing placement of a graft of sufficient size to accommodate growth. Additional factors can influence timing of surgery (family history, rate of aortic root growth, & aortic valve function). • **For adolescents/adults w/*TGFBR1*- & *TGFBR2*-related LDS (LDS1 & 2),** consider surgical repair of ascending aorta once maximal dimension approaches 4.0 cm. This is based on documented aortic dissection in adults w/aortic root dimensions ≤4.0 cm & excellent response to surgery. An extensive family history of larger aortic dimension w/o dissection could alter recommendations for affected persons. • **For *SMAD2*-, *SMAD3*- & *TGFB2*-related LDS,** consider surgical repair of ascending aorta once maximal dimension approaches 4.5 cm. • **For *TGFB3*-related LDS,** consider surgical repair of ascending aorta once maximal dimension approaches 5 cm. Note: Suggested surgical thresholds vary based on involved gene, family history, aortic root growth rate, & valve function, among other variables.	• Aortic dissection occurs at smaller aortic diameters in LDS than in Marfan syndrome. • Severe craniofacial manifestations are often assoc w/& can be used to predict severe cardiovascular manifestations. • Vascular disease is not limited to the aortic root. Imaging of the complete arterial tree from head to pelvis by MRA or CTA is necessary. • Many persons can undergo a valve-sparing procedure that precludes the need for chronic anticoagulation. • Surgical repair may not eliminate risk of dissection & death, & earlier intervention based on family history or affected person's personal assessment of risk vs benefit may be indicated.
	Consider subacute bacterial endocarditis prophylaxis in persons w/mitral &/or aortic regurgitation who are undergoing dental work or other procedures expected to contaminate the bloodstream w/bacteria.	
Pectus excavatum	Rarely, surgical intervention is medically (rather than cosmetically) indicated.	
Congenital hip dislocation / Other joint manifestations	Mgmt per orthopedist	
Clubfeet	Surgical correction by orthopedic surgeon	

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cervical spine instability	Surgical fixation may be necessary to prevent damage to spinal cord.	Because of high risk of cervical spine instability, cervical spine flexion & extension radiographs should be performed prior to intubation or any other procedure involving manipulation of neck.
Spondylolisthesis	Mgmt per orthopedist	
Scoliosis	Progressive scoliosis should be managed by orthopedist; surgical stabilization of spine may be required.	
Acetabular protrusion	Surgical intervention is rarely indicated; treatment focuses on pain control.	
Pes planus	Orthotics are only indicated for severe pes planus. Some persons prefer use of arch supports, while others find them irritating; the choice should be left to personal preference.	Surgical intervention is rarely indicated or successful.
Fracture/Osteoporosis	Severe osteoporosis w/pathologic fracture may require specific treatment under guidance of endocrinologist. [1]	
Cleft palate / Craniosynostosis	Standard mgmt by craniofacial team	
Hernias	A supporting mesh can be used during surgical repair to minimize recurrence risk.	Hernias tend to recur after surgical intervention.
Allergic/ Inflammatory	• Standard treatment for allergic complications such as seasonal allergies, food allergies, asthma, & eczema • Consider referral to allergist/immunologist in those w/ severe disease. • Inflammatory or allergic gastrointestinal findings are treated in standard fashion w/guidance of gastroenterologist.	
Ocular	• Mgmt by ophthalmologist w/expertise in connective tissue disorders • Careful & aggressive refraction & visual correction is mandatory in young children at risk for amblyopia.	
Pneumothorax	Optimal mgmt of pneumothorax to prevent recurrence may require chemical or surgical pleurodesis or surgical removal of pulmonary blebs.	
Organ rupture	Counseling regarding other life-threatening manifestations incl spontaneous rupture of spleen & bowel & pregnancy-assoc risks is recommended.	
Dural ectasia	Dural ectasia is usually asymptomatic; no effective therapies for symptomatic dural ectasia currently exist.	

CTA = CT angiogram; MRA = magnetic resonance angiography
1. Ben Amor et al [2012], Charoenngam et al [2023]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 are recommended.

Table 8. Loeys-Dietz Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cardiovascular	Echocardiography to monitor status of aortic root & ascending aorta	At least annually or more often per cardiologist
	MRA or CTA w/3D reconstruction from head to pelvis to identify arterial aneurysms & arterial tortuosity throughout the arterial tree	• At least every other year, or more frequently per cardiologist • More frequent imaging may be indicated based on genotype, family history, absolute vessel size or growth rate, or vascular pathology.
Pectus deformity	Clinical assessment	At each visit or as needed
Joint manifestations		
Cervical spine instability	Follow-up imaging	Per orthopedist
Scoliosis	Clinical &/or radiographic assessment	
Pes planus	Clinical assessment	At each visit or as needed
Hernias	Clinical assessment for hernias	At each visit or annually
Allergic/ Inflammatory	Assessment for clinical manifestations of asthma, food allergy, eczema, allergic rhinitis, &/or eosinophilic gastrointestinal disease	
Ocular	Eye exam by ophthalmologist w/expertise in connective tissue disorders incl: • Assessment for refractive error • Specific assessment for retinal detachment	Per ophthalmologist

CTA = computerized tomography angiography; MRA = magnetic resonance angiography

Agents/Circumstances to Avoid

The following should be avoided:

- Contact sports, competitive sports, and isometric exercise. Note: Individuals can and should remain active with aerobic activities performed in moderation.
- Agents that stimulate the cardiovascular system, including routine use of decongestants or triptan medications for migraine headache management
- Activities that cause joint injury or pain
- For individuals at risk for recurrent pneumothorax, breathing against a resistance (e.g., playing a brass instrument) or positive pressure ventilation (e.g., scuba diving)

Evaluation of Relatives at Risk

It is recommended that the genetic status of relatives of any age at risk for LDS be clarified either by molecular genetic testing or by clinical examination so that affected individuals can undergo regular cardiovascular screening to detect aortic aneurysms and initiate appropriate medical or surgical intervention (see Surveillance). Approaches include the following:

- Molecular genetic testing if the LDS-related pathogenic variant(s) in the family is known
- Examination for manifestations of LDS if the pathogenic variant(s) in the family is not known. Echocardiography and extensive vascular imaging of relatives is indicated upon identification of any

suggestive findings of LDS, and even in apparently unaffected individuals if findings are subtle in the index case.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy can be dangerous for women with LDS. Complications include aortic dissection/rupture or uterine rupture during pregnancy or delivery, or aortic dissection/rupture in the immediate postpartum period. Increased frequency of aortic imaging is recommended, both during pregnancy and in the weeks following delivery. However, with appropriate supervision and high-risk obstetric management, women with LDS can tolerate pregnancy and delivery [Gutman et al 2009, Frise et al 2017].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Loeys-Dietz syndrome (LDS) caused by a pathogenic variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* is inherited in an autosomal dominant manner.

IPO8-related LDS is inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Approximately 75% of individuals diagnosed with LDS have the disorder as the result of a *de novo* pathogenic variant.
- Approximately 25% of individuals diagnosed with LDS have an affected parent. Familial recurrence is more common in less severe presentations of LDS.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for both parents of the proband to evaluate their genetic status, inform recurrence risk assessment, and determine their need for surveillance. If a molecular diagnosis has not been established in the proband, it is appropriate to evaluate both parents for manifestations of LDS, including a comprehensive clinical examination.
- If a molecular diagnosis has been established in the proband, the pathogenic variant identified in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:

- The proband has a *de novo* pathogenic variant.
- The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism * (parental somatic and gonadal mosaicism have been reported in rare families [Baban et al 2018]). Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

  * Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

- A proband may appear to be the only family member with LDS because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, *de novo* occurrence of an LDS-related pathogenic variant in the proband cannot be confirmed unless appropriate clinical evaluation of the parents and/or molecular genetic testing has demonstrated that neither parent has the pathogenic variant.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the LDS-related pathogenic variant identified in the proband, the risk to the sibs is 50%.
- Clinical variability may be observed among individuals in the same family who have the same pathogenic variant.
- If the proband has a known LDS-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental gonadal mosaicism [Baban et al 2018]).
- If both parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but still increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or parental gonadal mosaicism.

Offspring of a proband

- Each child of an individual with LDS has a 50% chance of inheriting the pathogenic variant.
- The penetrance of *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* pathogenic variants is reported to be near 100%; thus, offspring who inherit a pathogenic variant from a parent will have LDS, although the severity cannot be predicted.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have the pathogenic variant identified in the proband, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *IPO8* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *IPO8* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:

- A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *IPO8* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *IPO8*-related LDS are obligate heterozygotes (carriers) for a pathogenic variant in *IPO8*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *IPO8* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *IPO8* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Pregnancy can be dangerous for women with LDS; appropriate supervision and high-risk obstetric management is recommended (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. If the LDS-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Ultrasound examination in the first two trimesters is insensitive in detecting manifestations of LDS, but prenatal occurrence of aortic dilatation has been described.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Loeys-Dietz syndrome Foundation Canada**
  Canada
  loeysdietzcanada.org
- **Loeys-Dietz Syndrome Foundation USA**
  loeysdietz.org
- **Marfan Foundation**
  Loeys-Dietz Syndrome
- **American Heart Association**
  Phone: 800-242-8721
  Types of Aneurysms
- **Medline Plus**
  Loeys-Dietz syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Loeys-Dietz Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
IPO8	12p11.21	Importin-8		IPO8	IPO8
SMAD2	18q21.1	Mothers against decapentaplegic homolog 2	SMAD2 database	SMAD2	SMAD2
SMAD3	15q22.33	Mothers against decapentaplegic homolog 3	CHD8 @ LOVD SMAD3 database	SMAD3	SMAD3
TGFB2	1q41	Transforming growth factor beta-2 proprotein	TGFB2 database	TGFB2	TGFB2
TGFB3	14q24.3	Transforming growth factor beta-3 proprotein	ARVD/C Genetic Variants Database - TGFB3 TGFB3 database	TGFB3	TGFB3
TGFBR1	9q22.33	TGF-beta receptor type-1	TGFBR1 database	TGFBR1	TGFBR1
TGFBR2	3p24.1	TGF-beta receptor type-2	TGFBR2 database	TGFBR2	TGFBR2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Loeys-Dietz Syndrome (View All in OMIM)

190181	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I; TGFBR1
190182	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE II; TGFBR2

Table B. continued from previous page.

190220	TRANSFORMING GROWTH FACTOR, BETA-2; TGFB2
190230	TRANSFORMING GROWTH FACTOR, BETA-3; TGFB3
601366	SMAD FAMILY MEMBER 2; SMAD2
603109	SMAD FAMILY MEMBER 3; SMAD3
605600	IMPORTIN 8; IPO8
609192	LOEYS-DIETZ SYNDROME 1; LDS1
610168	LOEYS-DIETZ SYNDROME 2; LDS2
613795	LOEYS-DIETZ SYNDROME 3; LDS3
614816	LOEYS-DIETZ SYNDROME 4; LDS4
615582	LOEYS-DIETZ SYNDROME 5; LDS5
619472	VISS SYNDROME; VISS
619656	LOEYS-DIETZ SYNDROME 6; LDS6

Molecular Pathogenesis

In the initial description of *TGFBR2* pathogenic variants causing a phenotype similar to Marfan syndrome, it was observed that recombinantly expressed mutated receptors in cells that were naïve for transforming growth factor beta (TGF-β) receptors could not support TGF-β signaling [Mizuguchi et al 2004]. Furthermore, there was no apparent dominant-negative interference on the function of coexpressed wild type receptor. These data were interpreted to indicate haploinsufficiency and consequent reduced TGF-β signaling as the relevant pathogenic mechanisms.

In keeping with this hypothesis, one of the original individuals with a Marfan syndrome-like phenotype was shown to contain a translocation breakpoint within *TGFBR2*. Complicating this hypothesis, however, is the observation of a distinct paucity of pathogenic nonsense or frameshift variants in either of the TGF-β receptor genes in persons with Loeys-Dietz syndrome (LDS) or related phenotypes. The mutated receptor subunits may not traffic to the cell surface or may not cycle, resulting in "functional haploinsufficiency." The only reported nonsense variant occurs at the very distal margin of the penultimate exon. As opposed to more proximal pathogenic nonsense variants, this context is not predicted to induce nonsense-mediated mRNA decay and clearance of the mutated transcripts. As a result, most (if not all) pathogenic variants in the TGF-β receptor genes associated with vascular phenotypes are predicted to give rise to a mutated receptor protein that has the ability to traffic to the cell surface and bind extracellular ligands, but that specifically lacks the ability to propagate the intracellular TGF-β signal. This hypothesis is also consistent with the finding that pathogenic variants cluster in the intracellular part of both *TGFBR1* and *TGFBR2* (serine-threonine kinase domains), with few pathogenic variants described in the extracellular domain. However, a model that singularly invokes decreased TGF-β signaling would be difficult to reconcile with the substantial evidence that many aspects of Marfan syndrome, including those that overlap with LDS, are caused by too much TGF-β signaling and can be attenuated or prevented by TGF-β antagonism in animal models.

Experiments exploring TGF-β signaling in cells that only express mutated receptors may not be informative for the situation in vivo when affected individuals are heterozygous for these pathogenic variants. Diminished but not absent function of TGF-β receptors may initiate chronic and dysregulated compensatory mechanisms that result in too much TGF-β signaling. Indeed, the study of fibroblasts derived from heterozygous individuals with LDS failed to reveal any defect in the acute phase response to administered ligand and showed an apparent increase in TGF-β signaling after 24 hours of ligand deprivation and a slower decline in the TGF-β signal after restoration of ligand. An even more informative result was the observation of increased nuclear accumulation of

phosphorylated mothers against decapentaplegic homolog 2 (the protein encoded by *SMAD2*) in the aortic wall of persons with either Marfan syndrome or LDS, and increased expression of TGF-β-dependent gene products such as collagen and CCN family member 2 (also called connective tissue growth factor, or CTGF; encoded by *CTGF*). Taken together, these data demonstrate increased TGF-β signaling in the vasculature of persons with LDS and in a context that is directly relevant to tissue development and homeostasis in vivo. Although the basis for this observation remains incompletely understood, it also seems possible that dysregulation of signaling requires the cell surface expression of receptors that can bind TGF-β ligands, but that cannot propagate signal because of a deficiency in kinase function. In support of this hypothesis, it was shown that transgenic expression of a mutated, kinase domain-deleted form of transforming growth factor beta receptor type-2 (TGFR-2) leads to increased TGF-β signaling, including stimulation of the intracellular signaling cascade and increased output of TGF-β-responsive genes. Recent work in animal models of LDS has shown that adjacent cell types in the arterial wall have different susceptibility to the influence of heterozygous loss-of-function variants in genes that encode positive effectors of TGF-β signaling. Attempts at compensation in more vulnerable cell types can include greatly enhanced secretion of TGF-β ligands, which can overdrive TGF-β signaling in less vulnerable adjacent cells. Notably, aortic aneurysm and dissection can be prevented in LDS mice through genetic manipulations that specifically attenuate TGF-β signaling in hyperresponsive vascular smooth muscle cells (i.e., those derived from the cardiac neural crest).

Mechanism of disease causation. Loss of function of the individual components of the TGF-β signaling pathway but overall a paradoxical gain of function of TGF-β-related signaling pathways

Table 9. Loeys-Dietz Syndrome: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
IPO8	There is no evidence for phenotypic expression in heterozygotes.
SMAD2	Missense variants in the MH1 and linker domain need to be considered w/more caution than those in the MH2 domain.
SMAD3	Missense variants in the MH1 and linker domain need to be considered w/more caution than those in the MH2 domain.
TGFB2	Missense variants affecting the RKKR consensus sequence and variants in the cytokine domain have a higher likelihood of being pathogenic.
TGFB3	Missense variants affecting the RKKR consensus sequence and variants in the cytokine domain have a higher likelihood of being pathogenic.
TGFBR1	• Variation in Ala repeat length (rs11466445) in exon 1 is not pathogenic for aortic aneurysm. • Missense variants in the extracellular cytokine-binding domain & variants leading to haploinsufficiency do not cause LDS.
TGFBR2	• Variants that do not escape nonsense-mediated decay are considered non-pathogenic. • Missense variants in the serine-threonine kinase domain have a higher likelihood of being pathogenic.

1. Genes from Table 1 in alphabetic order.

Chapter Notes

Author Notes

Gretchen Oswald (goswald1@jhmi.edu) is actively involved in clinical research regarding individuals with Loeys-Dietz syndrome (LDS). They would be happy to communicate with persons who have any questions regarding diagnosis of LDS or other considerations.

Prof Harry C Dietz (hdietz@jhmi.edu) and Prof Bart L Loeys (bart.loeys@uantwerp.be) are also interested in hearing from clinicians treating families affected by LDS in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in LDS.

Contact Prof Dietz and Prof Loeys to inquire about review of variants of uncertain significance in genes associated with LDS.

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References

Literature Cited

Attias D, Stheneur C, Roy C, Collod-Béroud G, Detaint D, Faivre L, Delrue MA, Cohen L, Francannet C, Béroud C, Claustres M, Iserin F, Khau Van Kien P, Lacombe D, Le Merrer M, Lyonnet S, Odent S, Plauchu H, Rio M, Rossi A, Sidi D, Steg PG, Ravaud P, Boileau C, Jondeau G. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. Circulation. 2009;120:2541–9. PubMed PMID: 19996017.

Atzinger CL, Meyer RA, Khoury PR, Gao Z, Tinkle BT. Cross-sectional and longitudinal assessment of aortic root dilation and valvular anomalies in hypermobile and classic Ehlers-Danlos syndrome. J Pediatr. 2011;158:826-30.e1. PubMed PMID: 21193204.

Baban A, Magliozzi M, Loeys B, Adorisio R, Alesi V, Secinaro A, Corica B, Vricella L, Dietz HC, Drago F, Novelli A, Amodeo A. First evidence of maternally inherited mosaicism in TGFBR1 and subtle primary myocardial changes in Loeys-Dietz syndrome: a case report. BMC Med Genet. 2018;19:170. PubMed PMID: 30219046.

Ben Amor IM, Edouard T, Glorieux FH, Chabot G, Tischkowitz M, Roschger P, Klaushofer K, Rauch F. Low bone mass and high material bone density in two patients with Loeys-Dietz syndrome caused by transforming growth factor beta receptor 2 mutations. J Bone Miner Res. 2012;27:713-8. PubMed PMID: 22095581.

Bertoli-Avella AM, Gillis E, Morisaki H, Verhagen JMA, de Graaf BM, van de Beek G, Gallo E, Kruithof BPT, Venselaar H, Myers LA, Laga S, Doyle AJ, Oswald G, van Cappellen GWA, Yamanaka I, van der Helm RM, Beverloo B, de Klein A, Pardo L, Lammens M, Evers C, Devriendt K, Dumoulein M, Timmermans J, Bruggenwirth HT, Verheijen F, Rodrigus I, Baynam G, Kempers M, Saenen J, Van Craenenbroeck EM, Minatoya K, Matsukawa R, Tsukube T, Kubo N, Hofstra R, Goumans MJ, Bekkers JA, Roos-Hesselink JW, van de Laar IMBH, Dietz HC, Van Laer L, Morisaki T, Wessels MW, Loeys BL. Mutations in a TGF-β ligand, TGFB3, cause syndromic aortic aneurysms and dissections. J Am Coll Cardiol. 2015;65:1324–36. PubMed PMID: 25835445.

Boileau C, Guo DC, Hanna N, Regalado ES, Detaint D, Gong L, Varret M, Prakash SK, Li AH, d'Indy H, Braverman AC, Grandchamp B, Kwartler CS, Gouya L, Santos-Cortez RL, Abifadel M, Leal SM, Muti C, Shendure J, Gross MS, Rieder MJ, Vahanian A, Nickerson DA, Michel JB. National Heart, Lung, and Blood Institute (NHLBI) Go Exome Sequencing Project, Jondeau G, Milewicz DM. TGFB2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nat Genet. 2012;44:916–21. PubMed PMID: 22772371.

Bowen JM, Sobey GJ, Burrows NP, Colombi M, Lavallee ME, Malfait F, Francomano CA. Ehlers-Danlos syndrome, classical type. Am J Med Genet C Semin Med Genet. 2017;175:27-39. PubMed PMID: 28192633.

Breckpot J, Budts W, De Zegher F, Vermeesch JR, Devriendt K. Duplication of the TGFBR1 gene causes features of Loeys-Dietz syndrome. Eur J Med Genet. 2010;53:408–10. PubMed PMID: 20813212.

Campbell IM, Kolodziejska KE, Quach MM, Wolf VL, Cheung SW, Lalani SR, Ramocki MB, Stankiewicz P. TGFBR2 deletion in a 20-month-old female with developmental delay and microcephaly. Am J Med Genet A. 2011;155A:1442–7. PubMed PMID: 21567932.

Cannaerts E, Kempers M, Maugeri A, Marcelis C, Gardeitchik T, Richer J, Micha D, Beauchesne L, Timmermans J, Vermeersch P, Meyten N, Chénier S, van de Beek G, Peeters N, Alaerts M, Schepers D, Van Laer L, Verstraeten A, Loeys B. Novel pathogenic SMAD2 variants in five families with arterial aneurysm and dissection: further delineation of the phenotype. J Med Genet. 2019;56:220-7. PubMed PMID: 29967133.

Charoenngam N, Rittiphairoj T, Ponvilawan B, Jaroenlapnopparat A, Waitayangkoon P, Suppakitjanusant P, Prasitsumrit V, Pongchaiyakul C, Holick MF. Bone fragility in hereditary connective tissue disorders: a systematic review and meta-analysis. Endocr Pract. 2023;29:589-600. PubMed PMID: 36804968.

Cornwall JW, Green RS, Nielsen JC, Gelb BD. Frequency of aortic dilation in Noonan syndrome. Am J Cardiol. 2014;113:368-71. PubMed PMID: 24220280.

Erkula G, Sponseller PD, Paulsen LC, Oswald GL, Loeys BL, Dietz HC. Musculoskeletal findings of Loeys-Dietz syndrome. J Bone Joint Surg Am. 2010;92:1876–83. PubMed PMID: 20686062.

Felgentreff K, Siepe M, Kotthoff S, von Kodolitsch Y, Schachtrup K, Notarangelo LD, Walter JE, Ehl S. Severe eczema and Hyper-IgE in Loeys-Dietz-syndrome - contribution to new findings of immune dysregulation in connective tissue disorders. Clin Immunol. 2014;150:43–50. PubMed PMID: 24333532.

Frischmeyer-Guerrerio PA, Guerrerio AL, Oswald G, Chichester K, Myers L, Halushka MK, Oliva-Hemker M, Wood RA, Dietz HC. TGFβ receptor mutations impose a strong predisposition for human allergic disease. Sci Transl Med. 2013;5:195ra94. PubMed PMID: 23884466.

Frise CJ, Pitcher A, Mackillop L. Loeys-Dietz syndrome and pregnancy: the first ten years. Int J Cardiol. 2017;226:21–5. PubMed PMID: 27780078.

Gaspar H, Lutz B, Reicherter K, Lühl S, Taurman R, Gabriel H, Brenner RE, Borck G. 4.7 Mb deletion encompassing TGFB2 associated with features of Loeys-Dietz syndrome and osteoporosis in adulthood. Am J Med Genet A. 2017;173:2289–92. PubMed PMID: 28544325.

Glancy DL, Wegmann M, Dhurandhar RW. Aortic dissection and patent ductus arteriosus in three generations. Am J Cardiol. 2001;87:813-5.A9.

Gouda P, Kay R, Habib M, Aziz A, Aziza E, Welsh R. Clinical features and complications of Loeys-Dietz syndrome: A systematic review. Int J Cardiol. 2022;362:158-67. PubMed PMID: 35662564.

Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, Wünnemann F, Bedja D, Moats CR, McClymont SA, Rose R, Sobreira N, Ling H, MacCarrick G, Kumar AA, Luyckx I, Cannaerts E, Verstraeten A, Björk HM, Lehsau AC, Jaskula-Ranga V, Lauridsen H, Shah AA, Bennett CL, Ellinor PT, Lin H, Isselbacher EM, Lino Cardenas CL, Butcher JT, Hughes GC, Lindsay ME; Baylor-Hopkins Center for Mendelian Genomics; MIBAVA Leducq Consortium; Mertens L, Franco-Cereceda A, Verhagen JMA, Wessels M, Mohamed SA, Eriksson P, Mital S, Van Laer L, Loeys BL, Andelfinger G, McCallion AS, Dietz

HC. ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. Nat Genet. 2019;51:42-50. PubMed PMID: 30455415.

Granadillo JL, Chung WK, Hecht L, Corsten-Janssen N, Wegner D, Nij Bijvank SWA, Toler TL, Pineda-Alvarez DE, Douglas G, Murphy JJ, Shimony J, Shinawi M. Variable cardiovascular phenotypes associated with SMAD2 pathogenic variants. Hum Mutat. 2018;39:1875-84. PubMed PMID: 30157302.

Greene D, Genomics England Research Consortium, Pirri D, Frudd K, Sackey E, Al-Owain M, Giese APJ, Ramzan K, Riaz S, Yamanaka I, Boeckx N, Thys C, Gelb BD, Brennan P, Hartill V, Harvengt J, Kosho T, Mansour S, Masuno M, Ohata T, Stewart H, Taibah K, Turner CLS, Imtiaz F, Riazuddin S, Morisaki T, Ostergaard P, Loeys BL, Morisaki H, Ahmed ZM, Birdsey GM, Freson K, Mumford A, Turro E. Genetic association analysis of 77,539 genomes reveals rare disease etiologies. Nat Med. 2023;29:679-88. PubMed PMID: 36928819.

Gutman G, Baris HN, Hirsch R, Mandel D, Yaron Y, Lessing JB, Kuperminc MJ. Loeys-Dietz syndrome in pregnancy: a case description and report of a novel mutation. Fetal Diagn Ther. 2009;26:35–7. PubMed PMID: 19816028.

Hilhorst-Hofstee Y, Scholte AJ, Rijlaarsdam ME, van Haeringen A, Kroft LJ, Reijnierse M, Ruivenkamp CA, Versteegh MI, Pals G, Breuning MH. An unanticipated copy number variant of chromosome 15 disrupting SMAD3 reveals a three-generation family at serious risk for aortic dissection. Clin Genet. 2013;83:337–44. PubMed PMID: 22803640.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Huguenard AL, Johnson GW, Osbun JW, Dacey RG, Braverman AC. Frequency of screening-detected intracranial aneurysms in patients with Loeys-Dietz syndrome. Circulation. 2022;146:142-3. PubMed PMID: 35713018.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Khau Van Kien P, Mathieu F, Zhu L, Lalande A, Betard C, Lathrop M, Brunotte F, Wolf JE, Jeunemaitre X. Mapping of familial thoracic aortic aneurysm/dissection with patent ductus arteriosus to 16p12.2-p13.13. Circulation. 2005;112:200–6. PubMed PMID: 15998682.

Khau Van Kien P, Wolf JE, Mathieu F, Zhu L, Salve N, Lalande A, Bonnet C, Lesca G, Plauchu H, Dellinger A, Nivelon-Chevallier A, Brunotte F, Jeunemaitre X. Familial thoracic aortic aneurysm/dissection with patent ductus arteriosus: genetic arguments for a particular pathophysiological entity. Eur J Hum Genet. 2004;12:173–80. PubMed PMID: 14722581.

Kiando SR, Tucker NR, Castro-Vega LJ, Katz A, D'Escamard V, Tréard C, Fraher D, Albuisson J, Kadian-Dodov D, Ye Z, Austin E, Yang ML, Hunker K, Barlassina C, Cusi D, Galan P, Empana JP, Jouven X, Gimenez-Roqueplo AP, Bruneval P, Hyun Kim ES, Olin JW, Gornik HL, Azizi M, Plouin PF, Ellinor PT, Kullo IJ, Milan DJ, Ganesh SK, Boutouyrie P, Kovacic JC, Jeunemaitre X, Bouatia-Naji N. PHACTR1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. PLoS Genet. 2016;12:e1006367. PubMed PMID: 27792790.

Kirmani S, Tebben PJ, Lteif AN, Gordon D, Clarke BL, Hefferan TE, Yaszemski MJ, McGrann PS, Lindor NM, Ellison JW. Germline TGF-beta receptor mutations and skeletal fragility: a report on two patients with Loeys-Dietz syndrome. Am J Med Genet A. 2010;152A:1016–9. PubMed PMID: 20358619.

Lindsay ME, Dietz H. Lessons on the pathogenesis of aneurysm from heritable conditions. Nature. 2011;473:308–16. PubMed PMID: 21593863.

Lindsay ME, Schepers D, Bolar NA, Doyle JJ, Gallo E, Fert-Bober J, Kempers MJ, Fishman EK, Chen Y, Myers L, Bjeda D, Oswald G, Elias AF, Levy HP, Anderlid BM, Yang MH, Bongers EM, Timmermans J, Braverman AC, Canham N, Mortier GR, Brunner HG, Byers PH, Van Eyk J, Van Laer L, Dietz HC, Loeys BL. Loss-of-function mutations in TGFB2 cause a syndromic presentation of thoracic aortic aneurysm. Nat Genet. 2012;44:922–7. PubMed PMID: 22772368.

Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005;37:275–81. PubMed PMID: 15731757.

Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, Roberts AE, Faravelli F, Greco MA, Pyeritz RE, Milewicz DM, Coucke PJ, Cameron DE, Braverman AC, Byers PH, De Paepe AM, Dietz HC. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006;355:788–98. PubMed PMID: 16928994.

Luyckx I, MacCarrick G, Kempers M, Meester J, Geryl C, Rombouts O, Peeters N, Claes C, Boeckx N, Sakalihasan N, Jacquinet A, Hoischen A, Vandeweyer G, Van Lent S, Saenen J, Van Craenenbroeck E, Timmermans J, Duijnhouwer A, Dietz H, Van Laer L, Loeys B, Verstraeten A. Confirmation of the role of pathogenic SMAD6 variants in bicuspid aortic valve-related aortopathy. Eur J Hum Genet. 2019;27:1044-53. PubMed PMID: 30796334.

MacCarrick G, Black JH 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, Sponseller PD, Loeys B, Dietz HC 3rd. Loeys-Dietz syndrome: a primer for diagnosis and management. Genet Med. 2014;16:576–87. PubMed PMID: 24577266.

Maleszewski JJ, Miller DV, Lu J, Dietz HC, Halushka MK. Histopathologic findings in ascending aortas from individuals with Loeys-Dietz syndrome (LDS). Am J Surg Pathol. 2009;33:194–201. PubMed PMID: 18852674.

Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:8–26. PubMed PMID: 28306229.

Malfait F, Symoens S, De Backer J, Hermanns-Le T, Sakalihasan N, Lapiere CM, Coucke P, De Paepe A. Three arginine to cysteine substitutions in the pro-alpha (I)-collagen chain cause Ehlers-Danlos syndrome with a propensity to arterial rupture in early adulthood. Hum Mutat. 2007;28:387–95. PubMed PMID: 17211858.

McDonnell NB, Gorman BL, Mandel KW, Schurman SH, Assanah-Carroll A, Mayer SA, Najjar SS, Francomano CA. Echocardiographic findings in classical and hypermobile Ehlers-Danlos syndromes. Am J Med Genet A. 2006;140:129-36. PubMed PMID: 16353246.

Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys- Dietz syndrome. Ann Cardiothorac Surg. 2017b;6:582–94. PubMed PMID: 29270370.

Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junien C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, Matsumoto N. Heterozygous TGFBR2 mutations in Marfan syndrome. Nat Genet. 2004;36:855–60. PubMed PMID: 15235604.

Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. Heart. 1999;82:19–22. PubMed PMID: 10377302.

Pannu H, Tran-Fadulu V, Papke CL, Scherer S, Liu Y, Presley C, Guo D, Estrera AL, Safi HJ, Brasier AR, Vick GW, Marian AJ, Raman CS, Buja LM, Milewicz DM. MYH11 mutations result in a distinct vascular pathology driven by insulin-like growth factor 1 and angiotensin II. Hum Mol Genet. 2007;16:2453–62. PubMed PMID: 17666408.

Redon R, Baujat G, Sanlaville D, Le Merrer M, Vekemans M, Munnich A, Carter NP, Cormier-Daire V, Colleaux L. Interstitial 9q22.3 microdeletion: clinical and molecular characterisation of a newly recognised overgrowth syndrome. Eur J Hum Genet. 2006;14:759–67. PubMed PMID: 16570072.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol. 1989;64:507–12. PubMed PMID: 2773795.

Schepers D, Tortora G, Morisaki H, MacCarrick G, Lindsay M, Liang D, Mehta SG, Hague J, Verhagen J, van de Laar I, Wessels M, Detisch Y, van Haelst M, Baas A, Lichtenbelt K, Braun K, van der Linde D, Roos-Hesselink J, McGillivray G, Meester J, Maystadt I, Coucke P, El-Khoury E, Parkash S, Diness B, Risom L, Scurr I, Hilhorst-Hofstee Y, Morisaki T, Richer J, Désir J, Kempers M, Rideout AL, Horne G, Bennett C, Rahikkala E, Vandeweyer G, Alaerts M, Verstraeten A, Dietz H, Van Laer L, Loeys B. A mutation update on the LDS-associated genes TGFB2/3 and SMAD2/3. Hum Mutat. 2018;39:621-34. PubMed PMID: 29392890.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Tessler I, Albuisson J, Piñeiro-Sabarís R, Verstraeten A, Kamber Kaya HE, Siguero-Álvarez M, Goudot G, MacGrogan D, Luyckx I, Shpitzen S, Levin G, Kelman G, Reshef N, Mananet H, Holdcraft J, Muehlschlegel JD, Peloso GM, Oppenheim O, Cheng C, Mazzella JM, Andelfinger G, Mital S, Eriksson P, Billon C, Heydarpour M, Dietz HC, Jeunemaitre X, Leitersdorf E, Sprinzak D, Blacklow SC, Body SC, Carmi S, Loeys B, de la Pompa JL, Gilon D, Messas E, Durst R. Novel association of the NOTCH pathway regulator MIB1 gene with the development of bicuspid aortic valve. JAMA Cardiol. 2023;8:721-31. PubMed PMID: 37405741.

van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, Hoedemaekers YM, Willemsen R, Severijnen LA, Venselaar H, Vriend G, Pattynama PM, Collée M, Majoor-Krakauer D, Poldermans D, Frohn-Mulder IM, Micha D, Timmermans J, Hilhorst-Hofstee Y, Bierma-Zeinstra SM, Willems PJ, Kros JM, Oei EH, Oostra BA, Wessels MW, Bertoli-Avella AM. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet. 2011;43:121–6. PubMed PMID: 21217753.

Van Gucht I, Krebsova A, Diness BR, Laga S, Adlam D, Kempers M, Samani NJ, Webb TR, Baranowska AA, Van Den Heuvel L, Perik M, Luyckx I, Peeters N, Votypka P, Macek M, Meester J, Van Laer L, Verstraeten A, Loeys BL. Novel *LOX* variants in five families with aortic/arterial aneurysm and dissection with variable connective tissue findings. Int J Mol Sci. 2021a;22:7111. PubMed PMID: 34281165.

Van Gucht I, Meester JAN, Bento JR, Bastiaansen M, Bastianen J, Luyckx I, Van Den Heuvel L, Neutel CHG, Guns PJ, Vermont M, Fransen E, Perik MHAM, Velchev JD, Alaerts M, Schepers D, Peeters S, Pintelon I, Almesned A, Ferla MP, Taylor JC, Dallosso AR, Williams M, Evans J; Genomics England Research Consortium; Rosenfeld JA, Sluysmans T, Rodrigues D, Chikermane A, Bharmappanavara G, Vijayakumar K, Mottaghi Moghaddam Shahri H, Hashemi N, Torbati PN, Toosi MB, Al-Hassnan ZN, Vogt J, Revencu N,

Maystadt I, Miller EM, Weaver KN, Begtrup A, Houlden H, Murphy D, Maroofian R, Pagnamenta AT, Van Laer L, Loeys BL, Verstraeten A. A human importin-β-related disorder: syndromic thoracic aortic aneurysm caused by bi-allelic loss-of-function variants in IPO8. Am J Hum Genet. 2021b;108:1115-25. PubMed PMID: 34010605.

Van Hemelrijk C, Renard M, Loeys B. The Loeys-Dietz syndrome: an update for the clinician. Curr Opin Cardiol. 2010;25:546–51. PubMed PMID: 20838339.

Wenstrup RJ, Meyer RA, Lyle JS, Hoechstetter L, Rose PS, Levy HP, Francomano CA. Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. Genet Med. 2002;4:112–7. PubMed PMID: 12180144.

Wischmeijer A, Van Laer L, Tortora G, Bolar NA, Van Camp G, Fransen E, Peeters N, di Bartolomeo R, Pacini D, Gargiulo G, Turci S, Bonvicini M, Mariucci E, Lovato L, Brusori S, Ritelli M, Colombi M, Garavelli L, Seri M, Loeys BL. Thoracic aortic aneurysm in infancy in aneurysms-osteoarthritis syndrome due to a novel SMAD3 mutation: further delineation of the phenotype. Am J Med Genet A. 2013;161A:1028–35. PubMed PMID: 23554019.

Yetman AT, Beroukhim RS, Ivy DD, Manchester D. Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. Pediatrics. 2007;119:e1199–202. PubMed PMID: 17470566.

Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, Romano-Adesman A, Bjornson RD, Breitbart RE, Brown KK, Carriero NJ, Cheung YH, Deanfield J, DePalma S, Fakhro KA, Glessner J, Hakonarson H, Italia MJ, Kaltman JR, Kaski J, Kim R, Kline JK, Lee T, Leipzig J, Lopez A, Mane SM, Mitchell LE, Newburger JW, Parfenov M, Pe'er I, Porter G, Roberts AE, Sachidanandam R, Sanders SJ, Seiden HS, State MW, Subramanian S, Tikhonova IR, Wang W, Warburton D, White PS, Williams IA, Zhao H, Seidman JG, Brueckner M, Chung WK, Gelb BD, Goldmuntz E, Seidman CE, Lifton RP. De novo mutations in histone-modifying genes in congenital heart disease. Nature. 2013;498:220–3. PubMed PMID: 23665959.

Zhu L, Vranckx R, Khau Van Kien P, Lalande A, Boisset N, Mathieu F, Wegman M, Glancy L, Gasc JM, Brunotte F, Bruneval P, Wolf JE, Michel JB, Jeunemaitre X. Mutations in myosin heavy chain 11 cause a syndrome associating thoracic aortic aneurysm/aortic dissection and patent ductus arteriosus. Nat Genet. 2006;38:343–9. PubMed PMID: 16444274.

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